ツシジノスタット
ハイヤスタ錠 10mg

第 2 部 CTD の概要

2.7 臨床概要
2.7.1 生物薬剤学及び関連する分析法の概要

Huya Japan 合同会社

2.7.1 生物薬剤学及び関連する分析法の概要

本申請は，既承認の製剤についての一部変更承認申請であり，本項目についての新たな記載事項はない。

ツシジノスタット
ハイヤスタ錠10mg

第2部 CTDの概要

2.7 臨床概要
2.7.2 臨床薬理の概要

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2.7.2　臨床薬理の概要

本申請は，既承認の製剤についての一部変更承認申請であり，本項目についての新たな記載事項はない。

ツシジノスタット
ハイヤスタ錠 10mg

第 2 部 CTD の概要

2.7 臨床概要
2.7.3 臨床的有効性の概要

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略号一覧表

略語・用語	内容
AE	adverse event 有害事象
AITL	angioimmunoblastic T-cell lymphoma 血管免疫芽球性 T 細胞リンパ腫
ALCL	anaplastic large cell lymphoma 未分化大細胞リンパ腫
ALK	anaplastic lymphoma kinase 未分化リンパ腫キナーゼ
ATL	adult T-cell lymphoma 成人 T 細胞白血病リンパ腫
BMI	body mass index 体格指数
BSA	body surface area 体表面積
CI	confidence interval 信頼区間
CPR	Central Pathology Review 中央病理評価委員会
CR	complete response 完全奏効
CRu	unconfirmed complete response 不確定完全奏効
CSR	clinical study report 治験総括報告書
CT	computed tomography コンピュータ断層撮影
CTCAE	Common Terminology Criteria for Adverse Events 有害事象共通用語規準
DCR	disease control rate 病勢コントロール率
DLT	dose-limiting toxicity 用量制限毒性
DOR	duration of response 奏効期間
EATL	enteropathy-associated T-cell lymphoma 腸管症関連 T 細胞リンパ腫
ECOG	Eastern Cooperative Oncology Group 米国東海岸がん臨床試験グループ
FAS	full analysis set 最大の解析対象集団
HSTCL	hepatosplenic T-cell lymphoma 肝脾 T 細胞リンパ腫
IOERC	Independent Overall Efficacy Review Committee 独立総合効果判定委員会
IRR	Independent Radiologist/Radiology Review 独立画像判定
mSWAT	modified Severity-Weighted Assessment Tool ―
NHL	non-Hodgkin's lymphoma 非ホジキンリンパ腫
ORR	objective response rate 客観的奏効率

略語・用語	内容
OS	overall survival 全生存期間
PD	progressive disease 進行
PET	positron-emission tomography 陽電子放出断層撮影
PET-CT	positron-emission tomography–computed tomography 陽電子放出断層撮影–コンピュータ断層撮影
PFS	progression-free survival 無増悪生存期間
PK	pharmacokinetic(s) 薬物動態
PPD	product of the perpendicular diameter 直交する径の積
PPS	per-protocol set 治験実施計画書に適合した対象集団
PR	partial response 部分奏効
PS	performance status パフォーマンスステータス
PTCL	peripheral T-cell lymphoma 末梢性 T 細胞リンパ腫
PTCL-NOS	peripheral T-cell lymphoma, not otherwise specified 非特定型末梢性 T 細胞リンパ腫
SD	stable disease 安定
SPD	sum of the products of the greatest diameters 二方向積和
SPTCL	subcutaneous panniculitis-like T-cell lymphoma 皮下脂肪織炎様 T 細胞リンパ腫
%TBSA	percentage of total body surface area 全体表面積に占める割合
TTR	time to response 奏効までの期間

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2.7.3 臨床的有効性の概要

2.7.3.1 背景及び概観

本項では、ツシジノスタット（HBI-8000 又は中国では chidamide）（以下、本薬）の有効性の概要を示す。

本薬の有効性は、日本人及び韓国人の再発又は難治性の末梢性 T 細胞リンパ腫（PTCL）患者を対象としたピボタル第 2b 相試験（HBI-8000-203 試験、以下 203 試験）（5.3.5.2-1）及び PTCL を含む非ホジキンリンパ腫（NHL）患者を対象とした日本人第 1 相試験（HBI-8000-201 試験、以下 201 試験）（5.3.3.2-1）から得られたデータを評価資料として検討した。中国人の再発又は難治性の PTCL 患者を対象とした第 2 相試験（TG0902CDM 試験、以下 902 試験）（5.3.5.4-1/TG0902CDM p2a、5.3.5.4-2/TG0902CDM p2b）のピボタル試験の結果（5.3.5.4-2）は、再発又は難治性の PTCL 患者に対する本薬の有効性を裏付けるデータを有すると考えられることから、参考資料とした。902 試験の結果により、本薬は中国で再発又は難治性の PTCL に対する承認を取得している。

有効性の評価に用いた、日本人、韓国人及び中国人の PTCL 患者に本薬が投与された試験の概要を表 2.7.3.1-1 に示す。

表 2.7.3.1-1 日本人、韓国人、中国人末梢性 T 細胞リンパ腫患者対象試験の概要

試験番号	HBI-8000-203 （評価試験）	HBI-8000-201 （評価試験）	TG0902CDM （参考試験）
試験期間	2017 年 3 月 ■ 日～20■ 年 ■ 月 ■ 日（主解析のデータカットオフ日） 継続中	2014 年 6 月 ■ 日～2016 年 10 月 ■ 日 完了	2009 年 3 月 ■ 日～2012 年 9 月 ■ 日（最後に組み入れた被験者のデータカットオフ日）
治験実施医療機関数	21 施設／日本 10 施設／韓国	8 施設／日本	探索的試験： 13 施設／中国 ピボタル試験： 15 施設／中国
相	2b	1	2
試験デザイン	非盲検、単一群	非盲検、用量漸増	探索的試験： 非盲検 ピボタル試験： 非盲検、単一群
用法・用量・投与期間	1 回 40 mg を 28 日サイクルで週 2 回経口投与、病勢進行又は許容できない毒性発現まで継続。	1 回 30 mg 又は 40 mg を 28 日サイクルで週 2 回経口投与、病勢進行又は許容できない毒性発現まで継続。	探索的試験： 1 回 30 mg 又は 50 mg を週 2 回経口投与、2 週投与の後、1 週休薬、6 週サイクル。 ピボタル試験： 1 回 30 mg を週 2 回経口投与、休薬なし、6 週サイクル。 探索的試験及びピボタル試験： 病勢進行又は安全性上の懸念による試験参加中止まで継続。

試験番号	HBI-8000-203 （評価試験）	HBI-8000-201 （評価試験）	TG0902CDM （参考試験）
対象被験者	抗がん剤による全身療法を 1 レジメン以上施行した後の再発又は難治性の末梢性 T 細胞リンパ腫であり、患者に適切と思われる他の標準的治療法がない患者	標準的治療法が適さない末梢性 T 細胞リンパ腫を含む非ホジキンリンパ腫患者	全身療法（化学療法、幹細胞移植等を含む）を 1 つ以上施行した後の再発又は難治性の末梢性 T 細胞リンパ腫患者
試験目的	主要目的：有効性 副次目的：安全性及び忍容性	主要目的：最大耐量の決定 副次目的：安全性、薬物動態、腫瘍縮小効果	探索的試験： 1. 異なる用量の週 2 回投与レジメンでの有効性（予備的評価）及び安全性 2. ピボタル試験の推奨用法・用量の決定 ピボタル試験： 主要目的：有効性 副次目的：安全性
有効性主要評価項目	独立画像判定及び独立総合効果判定委員会による評価に基づく客観的奏効率（完全奏効＋部分奏効）	治験担当医師評価による総合効果	客観的奏効率（完全奏効＋不確定完全奏効＋部分奏効）

2.7.3.1.1 日本人／韓国人第 2b 相試験（203 試験）（評価試験）

2.7.3.1.1.1 試験デザイン

本試験は、日本人及び韓国人の再発又は難治性の PTCL 患者を対象に、本薬の有効性及び安全性を評価した第 2b 相、非盲検、単一群試験である。

本試験の適格患者は、病理組織学的又は細胞学的に PTCL と診断され、測定可能病変を 1 つ以上有する 20 歳以上の日本人又は韓国人患者のうち、抗がん剤による全身療法を施行後に再発又は難治性の PTCL となり、ほかに適切な標準的治療法がない患者とした。本試験では、投与サイクルを 28 日とし、本薬 40 mg を 3～4 日間隔で週 2 回、通常の食事から約 30 分後に経口投与することとした。本薬の投与は、病勢進行が確認されるか、最適な支持療法を実施しても許容できない毒性が認められるまで継続することとした。

最後の被験者がサイクル 5 の Day 1 評価を完了した後（データカットオフ日：20[redacted] 年 [redacted] 月 [redacted] 日）に主解析を実施した。

PTCL の腫瘍縮小効果及び進行（PD）は、リンパ腫に対する効果判定基準の改訂版［Cheson 2014］及び皮膚病変がみられる場合は modified Severity-Weighted Assessment Tool（mSWAT）［Stevens 2002、Olsen 2011］に準じて評価した。腫瘍縮小効果判定基準の詳細を 2.7.3.6.3 項付録 3 に示した。

独立画像判定（IRR）によりすべての画像を評価した。IRR による画像評価、mSWAT スコア及び臨床所見を含むすべての有効性データは独立総合効果判定委員会（IOERC）が評価した。主要解析は IOERC 及び IRR の評価結果を用いて実施した。また、疾患の病理組織学的診断を中央病理評価委員会（CPR）が独立に確認した。

2.7.3.1.1.2 有効性評価項目

主要評価項目

主要評価項目は客観的奏効率（ORR）とし、治験実施計画書に適合した対象集団（PPS）での完全奏効（CR）又は部分奏効（PR）を達成した被験者の割合と定義した。

副次的評価項目

副次的評価項目は以下のとおりとした。

- CPR により確認された PTCL 病型分類（サブタイプ）別の ORR：非特定型末梢性 T 細胞リンパ腫（PTCL-NOS）、血管免疫芽球性 T 細胞リンパ腫（AITL）、未分化リンパ腫キナーゼ（ALK）陽性未分化大細胞リンパ腫（ALCL）、ALK 陰性 ALCL、腸管症関連 T 細胞リンパ腫（EATL）、肝脾 T 細胞リンパ腫（HSTCL）及び皮下脂肪織炎様 T 細胞リンパ腫（SPTCL）
- IOERC 評価による無増悪生存期間（PFS）
- IOERC 評価による奏効期間（DOR）

探索的評価項目

探索的評価項目は、全生存期間（OS）の中央値等とした。探索的評価項目の詳細は、5.3.5.2-1/HBI-8000-203/治験総括報告書（CSR）に記載した。

2.7.3.1.1.3 統計解析

PPS を対象に、すべての有効性評価を実施した。PPS は、適格基準をすべて満たし、サイクル 1 の投与を終了した被験者と定義した。臨床的 PD が認められ、サイクル 1 で本薬投与を中止した被験者は、治験実施計画書からの重要な逸脱がない限り、PPS に含めた。腫瘍評価のための画像検査を実施しなかった場合も、臨床的 PD のためサイクル 1 で本薬投与を中止した被験者は PPS に含めた。また、有効性の主要評価の感度分析として、最大の解析対象集団（FAS）を対象に解析を実施した。FAS は、適格基準をすべて満たし、1 回以上本薬を投与され、投与開始後に画像検査又は臨床所見により 1 回以上有効性評価を実施した被験者と定義した。

なお、CPR により疾患が PTCL であると確認されなかった被験者は有効性評価の FAS 及び PPS から除外した。

腫瘍の総合効果判定に基づく ORR は、正確な二項分布の 95%信頼区間（CI）で要約した。CI の下限値が 10%の閾値より高い場合、ORR は 10%より有意に優れていると結論付けた。PFS は、本薬の初回投与から PD 又は死亡のいずれか早い方までの期間と定義した。PD、死亡又は新たな（治験実施計画書外の）がん治療の開始が確認されない場合は、PD でないことが確認された最後の総合効果判定日で打ち切りとした。ただし、PD 又は死亡が確認されず、被験者が新たながん治療を開始した場合、又は、新たながん治療の開始後に PD 及び死亡が確認された場合、新たながん治療の開始前で PD でないことが確認された最後の総合効果判定日で打ち切りとした。DOR は、CR 又は PR と評価された被験者を対象とし、最初に CR 又は PR が認められてから PD 又は死亡までの期間と定義した。打ち切りとした場合は、最後の総合効果判定日までとした。Time-to-event 型変数は、Kaplan-Meier 法（中央値、95%CI、イベント数、打ち切り数及び Kaplan-Meier 曲線）

で要約した。

2.7.3.1.2 日本人第 1 相試験（201 試験）（評価試験）

2.7.3.1.2.1 試験デザイン

本試験は、標準的治療法が適さない日本人の NHL 患者（PTCL 患者を含む）を対象に、本薬の安全性、忍容性、薬物動態（PK）及び予備的な有効性を評価した第 1 相、非盲検、用量漸増試験である。本試験の適格患者は、病理組織学的又は細胞学的に NHL と診断された患者のうち、測定可能病変を 1 つ以上有する患者とした。

本試験では、投与サイクルを 28 日とし、本薬を週 2 回、朝食後に経口投与することとした。計画した用量は 30 mg、40 mg 及び 50 mg であり、標準的な 3＋3 デザインに従って、サイクル 1（投与開始後 28 日間）で観察された用量制限毒性（DLT）に基づき用量を漸増した。用量コホートの移行は 40 mg で終了したため、本試験では 30 mg 及び 40 mg の 2 用量のみが投与された。本薬の投与は、病勢進行又は許容できない毒性が認められるか、被験者が同意撤回するまで継続可能とした。

2.7.3.1.2.2 有効性評価項目

本試験では、治験担当医師の評価による総合効果により予備的な有効性を検討した。

腫瘍縮小効果は、Cheson の NHL に対する効果判定基準［Cheson 1999］及び日本臨床腫瘍研究グループの成人 T 細胞白血病リンパ腫（ATL）に対する効果判定基準［Tsukasaki 2009、日本血液学会ガイドライン 2013］を参考に作成した基準に従って評価した（5.3.3.2-1/HBI-8000-201/CSR 参照）。

2.7.3.1.2.3 統計解析

すべての有効性解析は、有効性解析対象集団を対象に実施した。有効性解析対象集団は、本薬が 2 回以上投与され、スクリーニング時及び本薬投与後に有効性の妥当な評価が可能であったすべての被験者と定義した。

本資料では PTCL 患者 1 例での治療効果のみを示した。

2.7.3.1.3 中国人第 2 相試験（902 試験）（参考試験）

2.7.3.1.3.1 試験デザイン

本試験は、Chipscreen 社が中国で実施した、中国人の再発又は難治性の PTCL 患者を対象に、本薬の安全性、有効性及び PK を評価した第 2 相、多施設共同、非盲検試験であり、探索的試験及びピボタル試験の 2 つのパートから構成された。探索的試験はピボタル試験の推奨用法・用量を決定するためにデザインされ、ピボタル試験は有効性と安全性を評価するためにデザインされた。

本試験の適格患者は、病理組織学的に PTCL と診断された 18 歳から 75 歳の中国人患者で、全身療法（化学療法、幹細胞移植等を含む）を施行後に再発した PTCL 又は難治性の PTCL を有する患者とした。

探索的試験では、被験者を 30 mg 投与又は 50 mg 投与に無作為に割り付け、本薬を週 2 回、朝

食後に経口投与することとした。投与は 2 週投与後、1 週休薬で、投与サイクルは 6 週とした。この探索的試験の結果からピボタル試験での推奨用法・用量を決定し、ピボタル試験では、本薬 30 mg を週 2 回、朝食後に経口投与することとした。投与サイクルは休薬なしの 6 週とした。探索的試験、ピボタル試験ともに、本薬の投与は、病勢進行が認められるか、安全性上の懸念から試験を中止するまで継続することとした。

2.7.3.1.3.2 有効性評価項目

主要評価項目

主要評価項目は ORR［対象集団での CR、不確定完全奏効（CRu）又は PR を達成した被験者の割合］とした。

PTCL の腫瘍縮小効果及び PD は、2008 年の National Comprehensive Cancer Network ガイドラインの Cheson の NHL に対する効果判定基準[Cheson 1999]に準じて評価した（5.3.5.4-1/TG0902CDM p2a/CSR 及び 5.3.5.4-2/TG0902CDM p2b/CSR 参照）。

副次的評価項目

副次的評価項目は、奏効までの期間（TTR）、DOR、PFS、3 ヵ月間（12 週間）の持続的奏効率（ピボタル試験のみ）及び OS（ピボタル試験のみ）とした。

2.7.3.1.3.3 統計解析

有効性評価は、FAS 及び PPS を対象に実施した。FAS は本試験の有効性の主要解析対象集団とし、PPS は有効性の副次的解析対象集団とした。

探索的試験での FAS の定義は、本試験組入れ後に 1 回以上本薬が投与され、主要評価項目の評価を実施した被験者とした。ベースライン時での主要評価項目の評価データが不足していた被験者は FAS から除外した。PPS の定義は、組入れ基準をすべて満たした被験者のうち、ベースライン評価が有効で、治験実施計画書のとおりに投与され、治験実施計画書からの逸脱（併用禁止薬の使用等）のない被験者とした。

ピボタル試験での FAS の定義は、中央検査機関で病理組織学的に PTCL と診断され、1 つ以上の全身療法への効果が認められない又は本試験組入れ前に再発した被験者で、本薬を 1 回以上投与された被験者とした。PPS の定義は、組入れ基準をすべて満たし、少なくとも 6 週の投与を完了して有効性評価を行った被験者のうち、ベースライン評価が有効で、治験実施計画書のとおりに投与され、治験実施計画書からの逸脱（併用禁止薬の使用等）のない被験者とした。

奏効率は 95%CI で要約した。ピボタル試験では、有効性主要評価項目の ORR は、奏効率が点推定値（27%）に達するかどうか、及び 95%CI の下限値が 15%を上回るかどうかにより評価した。TTR は、本薬の初回投与後、最初に効果（PR、CRu 又は CR）が認められるまでの期間とした。DOR は、最初に効果が認められてから最初の PD までの期間とした。PFS は、本薬の初回投与後、最初の PD 又は死亡までの期間とした。ピボタル試験で評価された 3 ヵ月間（12 週間）の持続的奏効率は、対象集団での全被験者のうち、最低でも 3 ヵ月間（12 週間）効果が持続した被験者の割合とした。OS（ピボタル試験のみ）は、本薬の初回投与から死亡までの期間とした。TTR、DOR、PFS 及び OS は Kaplan-Meier 法を用いて推定した。DOR が 12 週（3 ヵ月）以上の被験者の割合及び 95%CI を算出した。

2.7.3.2 個々の試験結果の要約

2.7.3.2.1 日本人／韓国人第 2b 相試験（203 試験）

本試験では、日本の 21 施設及び韓国の 10 施設で同意取得した 74 例のうち、スクリーニングで適格と判断された 55 例に本薬が投与された。このうち、49 例が FAS に採用され、46 例が PPS に採用された。データカットオフ日（20■ 年■ 月■ 日）までに、55 例中 47 例（85.5%）が本薬投与を中止した。

IOERC 評価に基づく ORR は、PPS で 45.7%（95%CI：30.9%～61.0%）であり、5 例（10.9%）が CR、16 例（34.8%）が PR を達成した。ORR は目標である 30%を超えており、また 95%CI の下限が規定した閾値である 10%を上回っていたため、ORR は、両側有意水準 5%で、規定した閾値を統計学的に有意に上回ったと判断された。

FAS の ORR は 42.9%［49 例中 21 例（95%CI：28.8%～57.8%）］であり、FAS での ORR は PPS での結果と同様であった。FAS では 5 例（10.2%）が CR を達成し、16 例（32.7%）が PR を達成した。

国別（日本及び韓国）の PPS の被験者の内訳は、日本人 34 例及び韓国人 12 例であった。PPS において、ORR は日本人被験者で 52.9%［34 例中 18 例（95%CI：35.1%～70.2%）］、韓国人被験者で 25.0%［12 例中 3 例（95%CI：5.5%～57.2%）］であった。

PTCL サブセット別（再発及び難治性）では、PPS の ORR は再発 PTCL を有する被験者で 53.6%［28 例中 15 例（95%CI：33.9%～72.5%）］、難治性の PTCL を有する被験者で 33.3%［18 例中 6 例（95%CI：13.3%～59.0%）］であった。

PPS での IOERC 評価に基づく PFS の中央値は 24.1 週（95%CI：12.7～58.1 週）［5.6 ヵ月（95%CI：2.9～13.4 ヵ月）］であった。24 例（52.2%）で PD が確認され、22 例（47.8%）は打ち切りとなった。PD 以外で死亡に至った被験者はなかった。

PPS での OS の中央値は 99.1 週（95%CI：54.9～99.1 週）［22.8 ヵ月（95%CI：12.6～22.8 ヵ月）］であった。14 例（30.4%）が死亡し、32 例（69.6%）は最後に生存が確認された日で打ち切りとなった。99.1 週（22.8 ヵ月）に at risk であった被験者は 1 例であり、この 1 例が 99.1 週（22.8 ヵ月）に死亡した。

2.7.3.2.2 日本人第 1 相試験（201 試験）

本試験では、NHL を有する被験者 22 例より同意取得し、このうち、14 例に 1 回以上本薬が投与された。14 例のうち、30 mg コホートの 2 例（被験者[redacted]及び[redacted]）が PTCL の診断を受けており、本資料では、これら 2 例のみについて記述した。2 例のうち 1 例（被験者[redacted]）は、本薬の投与が 1 回のみであったため、有効性解析対象集団から除外された。もう 1 例（被験者[redacted]）の最良総合効果は PD であった。

2.7.3.2.3 中国人第 2 相試験（902 試験）（参考試験）

本試験では、ピボタル試験での本薬の投与スケジュールが本承認申請の投与スケジュールと同様であったため、ピボタル試験の結果のみを含めた。

本試験のピボタル試験に組み入れた被験者 83 例全例に 1 回以上本薬が投与された。83 例のうち、79 例が FAS に採用され、69 例が PPS に採用された。83 例中 75 例（90.4%）が治験実施計画書の規定どおりに試験を完了し、8 例（9.6%）が試験を中止した。中止した 8 例について、5 例

（6.0%）が治療の継続を拒否し（被験者による治療不遵守）、3 例（3.6%）が追跡不能となった。

最初に効果が認められてから 4 週後に、治験担当医師による有効性の判定を行った。FAS での治験担当医師による有効性の判定に基づく ORR は 29.1%（95%CI：19.4%～40.4%）であり、8 例（10.1%）が CR、3 例（3.8%）が CRu、12 例（15.2%）が PR を達成した。

FAS の 79 例のうち、57 例で PD が確認され、22 例が打ち切りとなった。PFS の中央値は 64.0 日（95%CI：46～117 日）であった。

最後に組み入れた被験者のデータカットオフ日（2012 年 9 月 ■ 日）に、FAS の 79 例のうち 50 例の生存が確認された。残りの 29 例はデータカットオフ日よりも前に死亡しており、OS の中央値は 615.0 日（95%CI：343 日～－）であった。

2.7.3.3 全試験を通しての結果の比較と解析

203 試験、201 試験及び 902 試験では、対象患者及び腫瘍縮小効果の評価者が異なるため、各試験の結果を分けて叙述した。2.7.3.3.1 項から 2.7.3.3.2.12 項の 902 試験については、ピボタル試験での本薬の投与スケジュールが本承認申請の投与スケジュールと同様であったため、ピボタル試験の結果のみを含めた。

2.7.3.3.1 試験対象集団

2.7.3.3.1.1 日本人／韓国人第 2b 相試験（203 試験）

(1) 被験者の内訳

本試験では、日本の 21 施設及び韓国の 10 施設で同意取得した 74 例の被験者のうち、19 例がスクリーニングで脱落し、55 例に本薬が投与された。データカットオフ日までに、55 例中 47 例（85.5%）が本薬投与を中止した。投与中止の主な理由は、病勢進行［24 例（51.1%）］、許容できない毒性［17 例（36.2%）］、同意撤回［5 例（10.6%）］、被験者の治験実施計画書不遵守［1 例（2.1%）］であった。試験を完了した 27 例のうち、8 例（29.6%）が同意を撤回し、同意を撤回した被験者はすべて韓国人であった（表 2.7.3.3-1）。

治験実施計画書からの重要な逸脱が 35 例に認められた。多く報告された逸脱は、本薬の服薬遵守に関する逸脱（16 例）、併用薬の基準に関する逸脱（15 例）、治験手順の逸脱（12 例）、臨床検査に関する逸脱（10 例）であった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.2）。

本薬を投与された 55 例全例を安全性解析対象集団とした。安全性解析対象集団から 6 例を除外し、有効性の評価に使用する FAS とした。除外した 6 例の内訳は、組入れ基準に逸脱があった 3 例、CPR により PTCL 以外のリンパ腫であることが確認された 2 例、及び腫瘍生検検体の病理スライドが提出されず CPR による疾患の確認が行われなかった 1 例であった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.3）。さらに、FAS から 3 例を除外し、PPS とした。3 例のうち 2 例は有害事象（AE）が理由でサイクル 1 を完了（最初の 4 週中に本薬を 6 回以上投与）しなかった。もう 1 例は AE が理由でサイクル 1 を完了せず、その後同意を撤回した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.5.1, Listing 16.2.6.1, Listing 16.2.6.2, Appendix 16.1.9）。したがって、FAS には 49 例が採用され、PPS には 46 例が採用された（表 2.7.3.3-1）。

表 2.7.3.3-1 被験者の内訳（203 試験）（同意取得した全被験者）

Description	Japan (N=52)	Korea (N=22)	Total (N=74)
	n (%)	n (%)	n (%)
Consented	52	22	74
Screening failure	13	6	19
Treated with at least one dose of HBI-8000 (Safety Analysis Set)	39 (100.0%)	16 (100.0%)	55 (100.0%)
Full Analysis Set (FAS)	37 (94.9%)	12 (75.0%)	49 (89.1%)
Per Protocol Set	34 (87.2%)	12 (75.0%)	46 (83.6%)
Subjects who are on study drug treatment	7 (17.9%)	1 (6.3%)	8 (14.5%)
Subjects who had study drug treatment discontinuation	32 (82.1%)	15 (93.8%)	47 (85.5%)
Primary reason for study drug treatment discontinuation			
Unacceptable toxicity (adverse event)	15 (46.9%)	2 (13.3%)	17 (36.2%)
Progression disease	15 (46.9%)	9 (60.0%)	24 (51.1%)
Repeated subject noncompliance	0 (0.0%)	1 (6.7%)	1 (2.1%)
Withdrew consent	2 (6.3%)	3 (20.0%)	5 (10.6%)
Subjects completed the study participation	14 (35.9%)	13 (81.3%)	27 (49.1%)
Primary reason for completing the study participation			
Lost to follow-up	0 (0.0%)	1 (7.7%)	1 (3.7%)
Death	14 (100.0%)	4 (30.8%)	18 (66.7%)
Withdrew consent	0 (0.0%)	8 (61.5%)	8 (29.6%)

Source: Listing 16.2.1 and Listing 16.2.5.1 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the respective country within safety analysis set.
Percentages for study drug treatment discontinuation reasons are calculated based on the number of subjects in the respective country within safety analysis set who discontinued.
Progression disease in primary reason for study drug treatment discontinuation is defined as progression of the disease under study, which also included clinical progression disease, except for isolated progression in skin lesion.
Percentages for subjects who did or did not complete 1 cycle of treatment are calculated based on the number of subjects in the respective country within full analysis set.
Percentages for primary reason for completing the study participation are calculated based on the number of subjects who completed study participation in the respective country within safety analysis set.
Data cut-off date: [redacted] 20[redacted]

(2) 曝露量

安全性解析対象集団での本薬の曝露期間の中央値（最小値～最大値、以降同様）は 80.0 日（10～580 日）であった（5.3.5.2-1/HBI-8000-203/CSR/Table 14.4.1）。サイクル数の中央値は、2.857 サイクル（0.36～20.71 サイクル）であった。最大投与回数は 164 回であり、最大累積曝露量は 6560 mg であった。

本薬を投与された 55 例中、26 例（47.3%）で本薬が減量された。20 例（36.4%）は 40 mg から 30 mg に減量され、残りの 6 例（10.9%）は 40 mg から 30 mg に減量された後、さらに 20 mg へ減量された。

安全性解析対象集団の日本人被験者 39 例での本薬の曝露期間の中央値（最小値～最大値、以降同様）は 80.0 日（10～580 日）であった（2.7.4.1.2.1.1 項参照）。サイクル数の中央値は、2.857 サイクル（0.36～20.71 サイクル）であった。最大投与回数は 164 回であり、最大累積曝露量は 6560 mg であった。

本薬を投与された日本人被験者 39 例中、21 例（53.8%）で本薬が減量された。15 例（38.5%）は 40 mg から 30 mg に減量され、残りの 6 例（15.4%）は 40 mg から 30 mg に減量された後、さ

らに 20 mg へ減量された（2.7.4.1.2.1.1 項参照）。

(3) 人口統計学的及び他の基準値の特性

PPS の人口統計学的及び他の基準値の特性を表 2.7.3.3-2、表 2.7.3.3-3 及び表 2.7.3.3-4 に示した。

PPS の 46 例のうち、73.9%（34 例）が日本人、26.1%（12 例）が韓国人であった。67.4%（31 例）が男性であり、32.6%（15 例）が女性であった。年齢の平均値（標準偏差、以降同様）は 67.2 歳（12.2 歳）、中央値（最小値～最大値、以降同様）は 71.0 歳（38～84 歳）であり、41.3%（19 例）が 65 歳以上 75 歳未満であった。米国東海岸がん臨床試験グループ（ECOG）パフォーマンスステータス（PS）は、1 例を除くすべての被験者で、0［52.2%（24 例）］又は 1［45.7%（21 例）］であった。身長の平均値は 162.50 cm（9.04 cm）であり、体重の平均値は 58.23 kg（11.05 kg）、体格指数（BMI）の平均値は 21.970 kg/m^2（3.270 kg/m^2）であった（表 2.7.3.3-2）。日本人被験者 34 例では、76.5%（26 例）が男性であり、23.5%（8 例）が女性であった。年齢の平均値は 68.1 歳（12.4 歳）、中央値は 72.0 歳（38～84 歳）であり、44.1%（15 例）が 65 歳以上 75 歳未満であった。ECOG PS は、1 例を除くすべての被験者で、0［64.7%（22 例）］又は 1［32.4%（11 例）］であった。身長の平均値は 163.67 cm（8.58 cm）であり、体重の平均値は 58.71 kg（11.41 kg）、BMI の平均値は 21.807 kg/m^2（3.206 kg/m^2）であった（表 2.7.3.3-2）。

CPR により PTCL と確認された PPS の 46 例のうち、73.9%（34 例）が PTCL-NOS、17.4%（8 例）が AITL、6.5%（3 例）が ALK 陰性 ALCL、2.2%（1 例）が EATL であった。ALK 陽性 ALCL、HSTCL 及び SPTCL の被験者はなかった（表 2.7.3.3-4）。日本人被験者 34 例では、70.6%（24 例）が PTCL-NOS、20.6%（7 例）が AITL、5.9%（2 例）が ALK 陰性 ALCL、2.9%（1 例）が EATL であった（表 2.7.3.3-4）。

初診からの罹病期間は、被験者の 73.9%（46 例中 34 例）が 5 年以下であった。初診からの罹病期間の平均値（標準偏差、以降同様）及び中央値（最小値～最大値、以降同様）はそれぞれ 3.224 年（3.332 年）及び 1.561 年（0.06～12.88 年）であった（表 2.7.3.3-4）。日本人被験者では、初診からの罹病期間は、被験者の 70.6%（34 例中 24 例）が 5 年以下であった。初診からの罹病期間の平均値及び中央値はそれぞれ 3.371 年（3.306 年）及び 1.926 年（0.06～10.95 年）であった（表 2.7.3.3-4）。

直近の病勢進行から本薬の初回投与までの期間の平均値（標準偏差、以降同様）及び中央値（最小値～最大値、以降同様）はそれぞれ 54.5 日（93.1 日）及び 29.5 日（7～605 日）であり、52.2%（46 例中 24 例）で過去 1 ヵ月以内に病勢進行が認められた（表 2.7.3.3-4）。日本人被験者では、直近の病勢進行から本薬の初回投与までの期間の平均値及び中央値はそれぞれ 57.4 日（106.2 日）及び 28.5 日（12～605 日）であり、52.9%（34 例中 18 例）で過去 1 ヵ月以内に病勢進行が認められた（表 2.7.3.3-4）。

ECOG PS が 1 であった被験者の割合は韓国人［83.3%（12 例中 10 例）］が日本人［32.4%（34 例中 11 例）］よりも高かったものの（表 2.7.3.3-2）、韓国人の被験者数は日本人と比較して少なかったことから、日本と韓国の被験者背景及び疾患特性の比較は限定的であった。

被験者背景は FAS（5.3.5.2-1/HBI-8000-203/CSR/Table 14.1.2.2）と PPS で同様であった。

表 2.7.3.3-2 人口統計学的及び他の基準値の特性－1（203 試験）（PPS）

Characteristic (unit)	Category	Statistic	Japan (N=34)	Korea (N=12)	Total (N=46)
Age (years)		n	34	12	46
		Mean	68.1	64.8	67.2
		StD	12.4	11.8	12.2
		Median	72.0	69.0	71.0
		Minimum	38	44	38
		Maximum	84	79	84
	<65	n (%)	8 (23.5%)	5 (41.7%)	13 (28.3%)
	>=65 to <75	n (%)	15 (44.1%)	4 (33.3%)	19 (41.3%)
	>=75	n (%)	11 (32.4%)	3 (25.0%)	14 (30.4%)
Sex	Male	n (%)	26 (76.5%)	5 (41.7%)	31 (67.4%)
	Female	n (%)	8 (23.5%)	7 (58.3%)	15 (32.6%)
Ethnicity	Japanese	n (%)	34 (100.0%)	0 (0.0%)	34 (73.9%)
	Korean	n (%)	0 (0.0%)	12 (100.0%)	12 (26.1%)
ECOG Performance Status	0	n (%)	22 (64.7%)	2 (16.7%)	24 (52.2%)
	1	n (%)	11 (32.4%)	10 (83.3%)	21 (45.7%)
	2	n (%)	1 (2.9%)	0 (0.0%)	1 (2.2%)
	3	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height (cm)		n	34	12	46
		Mean	163.67	159.19	162.50
		StD	8.58	9.86	9.04
		Median	162.50	160.10	162.00
		Minimum	148.0	142.5	142.5
		Maximum	189.6	177.7	189.6
Weight (kg)		n	34	12	46
		Mean	58.71	56.84	58.23
		StD	11.41	10.28	11.05
		Median	58.25	58.70	58.40
		Minimum	36.4	41.3	36.4
		Maximum	88.2	69.0	88.2
BMI (kg/m^2)		n	34	12	46
		Mean	21.807	22.431	21.970
		StD	3.206	3.547	3.270
		Median	22.354	23.513	22.457
		Minimum	14.47	15.54	14.47
		Maximum	29.00	27.09	29.00

Source: Table 14.1.2.3 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set.
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; StD = standard deviation.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.3-3 人口統計学的及び他の基準値の特性－2（203 試験）（PPS）

Characteristic (unit)	Category	Statistic	Japan (N=34)	Korea (N=12)	Total (N=46)
HBsAg	Positive	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Negative	n (%)	34 (100.0%)	12 (100.0%)	46 (100.0%)
	Not Done	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anti-HBs	Positive	n (%)	4 (11.8%)	4 (33.3%)	8 (17.4%)
	Negative	n (%)	29 (85.3%)	8 (66.7%)	37 (80.4%)
	Not Done	n (%)	1 (2.9%)	0 (0.0%)	1 (2.2%)
Anti-HBc	Positive	n (%)	4 (11.8%)	3 (25.0%)	7 (15.2%)
	Negative	n (%)	29 (85.3%)	9 (75.0%)	38 (82.6%)
	Not Done	n (%)	1 (2.9%)	0 (0.0%)	1 (2.2%)
HBV-DNA	Positive	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Negative	n (%)	21 (61.8%)	9 (75.0%)	30 (65.2%)
	Not Done	n (%)	13 (38.2%)	3 (25.0%)	16 (34.8%)
HCV Antibody	Positive	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Negative	n (%)	34 (100.0%)	12 (100.0%)	46 (100.0%)
	Not Done	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatitis Assessment Result	Active	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Non Active	n (%)	34 (100.0%)	12 (100.0%)	46 (100.0%)
Maximum length of long dimension of target lesion (mm) based on Investigator Response Assessment		n	34	12	46
		Mean	32.5	30.5	32.0
		StD	14.2	11.9	13.5
		Median	28.0	28.5	28.0
		Minimum	17	16	16
		Maximum	70	51	70
Sum of 2-dimension products of target lesions (mm^2) based on Investigator Response Assessment		n	34	12	46
		Mean	1451.7	1859.4	1558.1
		StD	1095.3	1585.1	1235.6
		Median	1091.5	1249.5	1139.0
		Minimum	187	420	187
		Maximum	4487	5516	5516
Bone Marrow Infiltration	Positive	n (%)	10 (29.4%)	1 (8.3%)	11 (23.9%)
	Undetermined	n (%)	3 (8.8%)	0 (0.0%)	3 (6.5%)
	Negative	n (%)	21 (61.8%)	5 (41.7%)	26 (56.5%)
	Not Done	n (%)	0 (0.0%)	6 (50.0%)	6 (13.0%)
Hepatic enlargement and splenomegaly	Not Done	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatic enlargement result	Present	n (%)	0 (0.0%)	2 (16.7%)	2 (4.3%)
	Absent	n (%)	34 (100.0%)	10 (83.3%)	44 (95.7%)
Splenomegaly result	Present	n (%)	3 (8.8%)	1 (8.3%)	4 (8.7%)
	Absent	n (%)	31 (91.2%)	11 (91.7%)	42 (91.3%)
Hepatic enlargement result and splenomegaly result	Present	n (%)	0 (0.0%)	1 (8.3%)	1 (2.2%)

Characteristic (unit)	Category	Statistic	Japan (N=34)	Korea (N=12)	Total (N=46)
LDH (U/L)	<=ULN	n (%)	17 (50.0%)	6 (50.0%)	23 (50.0%)
	>ULN	n (%)	17 (50.0%)	6 (50.0%)	23 (50.0%)
LDH (U/L)	<=300 (U/L)	n (%)	27 (79.4%)	6 (50.0%)	33 (71.7%)
	>300 (U/L)	n (%)	7 (20.6%)	6 (50.0%)	13 (28.3%)

Source: Table 14.1.2.3 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set.
Anti-HBc = hepatitis B core antibody; Anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV-DNA = hepatitis B virus deoxyribonucleic acid; HCV = hepatitis C virus; LDH = lactate dehydrogenase; StD = standard deviation; ULN = upper limit of normal.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
For maximum length of long dimension of target lesion, subjects who had multiple target lesions only have the biggest length of long dimension target lesion included in this analysis.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.3-4 人口統計学的及び他の基準値の特性－3（203 試験）（PPS）

Description	Subtype/Category	Japan (N=34)	Korea (N=12)	Total (N=46)
		n (%)	n (%)	n (%)
Diagnosis confirmed by Central Pathology Review	Peripheral T-cell Lymphoma (PTCL):	34 (100.0%)	12 (100.0%)	46 (100.0%)
	Peripheral T-cell Lymphoma Not Otherwise Specified (PTCL-NOS)	24 (70.6%)	10 (83.3%)	34 (73.9%)
	Angioimmunoblastic T-cell Lymphoma (AITL)	7 (20.6%)	1 (8.3%)	8 (17.4%)
	Anaplastic Large-cell Lymphoma (ALCL), ALK+	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Anaplastic Large-cell Lymphoma (ALCL), ALK-	2 (5.9%)	1 (8.3%)	3 (6.5%)
	Enteropathy-Associated T-cell Lymphoma (EATL)	1 (2.9%)	0 (0.0%)	1 (2.2%)
	Hepatosplenic T-cell Lymphoma (HSTCL)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Subcutaneous Panniculitis-Like T-cell Lymphoma (SPTCL)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Non-PTCL	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diagnosis at screening assessed by Investigator	Peripheral T-cell Lymphoma (PTCL):	34 (100.0%)	12 (100.0%)	46 (100.0%)
	Peripheral T-cell Lymphoma Not Otherwise Specified (PTCL-NOS)	20 (58.8%)	4 (33.3%)	24 (52.2%)
	Angioimmunoblastic T-cell Lymphoma (AITL)	11 (32.4%)	6 (50.0%)	17 (37.0%)
	Anaplastic Large-cell Lymphoma (ALCL), ALK+	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Anaplastic Large-cell Lymphoma (ALCL), ALK-	2 (5.9%)	2 (16.7%)	4 (8.7%)
	Enteropathy-Associated T-cell Lymphoma (EATL)	1 (2.9%)	0 (0.0%)	1 (2.2%)
	Hepatosplenic T-cell Lymphoma (HSTCL)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Subcutaneous Panniculitis-Like T-cell Lymphoma (SPTCL)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other PTCL	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bone marrow test		34	6	40
	Bone marrow aspiration	22	3	25
	Biopsy	12	1	13
	Bone marrow aspiration and biopsy	0	2	2

Description	Subtype/Category	Japan (N=34)	Korea (N=12)	Total (N=46)
		n (%)	n (%)	n (%)
Duration since initial diagnosis (years)	n	34	12	46
	Mean	3.371	2.807	3.224
	StD	3.306	3.515	3.332
	Median	1.926	1.539	1.561
	Minimum	0.06	0.51	0.06
	Maximum	10.95	12.88	12.88
Duration since initial diagnosis by category	> 5 years	10 (29.4%)	2 (16.7%)	12 (26.1%)
	<= 5 years	24 (70.6%)	10 (83.3%)	34 (73.9%)
Duration from most recent progression (days)	n	34	12	46
	Mean	57.4	46.4	54.5
	StD	106.2	39.3	93.1
	Median	28.5	33.0	29.5
	Minimum	12	7	7
	Maximum	605	134	605
Duration from most recent progression by category	> 1 month	16 (47.1%)	6 (50.0%)	22 (47.8%)
	<= 1 month	18 (52.9%)	6 (50.0%)	24 (52.2%)

Source: Table 14.2.2.3 and Listing 16.2.5.9 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set.
ALK = anaplastic lymphoma kinase; StD = standard deviation.
Duration since initial diagnosis (years)= (informed consent date − date of 1st diagnosis + 1)/365.25.
Duration from most recent progression (days) = (first study drug date − date of most recent progression + 1).
Duration from most recent progression (months) = (first study drug date − date of most recent progression + 1)/ 30.4375.
Data cut-off date: [redacted] 20[redacted]

(4) がんに対する前治療

PPS の 46 例全例が、1 回以上のがんに対する前治療歴を有していた（表 2.7.3.3-5）。PPS の 46 例のうち 32.6%（15 例）が、化学療法に加えて他のがん治療を受けており、13.0%（6 例）は放射線療法、10.9%（5 例）は造血幹細胞移植を受けていた。PPS の日本人被験者 34 例のうち、38.2%（13 例）が化学療法に加えて他のがん治療を受けており、11.8%（4 例）は放射線療法、5.9%（2 例）は造血幹細胞移植を受けていた。

PPS の 46 例のうち、67.4%（31 例）が 2 レジメン以上のがんに対する前治療歴を有しており、17.4%（8 例）が 5 レジメン以上のがんに対する前治療歴を有していた。がんに対する前治療レジメン数の中央値は 2 であり、直近のがん治療終了から本薬の初回投与までの期間の中央値（最小値～最大値、以降同様）は 116.5 日（29～3861 日）であった。日本人被験者 34 例では、61.8%（21 例）が 2 レジメン以上のがんに対する前治療歴を有しており、14.7%（5 例）が 5 レジメン以上のがんに対する前治療歴を有していた。日本人被験者のがんに対する前治療レジメン数の中央値は 2 であり、直近のがん治療終了から本薬の初回投与までの期間の中央値は 106.0 日（29～3861 日）であった。

PPS の 46 例のうち、60.9%（28 例）が 2 レジメン以上の化学療法の前治療歴を有しており、10.9%（5 例）が 5 レジメン以上の化学療法の前治療歴を有していた。化学療法のレジメン数の中央値は 2 であった。日本人被験者 34 例では、55.9%（19 例）が 2 レジメン以上の化学療法の前治療歴を有しており、8.8%（3 例）が 5 レジメン以上の化学療法の前治療歴を有していた。日本人被験者での化学療法のレジメン数の中央値は 2 であった。

本試験に組み入れた被験者が有する PTCL について、直近の全身化学療法に対する反応に基づ

いて再発／難治性のサブセットに分類した。直近の PTCL 治療に対する反応に基づき、医学専門家の判断により下記のとおり分類した。

- 再発：直近の治療で CR、CRu 又は PR
- 難治性：直近の治療で安定（SD）又は PD

PPS の 46 例のうち、60.9%（28 例）は再発、39.1%（18 例）は難治性の PTCL であった。日本人被験者 34 例では、64.7%（22 例）が再発、35.3%（12 例）が難治性の PTCL であった。

がんに対する前治療の集計結果は、FAS（5.3.5.2-1/HBI-8000-203/CSR/Table 14.2.3.2）と PPS で同様であった。

表 2.7.3.3-5 がんに対する前治療（203 試験）（PPS）

Description	Category	Statistic	Japan (N=34)	Korea (N=12)	Total (N=46)
Number of subjects with at least one treatment agent type		n	34	12	46
Type of previous cancer therapy	Chemotherapy	n (%)	34 (100.0%)	12 (100.0%)	46 (100.0%)
	Other anticancer therapy	n (%)	13 (38.2%)	2 (16.7%)	15 (32.6%)
	Brentuximab vedotin	n (%)	1 (2.9%)	1 (8.3%)	2 (4.3%)
	Darinaparsin	n (%)	6 (17.6%)	1 (8.3%)	7 (15.2%)
	E7777	n (%)	2 (5.9%)	0 (0.0%)	2 (4.3%)
	Forodesine	n (%)	6 (17.6%)	0 (0.0%)	6 (13.0%)
	Mogamulizumab	n (%)	1 (2.9%)	0 (0.0%)	1 (2.2%)
	Rituximab	n (%)	2 (5.9%)	0 (0.0%)	2 (4.3%)
	Romidepsin	n (%)	3 (8.8%)	0 (0.0%)	3 (6.5%)
	Radiotherapy	n (%)	4 (11.8%)	2 (16.7%)	6 (13.0%)
	Hematopoietic stem cell transplantation	n (%)	2 (5.9%)	3 (25.0%)	5 (10.9%)
	Other prior therapy	n (%)	1 (2.9%)	1 (8.3%)	2 (4.3%)
Total number of previous cancer therapy regimens	1 regimen	n (%)	13 (38.2%)	2 (16.7%)	15 (32.6%)
	2 regimens	n (%)	9 (26.5%)	5 (41.7%)	14 (30.4%)
	3 regimens	n (%)	5 (14.7%)	1 (8.3%)	6 (13.0%)
	4 regimens	n (%)	2 (5.9%)	1 (8.3%)	3 (6.5%)
	5 or more regimens	n (%)	5 (14.7%)	3 (25.0%)	8 (17.4%)
	2 or more regimens	n (%)	21 (61.8%)	10 (83.3%)	31 (67.4%)
		Median	2.0	2.0	2.0
Relapsed, refractory and undetermined PTCL based on last previous treatment	Relapsed	n (%)	22 (64.7%)	6 (50.0%)	28 (60.9%)
	Refractory	n (%)	12 (35.3%)	6 (50.0%)	18 (39.1%)
Days from end of the last immediate previous treatment	< 3 months	n (%)	16 (47.1%)	4 (33.3%)	20 (43.5%)
	>=3 months	n (%)	18 (52.9%)	8 (66.7%)	26 (56.5%)
Number of days from end of the last immediate previous treatment (days)		n	34	12	46
		Mean	383.4	317.0	366.1
		StD	768.9	588.0	720.4
		Median	106.0	134.5	116.5
		Minimum	29	30	29
		Maximum	3861	2154	3861

Description	Category	Statistic	Japan (N=34)	Korea (N=12)	Total (N=46)
Chemotherapy	Total number of regimens				
	1 regimen	n (%)	15 (44.1%)	3 (25.0%)	18 (39.1%)
	2 regimens	n (%)	9 (26.5%)	4 (33.3%)	13 (28.3%)
	3 regimens	n (%)	4 (11.8%)	1 (8.3%)	5 (10.9%)
	4 regimens	n (%)	3 (8.8%)	2 (16.7%)	5 (10.9%)
	5 or more regimens	n (%)	3 (8.8%)	2 (16.7%)	5 (10.9%)
	2 or more regimens	n (%)	19 (55.9%)	9 (75.0%)	28 (60.9%)
		Median	2.0	2.0	2.0
The last immediate previous chemotherapy best response	Complete response (CR)	n (%)	13 (38.2%)	4 (33.3%)	17 (37.0%)
	Unconfirmed complete response (CRu)	n (%)	1 (2.9%)	0 (0.0%)	1 (2.2%)
	Partial response (PR)	n (%)	8 (23.5%)	2 (16.7%)	10 (21.7%)
	Stable disease (SD)	n (%)	8 (23.5%)	1 (8.3%)	9 (19.6%)
	Relapsed disease or progressive disease (PD)	n (%)	4 (11.8%)	4 (33.3%)	8 (17.4%)
	Not assessable	n	0	1	1
	Unknown	n	0	0	0
Type of transplantation	Autologous transplantation	n (%)	2 (5.9%)	3 (25.0%)	5 (10.9%)
	Allogeneic transplantation	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
The last immediate previous radiotherapy best response	Complete response (CR)	n (%)	2 (5.9%)	0 (0.0%)	2 (4.3%)
	Unconfirmed complete response (CRu)	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Partial response (PR)	n (%)	0 (0.0%)	1 (8.3%)	1 (2.2%)
	Stable disease (SD)	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Relapsed disease or progressive disease (PD)	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not assessable	n	0	0	0
	Unknown	n	2	1	3

Source: Table 14.2.3.3 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set.
PTCL = peripheral T-cell lymphoma; StD = standard deviation.
Subjects may have more than one type of therapy.
Subjects with relapsed, refractory, and undetermined PTCL are confirmed by Medical Expert.
Previous cancer therapy regimens included other prior therapy, radiotherapy and chemotherapy.
Number of days from end of the last immediate previous treatment (days) = date of first study drug − end date of last immediate previous treatment + 1.
Days from end of the last immediate previous treatment (months) = (date of first study drug − end date of last immediate previous treatment + 1)/30.4375.
Chemotherapy included molecular targeted therapy and others.
Data cut-off date: [redacted] 20[redacted]

2.7.3.3.1.2 日本人第 1 相試験（201 試験）

(1) 被験者の内訳

本試験では、NHL を有する被験者 22 例が同意取得後に組み入れられ、不適格とされた 8 例を除く 14 例に本薬が 1 回以上投与された。本薬を投与された 14 例のうち、PTCL を有する被験者は 30 mg コホートの 2 例（被験者 [redacted] 及び [redacted]）であった（5.3.3.2-1/HBI-8000-201/CSR/Table 14.1.1, Listing 16.2.4.4）。

30 mg コホートの PTCL の被験者は 2 例とも試験を中止した。中止理由はそれぞれ、本薬初回投与後の Day 13 に発現した AE 及び治験実施計画書からの重要な逸脱であった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.1, Listing 16.2.2, Listing 16.2.6.4）。

被験者 [redacted] には、組入れ基準及び併用薬の基準に関する 2 件の逸脱が認められた。当該被験者は、スクリーニング時及びサイクル 1 の Day 1 に、有害事象共通用語規準（CTCAE）Grade 2 のリンパ球数異常が認められ、以前に受けた化学療法、抗体又は放射線療法に関連する毒性が CTCAE の Grade 1 以下まで回復していることとする選択基準を満たしていなかった。また、本試験参加中にエトポシド及びソブゾキサンによる化学療法を開始した。当該被験者は、組入れ基準に関する逸脱により、本試験参加を中止した。当該被験者への本薬投与は 1 回のみであり、有効性解析対象集団の定義に合致しないため、除外された（2.7.3.1.2.3 項参照）。

(2) 曝露量

本試験では 50 mg への用量移行は実施されなかった。30 mg コホートの PTCL の被験者 2 例の本薬への曝露は限られていた。被験者 [redacted] はサイクル 1 を完了し、本薬 30 mg を 8 回投与された。累積投与量は 240 mg であった。被験者 [redacted] への本薬の投与は 30 mg を 1 回のみであった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.5.1）。

いずれの被験者についても本薬の減量はなかった。

(3) 人口統計学的及び他の基準値の特性

30 mg コホートの PTCL の被験者 2 例の人口統計学的及び他の基準値の特性は以下のとおりであった。被験者 [redacted] は 6[redacted] 歳の男性で、体重は 4[redacted].7 kg、BMI は 17.7 kg/m^2、ECOG PS は 0 であった。被験者 [redacted] は 8[redacted] 歳の男性で、体重は 6[redacted].8 kg、BMI は 21.8 kg/m^2、ECOG PS は 1 であった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.4.1, Listing 16.2.13.1）。

直近の再発時の Ann Arbor 分類は、被験者 [redacted] は Stage 4、被験者 [redacted] は Stage 2A であった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.4.4）。

(4) がんに対する前治療

30 mg コホートの PTCL の被験者 2 例は、化学療法の前治療を受けていた。被験者 [redacted] は 1 レジメン［CHOP 療法（シクロホスファミド、ドキソルビシン、ビンクリスチン及びプレドニゾンの併用）又は A-CHP 療法（ブレンツキシマブ ベドチン、シクロホスファミド、ドキソルビシン及びプレドニゾンの併用）を 6 サイクル］を実施し、CR を達成した。被験者 [redacted] は 2 レジメン［CHOP 療法を 6 サイクル及び EPOCH 療法（エトポシド、プレドニゾン、ビンクリスチン、シクロホスファミド及びドキソルビシンの併用）を 1 サイクル］を実施し、治療成績はどちらも SD であった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.4.5）。

前述の 203 試験（2.7.3.3.1.1 項）と同様に直近の PTCL 治療に対する反応に基づいて被験者の PTCL を再発／難治性に分類すると、被験者 [redacted] は再発、被験者 [redacted] は難治性の PTCL であった。

2.7.3.3.1.3 中国人第 2 相試験（902 試験）（参考試験）

(1) 被験者の内訳

本試験のピボタル試験に組み入れた被験者 83 例全例に 1 回以上本薬が投与され、このうち、75 例（90.4%）が治験実施計画書の規定どおりに試験を完了し、8 例（9.6%）が試験を中止した。中止した 8 例について、5 例（6.0%）が治療の継続を拒否し（被験者による治療不遵守）、3 例（3.6%）が追跡不能となった（5.3.5.4-2/TG0902CDM p2b/CSR/Section 7.1, Statistical Analysis

Report/Table 7.1.1)。

本試験のピボタル試験に組み入れた 83 例のうち、14 例（16.9%）に治験実施計画書からの重要な逸脱が認められた。重要な逸脱が認められた 14 例について、4 例（4.8%）は病理組織学的診断が本試験のピボタル試験の基準に合致せず、FAS 及び PPS から除外された。その他の 10 例は本薬の投与が 12 回未満で有効性評価を実施しておらず、またこのうち 8 例（9.6%）に死亡は確認されず、2 例（2.4%）に本薬の最終投与から 30 日超経過後の死亡が確認されたため、これら 10 例は PPS から除外された。したがって、FAS には 79 例が採用され、PPS には 69 例が採用された（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.1.2, Table 7.1.3)。

(2) 曝露量

安全性解析対象集団 83 例の投与サイクル数［中央値（最小値～最大値)］は 1.0 サイクル（0～13 サイクル）であった。59 例（71.1%）が 1 サイクル（6 週)、30 例（36.1%）が 2 サイクル、21 例（25.3%）が 3 サイクル、12 例（14.5%）が 4 サイクルの投与を完了した。本薬の累積曝露量の中央値（最小値～最大値）は 360.0 mg（30～4860 mg）であった（2.7.4.1.2.1.4 項参照)。

(3) 人口統計学的及び他の基準値の特性

本試験のピボタル試験で、FAS の 79 例では、年齢の平均値（標準偏差）及び中央値（最小値～最大値）はそれぞれ 49.6 歳（13.73 歳）及び 53.0 歳（20～77 歳）であった。79 例中、67.1%（53 例）が男性であった。ECOG PS は、FAS の 1 例を除くすべての被験者で 0［35.4%（28 例)］又は 1［63.3%（50 例)］であった。身長［平均値（標準偏差)、以降同様］は 167.56 cm（7.080 cm)、体重は 65.34 kg（11.686 kg）であり、BMI は 23.17 kg/m^2（3.492 kg/m^2）であった（2.7.4.1.3.1.4 項参照)。

初診時の PTCL の初診からの罹病期間について、FAS での中央値（最小値～最大値、以降同様）は 1.06 年（0.1～9.1 年）であった。FAS の 79 例中 63 例（79.7%）が再発しており、再発回数の中央値は 1.00 回（0.0～4.0 回）であった（2.7.4.1.3.1.4 項参照)。

PTCL の病期分類は IV 期が最も多く、次いで III 期が多かった。判定結果が得られた 74 例中、IV 期は 34 例（45.9%）であり、その内訳は IVA 期が 18 例（24.3%)、IVB 期が 16 例（21.6%）であった。III 期は 26 例（35.1%）であり、内訳は IIIA 期及び IIIB 期が各 13 例（17.6%）であった。II 期は 11 例（14.9%)、I 期は 3 例（4.1%）で報告された（2.7.4.1.3.1.4 項参照)。

FAS の 79 例のうち、PTCL-NOS が 23 例（29.1%)、ALCL 及び natural killer/T 細胞リンパ腫が各 16 例（20.3%)、その他のサブタイプの PTCL が 10 例（12.7%)、AITL が 9 例（11.4%)、EATL が 2 例（2.5%）並びに CD4 陽性 PTCL、レンネルト型 PTCL 及び転化した菌状息肉症が各 1 例（1.3%）であった（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.2.4)。

(4) がんに対する前治療

FAS の 79 例のうち、36 例（45.6%）が前治療として 3 種類以上の化学療法を受けており、24 例（30.4%）が 2 種類、18 例（22.8%）が 1 種類の化学療法を受けていた。残りの 1 例（1.3%）は前治療として化学療法を受けていたが、そのレジメン及び種類は不明であった（2.7.4.1.3.2.4 項参照)。

2.7.3.3.2 全有効性試験の結果の比較検討

2.7.3.3.2.1 客観的奏効率（ORR）

(1) 日本人／韓国人第 2b 相試験（203 試験）

本試験では、PPS の 46 例のうち、IOERC 評価に基づく最良総合効果は、5 例（10.9%）が CR、16 例（34.8%）が PR であり、ORR は 45.7%［46 例中 21 例（95%CI：30.9%～61.0%）］であった（表 2.7.3.3-6）。ORR は目標である 30%を超えており、また 95%CI の下限が規定した閾値である 10%を上回っていたため、ORR は、両側有意水準 5%で、規定した閾値を統計学的に有意に上回ったと判断された。

PPS で実施した主要評価項目の解析を FAS でも実施したところ、FAS の ORR は 42.9%［49 例中 21 例（95%CI：28.8%～57.8%）］であり、FAS と PPS の結果は同様であった。FAS では 5 例（10.2%）が CR、16 例（32.7%）が PR を達成した（付録 1 表 2.7.3.6-1）。

治験担当医師による評価に基づく ORR は 52.2%［46 例中 24 例（95%CI：36.9%～67.1%）］であった（付録 1 表 2.7.3.6-10）。

IOERC 評価に基づく ORR の部分集団解析の結果は 2.7.3.3.3.1 項に記載した。

安全性解析対象集団のうち、再発 PTCL を有する 1 例及び難治性の PTCL を有する 3 例の計 4 例に、ヒストン脱アセチル化酵素阻害剤であるロミデプシンの投与歴があった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.4）。ロミデプシン投与歴があった 4 例のうち、難治性の PTCL の 1 例は PPS から除外された。残り 3 例の本試験での最良総合効果は PR、SD 及び PD が各 1 例、すなわち、2 例が SD 以上であった。本薬の有効性はロミデプシン投与歴がある被験者に投与された場合でも確認された（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.5.10）。

表 2.7.3.3-6 客観的奏効率及び最良総合効果（203 試験）（PPS）

		40 mg (N=46)	
Response	**Status/Response rate**	**n (%)**	**(95% CI)**
Best overall response	Objective Response rate (CR or PR)	21 (45.7%)	(30.9, 61.0)
	Status		
	CR	5 (10.9%)	
	PR	16 (34.8%)	
	SD	12 (26.1%)	
	PD	13 (28.3%)	

Source: Table 14.3.4.1 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Objective response rate is defined as proportion of subjects with best overall response of CR or PR.
Data cut-off date: [redacted] 20[redacted]

(2) 日本人第 1 相試験（201 試験）

本試験では、30 mg コホートの PTCL の被験者 2 例のうち、1 例（被験者[redacted]）は有効性解析対象集団から除外された（2.7.3.3.1.2 項参照）。別の 1 例（被験者[redacted]）の最良総合効果は PD であった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.5.3）。

(3) 中国人第 2 相試験（902 試験）（参考試験）

最初に効果が認められてから 4 週後に、治験担当医師による有効性の判定を行った。FAS の 79

例のうち、8 例（10.1%）が CR、3 例（3.8%）が CRu、12 例（15.2%）が PR を達成し、治験担当医師による有効性の判定に基づく ORR は 29.1%（95%CI : 19.4%～40.4%）であった（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.3.1.2）。

2.7.3.3.2.2 無増悪生存期間（PFS）

(1) 日本人／韓国人第 2b 相試験（203 試験）

本試験では、IOERC 評価に基づく PFS を有効性の副次的評価項目とし、治験担当医師による評価に基づく PFS についても探索的に解析した。

PPS での IOERC 評価に基づく PFS の中央値は 24.1 週（95%CI : 12.7～58.1 週）［5.6 ヵ月（95%CI : 2.9～13.4 ヵ月）］であった。24 例（52.2%）で PD が確認され、22 例（47.8%）は打ち切りとなった（表 2.7.3.3-7）。PD 以外で死亡に至った被験者はなかった。PFS の Kaplan-Meier plot を図 2.7.3.3-1 に示した。

IOERC 評価に基づく PFS を国別（日本及び韓国）に解析した結果、日本人被験者の PFS の中央値は 32.9 週（95%CI : 14.7 週～－）［7.6 ヵ月（95%CI : 3.4 ヵ月～－）］であった。16 例（47.1%）で PD が確認され、18 例（52.9%）は打ち切りとなった。韓国人被験者の PFS の中央値は 12.7 週（95%CI : 4.4～31.3 週）［2.9 ヵ月（95%CI : 1.0～7.2 ヵ月）］であった。8 例（66.7%）で PD が確認され、4 例（33.3%）は打ち切りとなった（付録 1 表 2.7.3.6-11）。

IOERC 評価に基づく PFS を、PTCL サブセット別（再発及び難治性）に解析した結果、再発 PTCL を有する被験者の PFS の中央値は 24.1 週（95%CI : 14.7 週～－）［5.6 ヵ月（95%CI : 3.4 ヵ月～－）］であった。13 例（46.4%）で PD が確認され、15 例（53.6%）は打ち切りとなった。難治性の PTCL を有する被験者の PFS の中央値は 9.6 週（95%CI : 5.0～58.1 週）［2.2 ヵ月（95%CI : 1.1～13.4 ヵ月）］であった。11 例（61.1%）で PD が確認され、7 例（38.9%）は打ち切りとなった（付録 1 表 2.7.3.6-13）。

治験担当医師の評価に基づく PFS の中央値は 24.1 週（95%CI : 12.7～48.1 週）［5.6 ヵ月（95%CI : 2.9～11.1 ヵ月）］であり（付録 1 表 2.7.3.6-12）、IOERC 評価に基づく PFS と同様の結果であった。

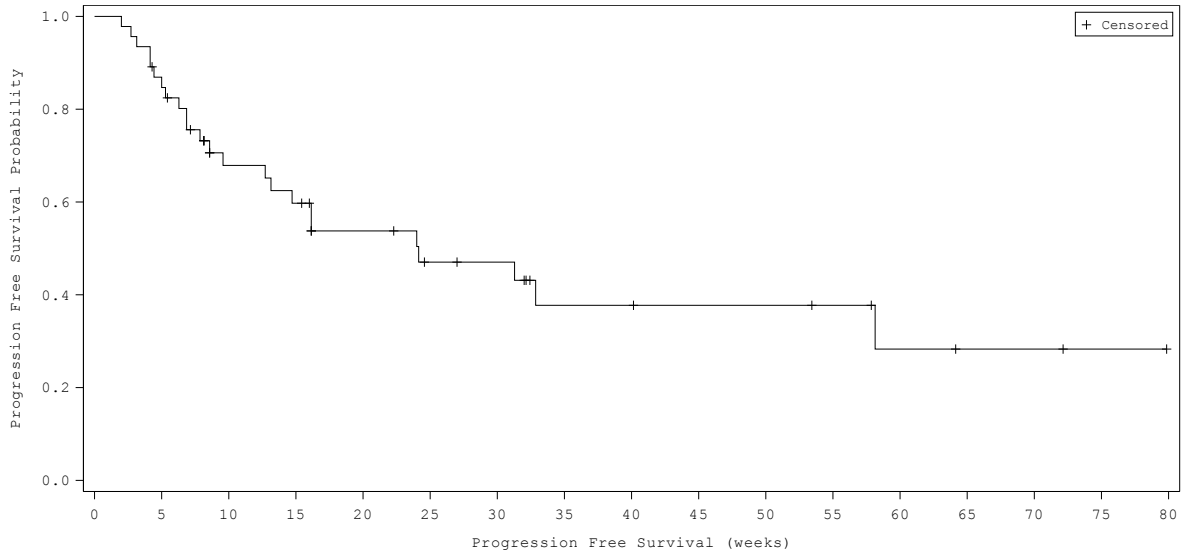
治験担当医師の評価に基づく PFS を、PTCL サブセット別（再発及び難治性）に解析した結果、再発 PTCL を有する被験者の PFS の中央値は、IOERC 評価に基づく PFS の中央値と同値であった［24.1 週（5.6 ヵ月）］。難治性の PTCL を有する被験者の PFS の中央値は、IOERC 評価に基づく PFS の中央値と同様であった［11.6 週（2.7 ヵ月）］（付録 1 表 2.7.3.6-14）。

表 2.7.3.3-7 無増悪生存期間（203 試験）（PPS）

	Event/Statistics	40 mg (N=46)	
Number of subjects, n (%)	Censored	22 (47.8%)	
	Last Tumor Assessment	22 (47.8%)	
	Any event	24 (52.2%)	
	Disease Progression	24 (52.2%)	
	Death	0 (0.0%)	
Progression Free Survival (weeks)	Median (95% CI)	24.1	(12.7, 58.1)
Progression Free Survival (months)	Median (95% CI)	5.6	(2.9, 13.4)

Source: Table 14.3.4.4 and Table 14.3.5.30 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
CI = confidence interval; PD = progressive disease.
Median of progression-free survival is estimated from Kaplan-Meier method.
95% CI is calculated based on log-log transformation.
Disease progression is defined as PD confirmed by Independent Overall Efficacy Review Committee.
Data cut-off date: [redacted] 20[redacted]

図 2.7.3.3-1 無増悪生存期間の Kaplan-Meier Plot（203 試験）（PPS）



Source: Figure 14.3.4.4 in CSR of Study HBI-8000-203
Data cut-off date: [redacted] 20[redacted]

(2) 日本人第 1 相試験（201 試験）

本試験では PFS は解析しなかった。

(3) 中国人第 2 相試験（902 試験）（参考試験）

FAS の 79 例のうち、57 例で PD が確認され、22 例が打ち切りとなった。PFS の中央値は 64.0 日（95%CI：46 ～ 117 日）であった（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.3.2.1.2）。

2.7.3.3.2.3 奏効期間（DOR）

(1) 日本人／韓国人第 2b 相試験（203 試験）

本試験では、IOERC 評価に基づく DOR を有効性の副次的評価項目とし、治験担当医師による評価に基づく DOR についても探索的に解析した。

DOR の中央値は 50.1 週（95%CI : 23.3 週～－）［11.5 ヵ月（95%CI : 5.4 ヵ月～－）］であった。客観的奏効がみられた 21 例のうち、5 例（23.8%）で PD が確認され、16 例（76.2%）が打ち切りとなった（表 2.7.3.3-8）。DOR の Kaplan-Meier plot を図 2.7.3.3-2 に示した。

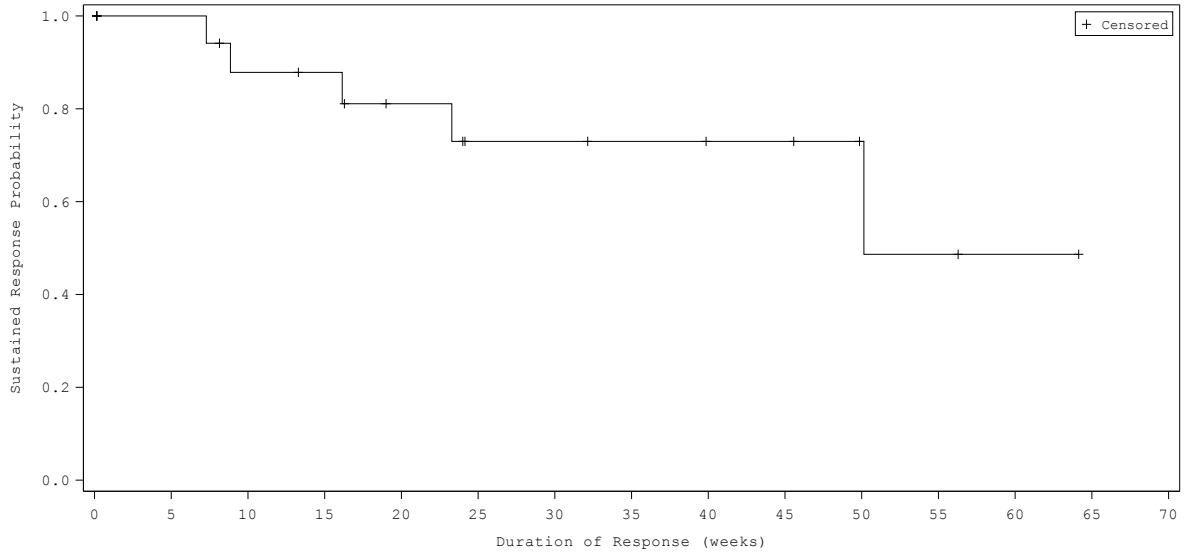
治験担当医師の評価に基づく DOR の中央値は 40.3 週（95%CI : 12.3 週～－）［9.3 ヵ月（95%CI : 2.8 ヵ月～－）］であった。客観的奏効がみられた 24 例のうち、9 例（37.5%）で PD が確認され（うち 1 例は臨床的 PD）、15 例（62.5%）が打ち切りとなった（付録 1 表 2.7.3.6-15）。

表 2.7.3.3-8 奏効期間（203 試験）（PPS）

	Event/Statistics	40 mg (N=46)	
The number of subjects with CR or PR, n (%)		21	
	Censored	16 (76.2%)	
	Any event	5 (23.8%)	
	Disease Progression	5 (23.8%)	
	Death	0 (0.0%)	
Duration of Response (weeks)	Median (95% CI)	50.1	(23.3, -)
Duration of Response (months)	Median (95% CI)	11.5	(5.4, -)

Source: Table 14.3.4.5 and Table 14.3.5.31 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects with either CR or PR in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response.
Median of duration of response is estimated from Kaplan-Meier method.
95% CI is calculated based on log-log transformation.
Disease progression is defined as PD confirmed by Independent Overall Efficacy Review Committee.
Data cut-off date: [redacted] 20[redacted]

図 2.7.3.3-2 奏効期間の Kaplan-Meier Plot（203 試験）（PPS）



Source: Figure 14.3.4.5 in CSR of Study HBI-8000-203
Data cut-off date: [redacted] 20[redacted]

(2) 日本人第 1 相試験（201 試験）

本試験では DOR は解析しなかった。

(3) 中国人第 2 相試験（902 試験）（参考試験）

FAS の 79 例のうち、最初に効果が認められてから 4 週後に治験担当医師により客観的奏効と判定された被験者は、23 例（29.1%）であった（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.3.1.2）。このうち、12 例で PD 又は死亡が確認され、残りの 11 例は打ち切りとなった。DOR の中央値は 182.0 日（95%CI : 152～421 日）であった（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.3.2.1.2）。

2.7.3.3.2.4 全生存期間（OS）

(1) 日本人／韓国人第 2b 相試験（203 試験）

本試験の PPS での OS の中央値は 99.1 週（95%CI : 54.9～99.1 週）［22.8 ヵ月（95%CI : 12.6～22.8 ヵ月）］であった。14 例（30.4%）が死亡し、32 例（69.6%）は最後に生存が確認された日で打ち切りとなった（表 2.7.3.3-9）。99.1 週（22.8 ヵ月）に at risk であった被験者は 1 例であり、この 1 例が 99.1 週（22.8 ヵ月）に死亡した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.5.12）。OS の Kaplan-Meier plot を図 2.7.3.3-3 に示した。

FAS を対象に解析した結果では、OS の中央値は 99.1 週（95%CI : 50.7～99.1 週）［22.8 ヵ月（95%CI : 11.7～22.8 ヵ月）］であった。16 例（32.7%）が死亡し、33 例（67.3%）は最後に生存が確認された日で打ち切りとなった（付録 1 表 2.7.3.6-16）。FAS での OS の結果は PPS での結果と同様であった。

国別（日本及び韓国）に解析した結果、日本人被験者の OS の中央値は 99.1 週（95%CI : 50.7～99.1 週）［22.8 ヵ月（95%CI : 11.7～22.8 ヵ月）］であった。11 例が死亡し、23 例は最後に生存が確認された日で打ち切りとなった。韓国人被験者の OS の中央値は 71.7 週（95%CI : 8.4 週～－）［16.5 ヵ月（95%CI : 1.9 ヵ月～－）］であった。3 例が死亡し、9 例は最後に生存が確認された日で打ち切りとなった（付録 1 表 2.7.3.6-17）。

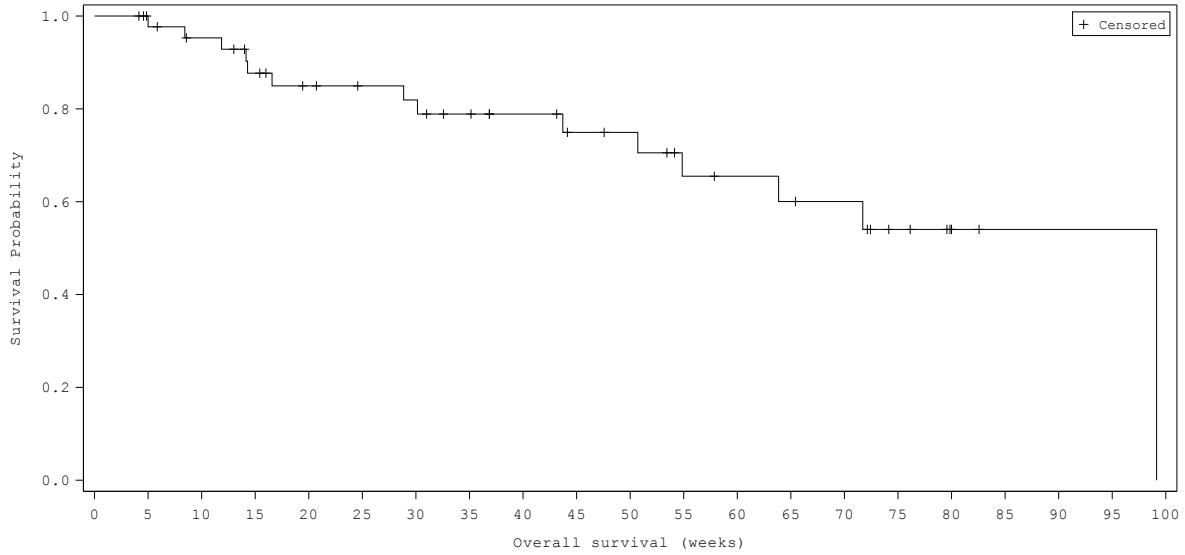
PTCL サブセット別（再発及び難治性）に解析した結果、再発 PTCL を有する被験者 28 例の OS の中央値は 99.1 週（95%CI : 63.9～99.1 週）［22.8 ヵ月（95%CI : 14.7～22.8 ヵ月）］であった。8 例が死亡し、20 例は最後に生存が確認された日で打ち切りとなった。難治性の PTCL を有する被験者 18 例の OS の中央値は 54.9 週（95%CI : 14.3 週～－）［12.6 ヵ月（95%CI : 3.3 ヵ月～－）］であった。6 例が死亡し、12 例は最後に生存が確認された日で打ち切りとなった（付録 1 表 2.7.3.6-18）。

表 2.7.3.3-9 全生存期間（203 試験）（PPS）

	Event/Statistics	40 mg (N=46)	
Number of subjects, n (%)	Censored	32 (69.6%)	
	Death	14 (30.4%)	
Overall survival (weeks)	Median (95% CI)	99.1	(54.9, 99.1)
Overall survival (months)	Median (95% CI)	22.8	(12.6, 22.8)

Source: Table 14.3.5.1.1 and Table 14.3.5.32 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
CI = confidence interval.
Median of overall survival is estimated from Kaplan-Meier method.
95% CI is calculated based on log-log transformation.
Data cut-off date: [redacted] 20[redacted]

図 2.7.3.3-3 全生存期間の Kaplan-Meier Plot（203 試験）（PPS）



Source: Figure 14.3.5.1.1 in CSR of Study HBI-8000-203
Data cut-off date: [redacted] 20[redacted]

(2) 日本人第 1 相試験（201 試験）

本試験では OS は解析しなかった。

(3) 中国人第 2 相試験（902 試験）（参考試験）

最後に組み入れた被験者のデータカットオフ日（2012 年 9 月[redacted]日）に、FAS の 79 例のうち 50 例の生存が確認された。残りの 29 例はデータカットオフ日よりも前に死亡しており、OS の中央値は 615.0 日（95%CI：343 日～－）であった（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.3.2.1.2）。

2.7.3.3.2.5 完全奏効率

(1) 日本人／韓国人第 2b 相試験（203 試験）

最良総合効果が CR であった被験者の割合を完全奏効率と定義した。

IOERC 評価に基づく完全奏効率は 10.9%（46 例中 5 例、95%CI：3.6%～23.6%）であった（表

2.7.3.3-10)。治験担当医師の評価では、被験者 2 例の判定が異なり、完全奏効率は 15.2%（46 例中 7 例、95%CI：6.3%～28.9%）であった（付録 1 表 2.7.3.6-19)。

表 2.7.3.3-10 完全奏効率（203 試験）（PPS）

		40 mg (N=46)	
Response	**Status/Response rate**	**n (%)**	**(95% CI)**
Best overall response	Complete Response (CR)	5 (10.9%)	(3.6, 23.6)
	Status		
	CR	5 (10.9%)	
	PR	16 (34.8%)	
	SD	12 (26.1%)	
	PD	13 (28.3%)	

Source: Table 14.3.5.11 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Complete Response is defined as proportion of subjects with best overall response of CR.
Data cut-off date: [redacted]20[redacted]

(2) 日本人第 1 相試験（201 試験）

本試験では完全奏効率は解析しなかった。PTCL を有する被験者のうち、最良総合効果が CR 又は CRu の被験者はなかった。

(3) 中国人第 2 相試験（902 試験）（参考試験）

本試験のピボタル試験の有効性評価項目として完全奏効率を設定していなかったが、FAS で CR を達成した被験者の割合は 10.1%［79 例中 8 例（95% CI：4.5%～19.0%)］、CRu を達成した被験者の割合は 3.8%［79 例中 3 例（95% CI: 0.8%～10.7%）］であった（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.3.1.2)。

2.7.3.3.2.6 完全奏効期間

(1) 日本人／韓国人第 2b 相試験（203 試験）

本試験では、IOERC 評価に基づく完全奏効期間は中央値に到達しなかった。CR を達成した 5 例のうち、1 例で PD が確認され、4 例は打ち切りとなった（表 2.7.3.3-11)。

治験担当医師による評価でも、完全奏効期間は中央値に到達しなかった。CR を達成した 7 例のうち、2 例で PD が確認され、5 例は打ち切りとなった（付録 1 表 2.7.3.6-20)。

表 2.7.3.3-11 完全奏効期間（203 試験）（PPS）

	Event/Statistics	40 mg (N=46)	
The number of subjects with CR, n (%)		5	
	Censored	4 (80.0%)	
	Any event	1 (20.0%)	
	Disease Progression	1 (20.0%)	
	Death	0 (0.0%)	
Duration of Complete Response (weeks)	Median (95% CI)	-	(16.3, -)

Source: Table 14.3.5.18 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects with CR in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease.
Median of duration of complete response is estimated from Kaplan-Meier method.
Disease progression is defined as PD confirmed by Independent Overall Efficacy Review Committee.
Data cut-off date: [redacted] 20[redacted]

(2) 日本人第 1 相試験（201 試験）

本試験では完全奏効期間は解析しなかった。PTCL を有する被験者のうち、最良総合効果が CR 又は CRu の被験者はなかった。

(3) 中国人第 2 相試験（902 試験）（参考試験）

本試験のピボタル試験では完全奏効期間は解析しなかった。

2.7.3.3.2.7 病勢コントロール率（DCR）

(1) 日本人／韓国人第 2b 相試験（203 試験）

本試験での病勢コントロール率（DCR）は、最良総合効果が CR、PR 又は SD である被験者の割合と定義した。

IOERC 評価に基づく DCR は 71.7%であった［46 例中 33 例（95%CI：56.5%～84.0%）］（表 2.7.3.3-12）。

治験担当医師による評価に基づく DCR は 76.1%であった［46 例中 35 例（95%CI：61.2%～87.4%）］（付録 1 表 2.7.3.6-21）。

PTCL サブセット別（再発及び難治性）の DCR は、再発 PTCL を有する被験者で 82.1%（28 例中 23 例）、難治性の PTCL を有する被験者で 55.6%（18 例中 10 例）であった（付録 1 表 2.7.3.6-8）。

表 2.7.3.3-12 病勢コントロール率（203 試験）（PPS）

		40 mg (N=46)	
Response	**Status/Response rate**	**n (%)**	**(95% CI)**
Best overall response	Disease Control Rate (CR, PR or SD)	33 (71.7%)	(56.5, 84.0)
	Status		
	CR	5 (10.9%)	
	PR	16 (34.8%)	
	SD	12 (26.1%)	
	PD	13 (28.3%)	

Source: Table 14.3.5.20 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Disease control rate is defined as proportion of subjects with best overall response of CR, PR or SD.
Data cut-off date: [redacted] 20[redacted]

(2) 日本人第 1 相試験（201 試験）

本試験では DCR は解析しなかった。PTCL を有する被験者のうち、最良総合効果が CR、CRu、PR 又は SD の被験者はなかった。

(3) 中国人第 2 相試験（902 試験）（参考試験）

本試験のピボタル試験では DCR は解析しなかった。

2.7.3.3.2.8 節性／節外性標的病変の総腫瘍サイズのベースラインからの最大変化

(1) 日本人／韓国人第 2b 相試験（203 試験）

腫瘍サイズは最大径とその直交する径の和として算出した。

IRR により、被験者 45 例の節性／節外性病変の計測評価を行った結果、標的病変の腫瘍サイズのベースラインからの最大変化率の中央値は−42.28%［平均値（標準偏差）−39.41%（47.72%）］であった。1 例（被験者[redacted]）はベースライン後の評価が行われなかったため、解析に含めなかった（表 2.7.3.3-13）。Waterfall plot 及び Spider plot をそれぞれ図 2.7.3.3-4 及び図 2.7.3.3-5 に示した。

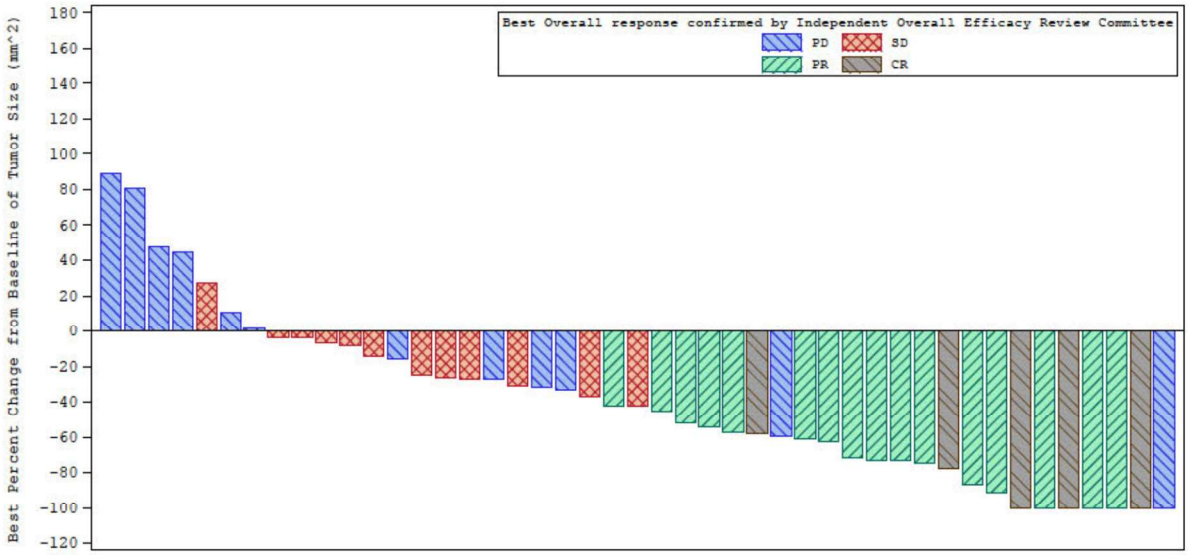
治験担当医師により、被験者 44 例の節性／節外性病変の計測評価を行った結果、標的病変の腫瘍サイズのベースラインからの最大変化率の中央値は−54.23%であった。ベースライン後の評価が行われなかった 2 例（被験者[redacted] 及び[redacted]）は解析に含めなかった（付録 1 表 2.7.3.6-22）。

表 2.7.3.3-13 独立画像判定による節性／節外性標的病変の総腫瘍サイズのベースラインからの最大変化（203 試験）（PPS）

Total Tumor Size of Nodal and Extranodal Target Lesion(mm^2)	**Statistic**	**40 mg (N=46)**
Baseline	n	45
	Mean	1118.4
	StD	965.1
	Median	823.0
	Minimum	180
	Maximum	5784
Best Tumor Size at post-baseline	n	45
	Mean	809.8
	StD	1166.5
	Median	443.0
	Minimum	0
	Maximum	6405
The Best Change from Baseline	n	45
	Mean	-308.6
	StD	585.9
	Median	-284.0
	Minimum	-1525
	Maximum	1920
The Best Percent Change from Baseline (%)	n	45
	Mean	-39.41
	StD	47.72
	Median	-42.28
	Minimum	-100.0
	Maximum	88.9

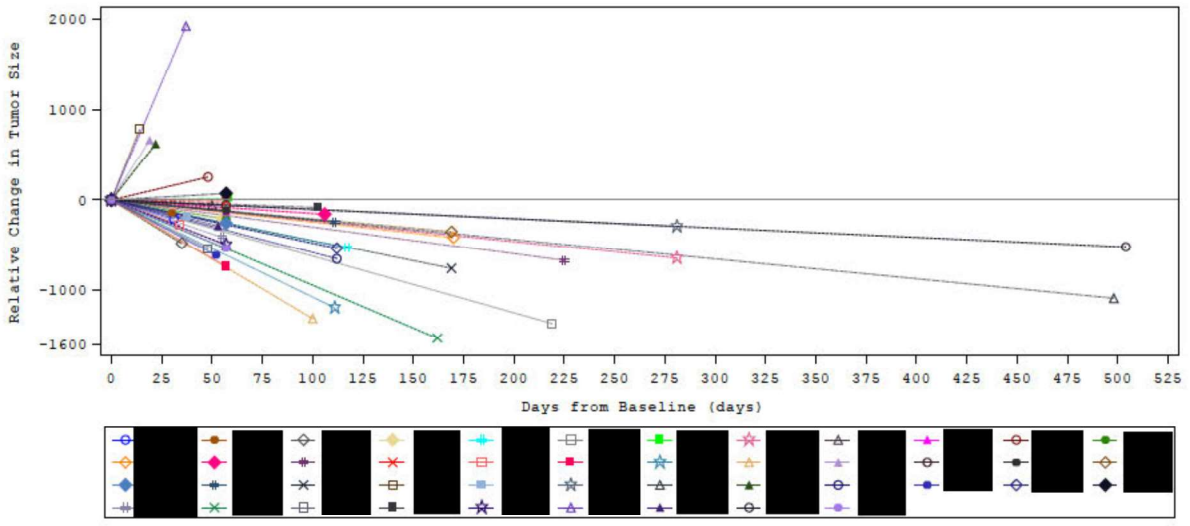
Source: Table 14.3.5.22 in CSR of Study HBI-8000-203
n = number of subjects.
IRR = independent radiologist review; StD = standard deviation.
This analysis included tumor sizes assessed by IRR, in the event when tumor sizes were not provided by IRR, investigator assessed tumor sizes were used instead.
Best change from baseline in tumor size is defined as the maximum reduction in the change of total tumor size of nodal and extranodal target lesions up to End of Treatment.
Only subjects with post baseline nodal and extranodal target lesion assessment are presented in this table.
Subject [redacted] did not have post baseline nodal and extranodal assessment hence is not included in the analysis.
Data cut-off date: [redacted] 20[redacted]

図 2.7.3.3-4 独立画像判定による節性／節外性標的病変の総腫瘍サイズのベースラインからの最大変化の Waterfall Plot（203 試験）（PPS）



Source: Figure 14.3.5.22.1 in CSR of Study HBI-8000-203
CR = complete response; IRR = Independent Radiologist Review; PD = progressive disease; PR = partial response; SD = stable disease.
Best change from baseline in tumor size is defined as the maximum reduction in the change of total tumor size of nodal and extranodal target lesions up to End of Treatment.
This figure presented tumor sizes assessed by IRR, in the event when tumor sizes were not provided by IRR, investigator assessed tumor sizes were used instead.
Subject [redacted] did not have post baseline assessment hence is not included in this figure.
Data cut-off date: [redacted]20[redacted]

図 2.7.3.3-5 独立画像判定による節性／節外性標的病変の総腫瘍サイズのベースラインからの最大変化の Spider Plot（203 試験）（PPS）



Source: Figure 14.3.5.22.2 in CSR of Study HBI-8000-203
IRR = Independent Radiologist Review.
This figure presented tumor sizes assessed by IRR, in the event when tumor sizes were not provided by IRR, investigator assessed tumor sizes were used instead.
Only subject with post baseline nodal and extranodal target lesion assessment are presented in this figure.
Subject [redacted] did not have post baseline assessment hence is not included in this figure.
Data cut-off date: [redacted]20[redacted]

(2) 日本人第 1 相試験（201 試験）

本試験では、節性／節外性標的病変の総腫瘍サイズのベースラインからの最大変化は算出しなかった。

(3) 中国人第 2 相試験（902 試験）（参考試験）

本試験のピボタル試験では、節性／節外性標的病変の総腫瘍サイズのベースラインからの最大変化は算出しなかった。

2.7.3.3.2.9 治験担当医師による評価に基づく皮膚病変の Modified Severity-Weighted Assessment Tool（mSWAT）スコア

(1) 日本人／韓国人第 2b 相試験（203 試験）

皮膚病変の mSWAT スコアは、ベースラインスコアを有する 8 例を対象に治験担当医師が評価した。mSWAT スコアのベースラインからの最大変化の平均値（標準偏差、以降同様）は−8.03（13.37）であった。ベースラインからの最大変化率の平均値は−41.73%（48.47%）であった（表 2.7.3.3-14）。mSWAT スコアのベースラインからの最大変化の中央値（最小値～最大値、以降同様）は−0.72（−33.7～2.0）であった。ベースラインからの最大変化率の中央値は−43.92%（−100.0%～25.0%）であった。

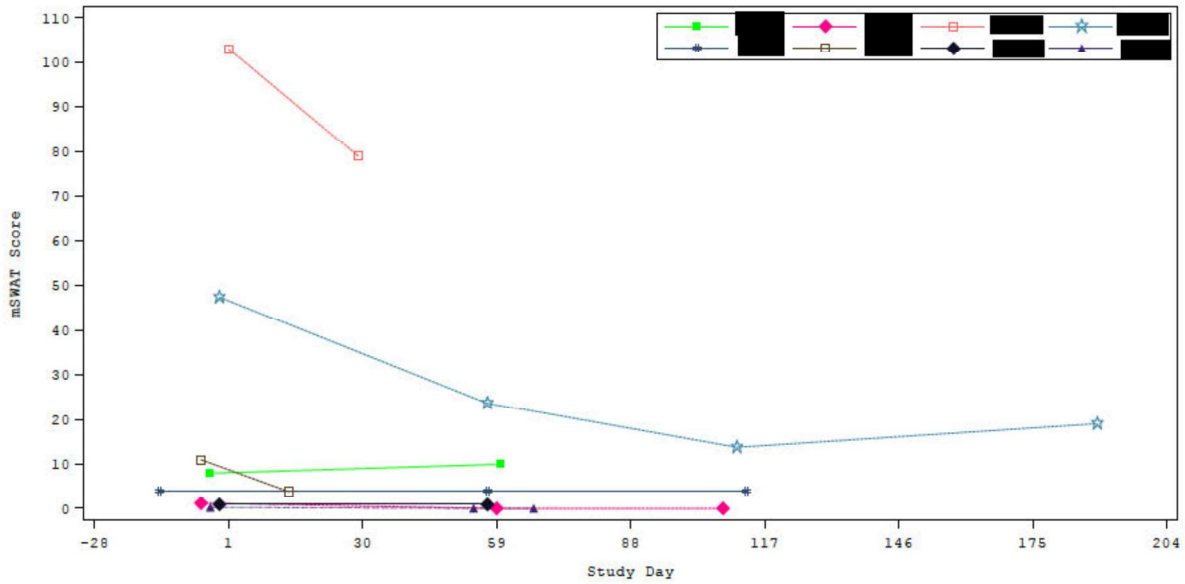
被験者ごとの mSWAT スコアの推移を図 2.7.3.3-6 に示した。被験者ごとの mSWAT スコアのベースラインからの最大変化率の Spider plot を図 2.7.3.3-7 に示した。

表 2.7.3.3-14 治験担当医師による評価に基づく皮膚病変の mSWAT スコアのベースラインからの最大変化（203 試験）（PPS）

mSWAT score	Statistic	40 mg (N=46)
Baseline	n	8
	Mean	21.97
	StD	36.25
	Median	6.00
	Minimum	0.2
	Maximum	103.0
Best Score at post-baseline	n	8
	Mean	13.94
	StD	26.74
	Median	3.95
	Minimum	0.0
	Maximum	79.0
The Best Change from Baseline	n	8
	Mean	-8.03
	StD	13.37
	Median	-0.72
	Minimum	-33.7
	Maximum	2.0
The Best Percent Change from Baseline (%)	n	8
	Mean	-41.73
	StD	48.47
	Median	-43.92
	Minimum	-100.0
	Maximum	25.0

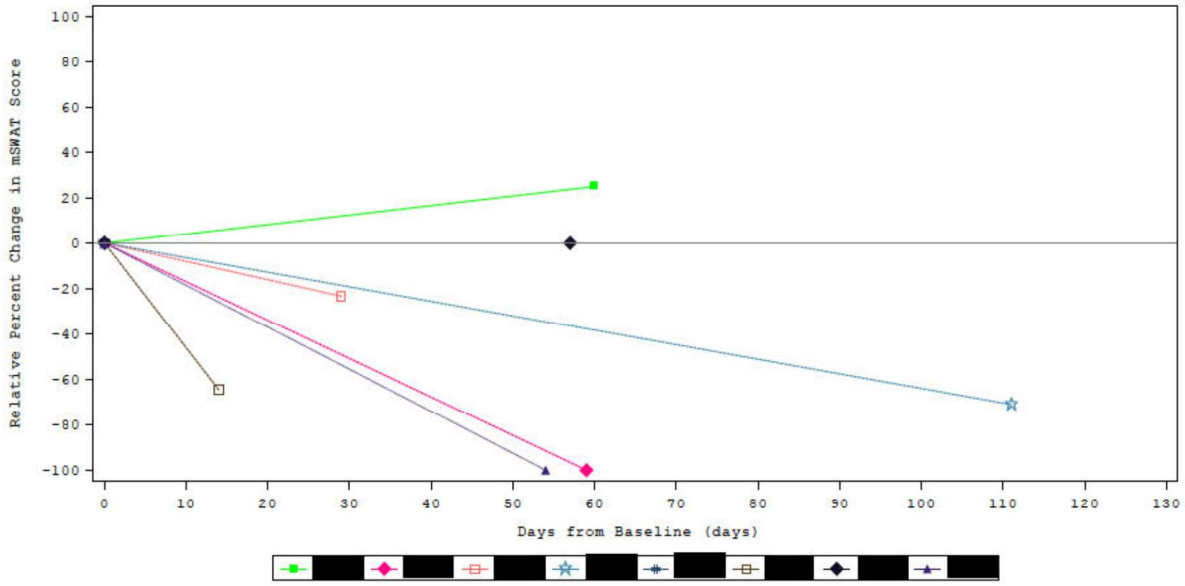
Source: Table 14.3.5.24 in CSR of Study HBI-8000-203
n = number of subjects.
mSWAT = Modified Severity-Weighted Assessment Tool; StD = standard deviation.
Only subjects who had skin lesion identified at screening are included in this analysis.
Best change from baseline in mSWAT score is defined as the maximum reduction in the change of mSWAT score up to End of Treatment.
Data cut-off date: [redacted] 20[redacted]

図 2.7.3.3-6 治験担当医師による評価に基づく皮膚病変の mSWAT スコアの被験者別推移（203 試験）（PPS）



Source: Figure 14.3.5.24.1 in CSR of Study HBI-8000-203
mSWAT = Modified Severity-Weighted Assessment Tool.
Only subjects who had skin lesion at screening are included in this figure.
Data cut-off date: [redacted]20[redacted]

図 2.7.3.3-7 治験担当医師による評価に基づく皮膚病変の mSWAT スコアのベースラインからの最大変化率の Spider Plot（203 試験）（PPS）



Source: Figure 14.3.5.24.3 in CSR of Study HBI-8000-203
mSWAT = Modified Severity-Weighted Assessment Tool.
Only subjects who had skin lesion at screening are included in this figure.
Data cut-off date: [redacted]20[redacted]

(2) 日本人第 1 相試験（201 試験）

本試験では mSWAT スコアの変化は解析しなかった。

(3) 中国人第 2 相試験（902 試験）（参考試験）

本試験のピボタル試験では mSWAT スコアの変化は解析しなかった。

2.7.3.3.2.10 標的病変及び皮膚病変における腫瘍縮小効果

(1) 日本人／韓国人第 2b 相試験（203 試験）

IOERC 評価に基づく節性及び節外性標的病変の腫瘍縮小効果（CR 又は PR）は 50.0%［46 例中 23 例（95%CI：34.9%～65.1%）］で認められ、15 例で CR、8 例で PR と判定された（表 2.7.3.3-15）。

治験担当医師の評価に基づく結果（付録 1 表 2.7.3.6-23）は IOERC 評価に基づく結果と同様であった。

皮膚病変は治験担当医師により評価され、IOERC が総合評価に使用した。皮膚病変の腫瘍縮小効果（CR 又は PR）は 50.0%［8 例中 4 例（95%CI：15.7%～84.3%）］で認められ、CR 及び PR が各 2 例であった（表 2.7.3.3-15）。

表 2.7.3.3-15 測定可能な節性及び節外性標的病変、皮膚病変の腫瘍縮小効果（203 試験）（PPS）

		40 mg	
Lesion	**Status/Response rate**	**n (%)**	**(95% CI)**
Measurable Nodal and Extranodal Target Lesion Response (N=46)	Objective Response rate (CR or PR)	23 (50.0%)	(34.9, 65.1)
	Status		
	CR	15 (32.6%)	
	PR	8 (17.4%)	
	SD	17 (37.0%)	
	PD	5 (10.9%)	
	NE	0 (0.0%)	
	NA	1 (2.2%)	
Skin Lesion Response (N=8)	Objective Response rate (CR or PR)	4 (50.0%)	(15.7, 84.3)
	Status		
	CR	2 (25.0%)	
	PR	2 (25.0%)	
	SD	3 (37.5%)	
	PD	1 (12.5%)	
	NE	0 (0.0%)	
	NA	0 (0.0%)	

Source: Table 14.3.5.25 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in each lesion category within the analysis set.
CI = confidence interval; CR = complete response; NA = not assessable.; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI
Objective response rate is defined as proportion of subjects with best overall response of CR or PR.
Data cut-off date: [redacted] 20[redacted]

(2) 日本人第 1 相試験（201 試験）

本試験では、節性／節外性病変及び皮膚病変における本薬の有効性を治験担当医師が評価した。

最良総合効果が PD と判定された被験者 [redacted] は、試験終了時評価で皮膚病変の腫瘍縮小効果が認められ、皮膚病変に対しては CR と判定された（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.5.2, Listing 16.2.5.3, Listing 16.2.5.5）。

(3) 中国人第 2 相試験（902 試験）（参考試験）

本試験のピボタル試験では標的病変及び皮膚病変の腫瘍縮小効果は解析しなかった。個々の被験者の標的病変及び皮膚病変を含む腫瘍の評価結果については、5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.6.7.2、Table 7.6.7.3、Table 7.6.7.4 及び Table 7.6.7.5 に示した。

2.7.3.3.2.11 治験担当医師による評価に基づく新病変評価

(1) 日本人／韓国人第 2b 相試験（203 試験）

本試験での PPS の被験者 46 例のうち、12 例（26.1%）で治験担当医師による評価に基づく新病変が 1 つ以上認められた。このうち、6 例（13.0%）にリンパ節で、8 例（17.4%）にリンパ節以外で新病変が認められた（表 2.7.3.3-16）。

表 2.7.3.3-16 治験担当医師による評価に基づく新病変が認められた被験者数（203 試験）（PPS）

		40 mg (N=46)
Number of subjects with at least one new lesion	n (%)	12 (26.1%)
New lesion - lymph node	n (%)	6 (13.0%)
New lesion - Non-lymph node	n (%)	8 (17.4%)

Source: Table 14.3.5.27 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
New lesions identified up to survival follow-up period are also included in this table.
Data cut-off date: [redacted] 20[redacted]

(2) 日本人第 1 相試験（201 試験）

本試験で新病変は報告されなかった。

(3) 中国人第 2 相試験（902 試験）（参考試験）

本試験のピボタル試験では新病変を発現した被験者の割合は集計しなかった。新病変が発現した被験者を含む個々の被験者に対する腫瘍の評価結果については、5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.6.7.1、Table 7.6.7.2、Table 7.6.7.3、Table 7.6.7.4、Table 7.6.7.5 及び Table 7.6.7.6 に示した。

2.7.3.3.2.12 奏効までの期間（TTR）

(1) 日本人／韓国人第 2b 相試験（203 試験）

IOERC 評価に基づく最良総合効果が CR 又は PR であった被験者 21 例について、TTR の中央値は 8.1 週（95%CI : 8.0～8.4 週）であった（表 2.7.3.3-17）。TTR の Kaplan-Meier plot を図 2.7.3.3-8 に示した。

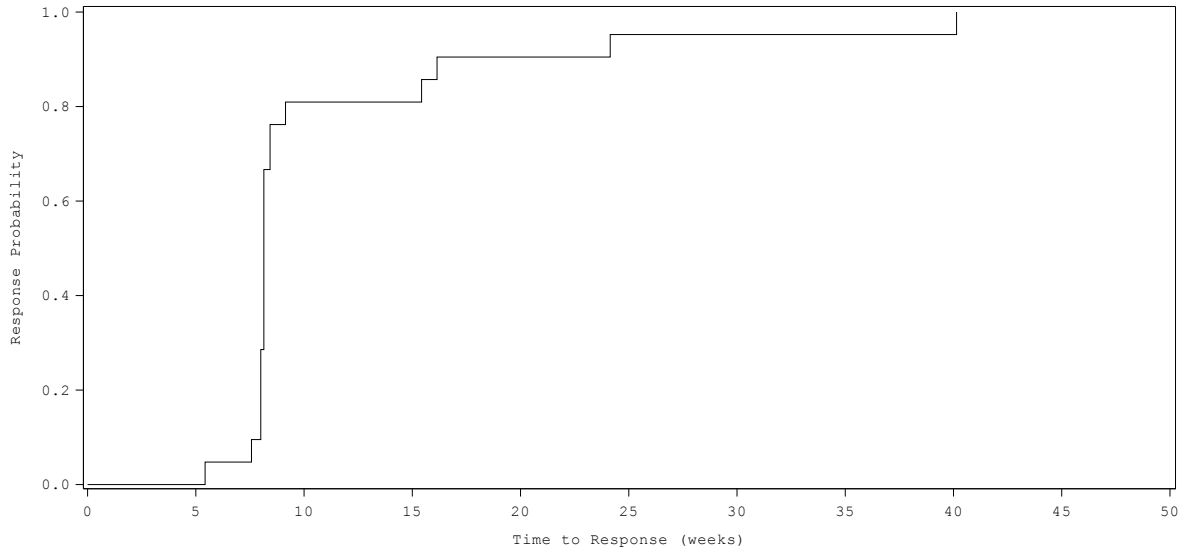
治験担当医師による評価に基づく最良総合効果が CR 又は PR であった被験者 24 例については、TTR の中央値は 8.1 週（95%CI : 8.1～9.1 週）であり（付録 1 表 2.7.3.6-24）、IOERC 評価に基づく TTR と同様であった。

表 2.7.3.3-17 奏効までの期間（203 試験）（PPS）

	Event/Statistics	40 mg (N=46)	
Number of subjects, n (%)	CR or PR	21 (45.7%)	
Time to response (weeks)	Median (95% CI)	8.1	(8.0, 8.4)

Source: Table 14.3.5.28 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects with either CR or PR in the analysis set.
CI = confidence interval; CR = complete response; PR = partial response.
Median of time to response is estimated from Kaplan-Meier method.
95% CI is calculated based on log-log transformation.
Data cut-off date: [redacted] 20[redacted]

図 2.7.3.3-8 奏効までの期間の Kaplan-Meier Plot（203 試験）（PPS）



Source: Figure 14.3.5.28 in CSR of Study HBI-8000-203
Data cut-off date: [redacted] 20[redacted]

(2) 日本人第 1 相試験（201 試験）

本試験では TTR は解析しなかった。

(3) 中国人第 2 相試験（902 試験）（参考試験）

FAS の 79 例のうち、最初に効果が認められてから 4 週後に治験担当医師により客観的奏効と判定された被験者は、23 例（29.1%）であった。TTR の中央値は 43.0 日（95%CI：42～46 日）であった（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.3.1.2, Table 7.3.2.1.2）。

2.7.3.3.2.13 203 試験の被験者の陽電子放出断層撮影（PET）及びコンピュータ断層撮影（CT）検査結果に関する検討

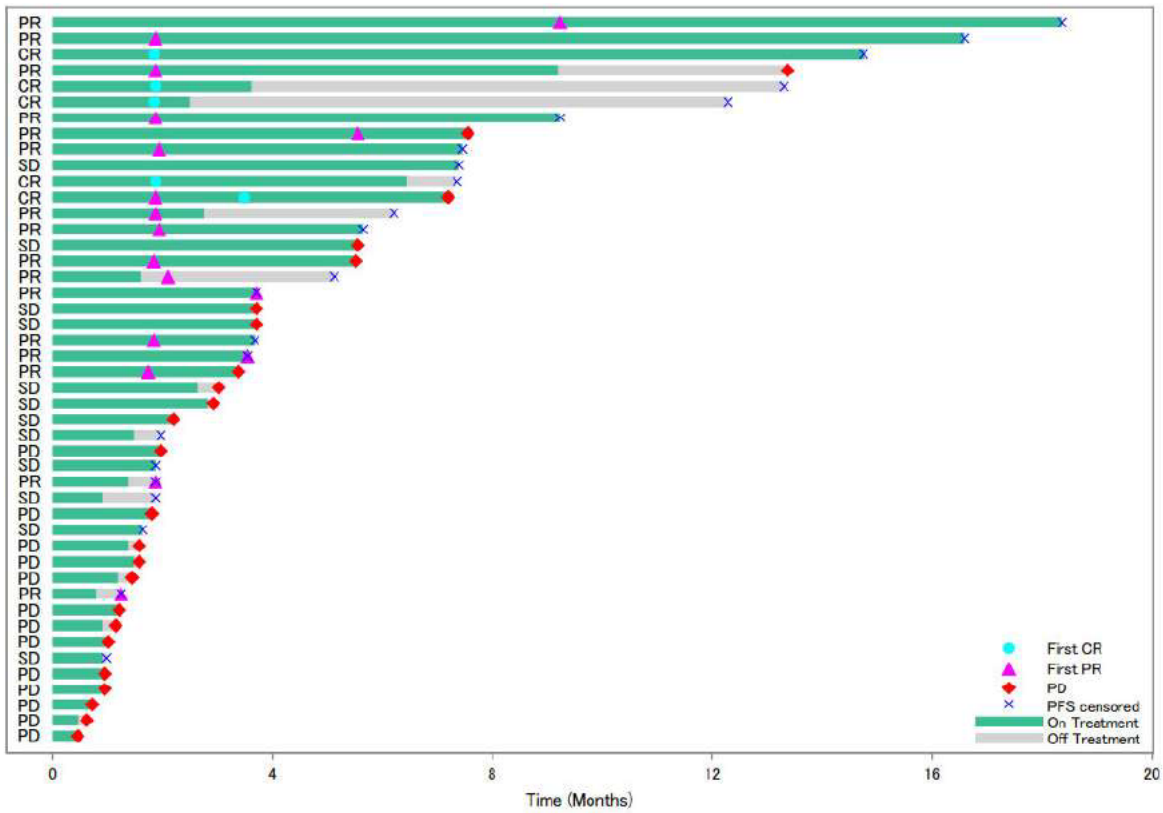
韓国で 203 試験に参加した被験者 5 例（被験者[redacted]、[redacted]、[redacted]、[redacted] 及び[redacted]）は、陽電子放出断層撮影（PET）又は陽電子放出断層撮影–コンピュータ断層撮影（PET-CT）により腫瘍を評価され、PET 検査とコンピュータ断層撮影（CT）検査の結果に大きな差異は認められなかった。この 5 例のほかに 6 例で PET-CT 又は PET 検査が実施されたが、次の理由により有効性解

析対象集団から除外されたか、PET データが不十分であったため、いずれも評価対象とならなかった。4 例（被験者[redacted]、[redacted]、[redacted] 及び[redacted]）は FAS 及び PPS から除外され、1 例（被験者[redacted]）はスクリーニング時のデータのみが利用可能であり、もう 1 例（被験者[redacted]）はスクリーニング時に PET 検査が実施されなかったため、データ評価が行われなかった（5.3.5.2-1/HBI-8000-203/CSR/Section 11.4.1.3.9, Listing 16.2.5.10, Listing 16.2.5.14）。

2.7.3.3.2.14 203 試験の各被験者の奏効及び病勢進行の確認時点

独立画像判定に基づき、PPS の各被験者の奏効及び病勢進行が確認された時点を Swimmer plot で図 2.7.3.3-9 に示した。

図 2.7.3.3-9 独立画像判定による各被験者の奏効及び病勢進行の確認時点（203 試験）（PPS）



*On Treatment（治験薬投与期間）及び Off treatment（追跡期間） は、 PD の確認又は打ち切り時点（PFS censored）までを表示した。

2.7.3.3.3 部分集団における結果の比較

ORR について、203 試験のみ部分集団解析を行った。

2.7.3.3.3.1 部分集団別の客観的奏効率（203 試験）

PPS の ORR について、以下の患者背景で部分集団解析を行った。

- 国別：日本、韓国
- 性別：男性、女性
- 年齢別：65 歳未満、65 歳以上 75 歳未満、75 歳以上
- ベースライン時の ECOG PS 別：0、1、2

- PTCL サブセット別：再発、難治性、不確定
- PTCL サブタイプ別：PTCL-NOS、AITL、ALK 陽性 ALCL、ALK 陰性 ALCL、EATL、HSTCL、SPTCL
- がんに対する前治療のレジメン数別：3 レジメン未満、3 レジメン以上
- 直近のがん治療終了から本薬の初回投与までの期間別：3 ヵ月未満、3 ヵ月以上

各部分集団解析の結果を付録 1 表 2.7.3.6-2～表 2.7.3.6-9 に示した。

国別（日本及び韓国）の ORR は、日本人で 52.9%［34 例中 18 例（95%CI：35.1%～70.2%）］、韓国人で 25.0%［12 例中 3 例（95%CI：5.5%～57.2%）］であった。

性別の ORR は、男性で 48.4%［31 例中 15 例（95%CI：30.2%～66.9%）］、女性で 40.0%［15 例中 6 例（95%CI：16.3%～67.7%）］であった。

年齢別の ORR は、65 歳未満で 53.8%［13 例中 7 例（95%CI：25.1%～80.8%）］、65 歳以上 75 歳未満で 52.6%［19 例中 10 例（95%CI：28.9%～75.6%）］、75 歳以上で 28.6%［14 例中 4 例（95%CI：8.4%～58.1%）］であった。

スクリーニング時の ECOG PS 別の ORR は、0 で 50.0%［24 例中 12 例（95%CI：29.1%～70.9%）］、1 で 42.9%［21 例中 9 例（95%CI：21.8%～66.0%）］、2 で 0%［1 例中 0 例（95%CI：0.0%～97.5%）］であった。

PTCL サブセット別（再発及び難治性）の ORR は、再発 PTCL を有する被験者で 53.6%［28 例中 15 例（95%CI：33.9%～72.5%）］、難治性の PTCL を有する被験者で 33.3%［18 例中 6 例（95%CI：13.3%～59.0%）］であった。

副次的評価項目とした PTCL サブタイプ別の ORR は、PTCL-NOS で 35.3%［34 例中 12 例（95%CI：19.7%～53.5%）］、AITL で 87.5%［8 例中 7 例（95%CI：47.3%～99.7%）］、ALK 陰性 ALCL で 33.3%［3 例中 1 例（95%CI：0.8%～90.6%）］、EATL で 100.0%［1 例中 1 例（95%CI：2.5%～100.0%）］であった。サブタイプが ALK 陽性 ALCL、HSTCL 又は SPTCL の被験者はなかった。

がんに対する前治療のレジメン数別の ORR は、3 レジメン未満の被験者で 58.6%［29 例中 17 例（95%CI：38.9%～76.5%）］、3 レジメン以上の被験者で 23.5%［17 例中 4 例（95%CI：6.8%～49.9%）］であった。

直近のがん治療終了から本薬の初回投与までの期間別の ORR は、直近のがん治療終了後 3 ヵ月以上の被験者で 53.8%［26 例中 14 例（95%CI：33.4%～73.4%）］、3 ヵ月未満で 35.0%［20 例中 7 例（95%CI：15.4%～59.2%）］であった。

被験者数は限られるものの、部分集団解析ではほとんどの部分集団において腫瘍縮小効果が認められた。

2.7.3.3.3.2 国別の結果の比較検討（203 試験）

ORR、PFS 及び OS の国別（日本及び韓国）の結果は、それぞれ 2.7.3.3.3.1 項、2.7.3.3.2.2 項及び 2.7.3.3.2.4 項に示した。

日本人被験者の ORR は 52.9%［34 例中 18 例（95%CI：35.1%～70.2%）］であり、本薬の有効性は日本人被験者のみでも示された。

韓国人被験者の ORR、PFS 及び OS といった有効性パラメータは、日本人被験者よりも低い又

は短い数値を示したが、韓国人及び日本人の被験者数は限られていることから意義のある比較は困難であった。

2.7.3.4 推奨用法・用量に関する臨床情報の解析

本薬は、中国において、2014 年に再発又は難治性の PTCL の治療に対して 30 mg 週 2 回投与が承認され、2019 年に局所進行性又は転移性の乳がんの治療に対してアロマターゼ阻害剤との併用で 30 mg 週 2 回投与が承認された。

PTCL 患者を対象とした試験（902 試験）を含む、中国で実施された複数の第 2 相試験において 150 例以上の被験者に本薬が投与され、30 mg 週 2 回の開始用量を支持する有効性及び安全性データが得られていた。

中国での試験成績に基づいて、本邦における PTCL を含む NHL を有する成人患者を対象とした第 1 相試験（201 試験）の開始用量として、30 mg 週 2 回が選択された。

201 試験で計画した用量は 30 mg、40 mg 及び 50 mg であった。用量コホートの移行は 40 mg で終了したため、本試験では 30 mg 及び 40 mg の 2 用量のみが投与された。

201 試験では 40 mg コホートの 7 例に PD は認められず、本コホートでの有効性シグナルが確認された。40 mg コホートでは、ATL を有する 4 例中 3 例が PR を達成し、ATL 以外の NHL を有する 3 例中 2 例が CR 及び CRu を達成した。

40 mg コホートで 2 件の DLT が発現したが、いずれも標準的な処置で管理可能であったことから、40 mg の週 2 回投与は忍容であると考えられた。PTCL を含む NHL を有する患者を対象とした 201 試験の全被験者から得られた結果に基づき、データモニタリング委員会／安全性モニタリング委員会は日本人患者に本薬を週 2 回投与する場合の最大耐量を 40 mg と決定した。

全体としてリスクベネフィットを検討した結果、日本人及び韓国人の再発又は難治性の PTCL 患者を対象とした第 2 相試験（203 試験）の開始用量として 40 mg 週 2 回が選択された。203 試験では、再発又は難治性の PTCL を有する被験者 55 例に本薬が開始用量 40 mg で週 2 回、3～4 日間隔で投与され、PPS の被験者 46 例の ORR は 45.7%であった。PTCL サブセット別（再発及び難治性）の ORR は、PPS の再発 PTCL を有する被験者 28 例で 53.6%であり、PPS の難治性の PTCL を有する被験者 18 例で 33.3%であった。

本薬 40 mg 週 2 回を通常の食事後に経口投与したときの忍容性は良好であった。AE の多くは、標準的な処置及び用量調節のガイドラインに従うことで管理可能であった。

日本人の再発又は難治性の PTCL 患者に対して推奨される本薬の用法及び用量は、「通常、成人にはツシジノスタットとして 1 日 1 回 40 mg を週 2 回、3 又は 4 日間隔で食後に経口投与する。なお、患者の状態により適宜減量する。」である。

2.7.3.5 効果の持続、耐薬性

203 試験のデータカットオフ日時点（20[redacted] 年[redacted] 月[redacted] 日）では、PFS の中央値は 24.1 週（95%CI：12.7～58.1 週）［5.6 ヵ月（95%CI：2.9～13.4 ヵ月）］、DOR の中央値は 50.1 週（95%CI：23.3 週～－）［11.5 ヵ月（95%CI：5.4 ヵ月～－）］、OS の中央値は 99.1 週（95%CI：54.9～99.1 週）［22.8 ヵ月（95%CI：12.6～22.8 ヵ月）］であった（2.7.3.3.2.2 項、2.7.3.3.2.3 項及び 2.7.3.3.2.4 項）。

2.7.3.6 付録

2.7.3.6.1 付録 1 その他の有効性の表（203 試験）

表 2.7.3.6-1 客観的奏効率及び最良総合効果（203 試験）（FAS）

		40 mg (N=49)	
Response	**Status/Response rate**	**n (%)**	**(95% CI)**
Best overall response	Objective Response rate (CR or PR)	21 (42.9%)	(28.8, 57.8)
	Status		
	CR	5 (10.2%)	
	PR	16 (32.7%)	
	SD	14 (28.6%)	
	PD	14 (28.6%)	

Source: Table 14.3.4.2 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Objective response rate is defined as proportion of subjects with best overall response of CR or PR.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-2 中央病理評価委員会により確認された末梢性 T 細胞リンパ腫サブタイプ別の客観的奏効率及び最良総合効果（203 試験）（PPS）

		40 mg (N=46)	
PTCL subtype	**Status/Response rate**	**n(%)**	**(95% CI)**
Peripheral T-cell Lymphoma Not Otherwise Specified (PTCL-NOS)		34	
Best overall response	Objective Response rate (CR or PR)	12 (35.3%)	(19.7, 53.5)
	Status		
	CR	3 (8.8%)	
	PR	9 (26.5%)	
	SD	10 (29.4%)	
	PD	12 (35.3%)	
Angioimmunoblastic T-cell Lymphoma (AITL)		8	
Best overall response	Objective Response rate (CR or PR)	7 (87.5%)	(47.3, 99.7)
	Status		
	CR	2 (25.0%)	
	PR	5 (62.5%)	
	SD	1 (12.5%)	
	PD	0 (0.0%)	
Anaplastic Large-cell Lymphoma (ALCL), ALK+		0	
Best overall response	Objective Response rate (CR or PR)	0 (0.0%)	-
	Status		
	CR	0 (0.0%)	
	PR	0 (0.0%)	
	SD	0 (0.0%)	
	PD	0 (0.0%)	
Anaplastic Large-cell Lymphoma (ALCL), ALK-		3	
Best overall response	Objective Response rate (CR or PR)	1 (33.3%)	(0.8, 90.6)
	Status		
	CR	0 (0.0%)	
	PR	1 (33.3%)	
	SD	1 (33.3%)	
	PD	1 (33.3%)	
Enteropathy-Associated T-cell Lymphoma (EATL)		1	
Best overall response	Objective Response rate (CR or PR)	1 (100.0%)	(2.5, 100.0)
	Status		
	CR	0 (0.0%)	
	PR	1 (100.0%)	
	SD	0 (0.0%)	
	PD	0 (0.0%)	

PTCL subtype	Status/Response rate	40 mg (N=46) n(%)	(95% CI)
Hepatosplenic T-cell Lymphoma (HSTCL)		0	
Best overall response	Objective Response rate (CR or PR)	0 (0.0%)	-
	Status		
	CR	0 (0.0%)	
	PR	0 (0.0%)	
	SD	0 (0.0%)	
	PD	0 (0.0%)	
Subcutaneous Panniculitis-Like T-cell Lymphoma (SPTCL)		0	
Best overall response	Objective Response rate (CR or PR)	0 (0.0%)	-
	Status		
	CR	0 (0.0%)	
	PR	0 (0.0%)	
	SD	0 (0.0%)	
	PD	0 (0.0%)	

Source: Table 14.3.4.3 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
ALK = anaplastic lymphoma kinase; CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; PTCL= peripheral T-cell lymphoma; SD = stable disease.
95% exact binomial CI.
Objective response rate is defined as proportion of subjects with best overall response of CR or PR.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-3 国別の客観的奏効率及び最良総合効果（203 試験）（PPS）

		40 mg (N=46)	
Country	**Status/Response rate**	**n(%)**	**(95% CI)**
Japan		34	
Best overall response	Objective Response rate (CR or PR)	18 (52.9%)	(35.1, 70.2)
	Status		
	CR	3 (8.8%)	
	PR	15 (44.1%)	
	SD	8 (23.5%)	
	PD	8 (23.5%)	
Korea		12	
Best overall response	Objective Response rate (CR or PR)	3 (25.0%)	(5.5, 57.2)
	Status		
	CR	2 (16.7%)	
	PR	1 (8.3%)	
	SD	4 (33.3%)	
	PD	5 (41.7%)	

Source: Table 14.3.5.3 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Objective response rate is defined as proportion of subjects with best overall response of CR or PR.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-4 性別の客観的奏効率及び最良総合効果（203 試験）（PPS）

		40 mg (N=46)	
Sex	**Status/Response rate**	**n(%)**	**(95% CI)**
Male		31	
Best overall response	Objective Response rate (CR or PR)	15 (48.4%)	(30.2, 66.9)
	Status		
	CR	3 (9.7%)	
	PR	12 (38.7%)	
	SD	8 (25.8%)	
	PD	8 (25.8%)	
Female		15	
Best overall response	Objective Response rate (CR or PR)	6 (40.0%)	(16.3, 67.7)
	Status		
	CR	2 (13.3%)	
	PR	4 (26.7%)	
	SD	4 (26.7%)	
	PD	5 (33.3%)	

Source: Table 14.3.5.4 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Objective response rate is defined as proportion of subjects with best overall response of CR or PR.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-5 年齢別の客観的奏効率及び最良総合効果（203 試験）（PPS）

		40 mg (N=46)	
Age (years)	**Status/Response rate**	**n(%)**	**(95% CI)**
<65		13	
Best overall response	Objective Response rate (CR or PR)	7 (53.8%)	(25.1, 80.8)
	Status		
	CR	2 (15.4%)	
	PR	5 (38.5%)	
	SD	3 (23.1%)	
	PD	3 (23.1%)	
>=65 to <75		19	
Best overall response	Objective Response rate (CR or PR)	10 (52.6%)	(28.9, 75.6)
	Status		
	CR	2 (10.5%)	
	PR	8 (42.1%)	
	SD	5 (26.3%)	
	PD	4 (21.1%)	
>=75		14	
Best overall response	Objective Response rate (CR or PR)	4 (28.6%)	(8.4, 58.1)
	Status		
	CR	1 (7.1%)	
	PR	3 (21.4%)	
	SD	4 (28.6%)	
	PD	6 (42.9%)	

Source: Table 14.3.5.5 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Objective response rate is defined as proportion of subjects with best overall response of CR or PR.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-6 前治療のレジメン数別の客観的奏効率及び最良総合効果（203 試験）（PPS）

		40 mg (N=46)	
Number of regimens before the study treatment	**Status/Response rate**	**n(%)**	**(95% CI)**
Less than 3 regimens		29	
Best overall response	Objective Response rate (CR or PR)	17 (58.6%)	(38.9, 76.5)
	Status		
	CR	5 (17.2%)	
	PR	12 (41.4%)	
	SD	7 (24.1%)	
	PD	5 (17.2%)	
3 or more regimens		17	
Best overall response	Objective Response rate (CR or PR)	4 (23.5%)	(6.8, 49.9)
	Status		
	CR	0 (0.0%)	
	PR	4 (23.5%)	
	SD	5 (29.4%)	
	PD	8 (47.1%)	

Source: Table 14.3.5.6 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Objective response rate is defined as proportion of subjects with best overall response of CR or PR.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-7 直近のがん治療終了からの期間別の客観的奏効率及び最良総合効果（203 試験）（PPS）

Days from End of the Last Immediate Previous Treatment	Status/Response rate	40 mg (N=46) n(%)	40 mg (N=46) (95% CI)
< 3 months		20	
Best overall response	Objective Response rate (CR or PR)	7 (35.0%)	(15.4, 59.2)
	Status		
	CR	1 (5.0%)	
	PR	6 (30.0%)	
	SD	4 (20.0%)	
	PD	9 (45.0%)	
>=3 months		26	
Best overall response	Objective Response rate (CR or PR)	14 (53.8%)	(33.4, 73.4)
	Status		
	CR	4 (15.4%)	
	PR	10 (38.5%)	
	SD	8 (30.8%)	
	PD	4 (15.4%)	

Source: Table 14.3.5.7 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Objective response rate is defined as proportion of subjects with best overall response of CR or PR.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-8 再発、難治性及び不確定末梢性 T 細胞リンパ腫別の客観的奏効率及び最良総合効果（203 試験）（PPS）

		40 mg (N=46)	
Relapsed, Refractory or Undetermined PTCL	**Status/Response rate**	**n(%)**	**(95% CI)**
Relapsed		28	
Best overall response	Objective Response rate (CR or PR)	15 (53.6%)	(33.9, 72.5)
	Status		
	CR	4 (14.3%)	
	PR	11 (39.3%)	
	SD	8 (28.6%)	
	PD	5 (17.9%)	
Refractory		18	
Best overall response	Objective Response rate (CR or PR)	6 (33.3%)	(13.3, 59.0)
	Status		
	CR	1 (5.6%)	
	PR	5 (27.8%)	
	SD	4 (22.2%)	
	PD	8 (44.4%)	
Undetermined		0	
Best overall response	Objective Response rate (CR or PR)	0 (0.0%)	-
	Status		
	CR	0 (0.0%)	
	PR	0 (0.0%)	
	SD	0 (0.0%)	
	PD	0 (0.0%)	

Source: Table 14.3.5.8 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; PTCL = peripheral T-cell lymphoma; SD = stable disease.
95% exact binomial CI.
Objective response rate is defined as proportion of subjects with best overall response of CR or PR.
Subjects with relapsed, refractory, and undetermined PTCL are confirmed by Medical Expert.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-9 ECOG PS 別の客観的奏効率及び最良総合効果（203 試験）（PPS）

		40 mg (N=46)	
Eastern Cooperative Oncology Group (ECOG) Performance Status at baseline	**Status/Response rate**	**n(%)**	**(95% CI)**
0		24	
Best overall response	Objective Response rate (CR or PR)	12 (50.0%)	(29.1, 70.9)
	Status		
	CR	2 (8.3%)	
	PR	10 (41.7%)	
	SD	6 (25.0%)	
	PD	6 (25.0%)	
1		21	
Best overall response	Objective Response rate (CR or PR)	9 (42.9%)	(21.8, 66.0)
	Status		
	CR	3 (14.3%)	
	PR	6 (28.6%)	
	SD	6 (28.6%)	
	PD	6 (28.6%)	
2		1	
Best overall response	Objective Response rate (CR or PR)	0 (0.0%)	(0.0, 97.5)
	Status		
	CR	0 (0.0%)	
	PR	0 (0.0%)	
	SD	0 (0.0%)	
	PD	1 (100.0%)	

Source: Table 14.3.5.9 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Objective response rate is defined as proportion of subjects with best overall response of CR or PR.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-10 治験担当医師による評価に基づく客観的奏効率及び最良総合効果（203 試験）（PPS）

Response	Status/Response rate	40 mg (N=46) n (%)	(95% CI)
Best overall response	Objective Response rate (CR or PR)	24 (52.2%)	(36.9, 67.1)
	Status		
	CR	7 (15.2%)	
	PR	17 (37.0%)	
	SD	11 (23.9%)	
	PD	11 (23.9%)	

Source: Table 14.3.5.10 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Objective response rate is defined as proportion of subjects with best overall response of CR or PR.
For subjects who do not have overall response assessment of CR, PR, SD or PD, the investigator response assessments of Clinical PD may be included as the best overall response.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-11 国別の無増悪生存期間（203 試験）（PPS）

	Event/Statistics	40 mg	
Japan (N=34)			
Number of subjects, n (%)	Censored	18 (52.9%)	
	Last Tumor Assessment	18 (52.9%)	
	Any event	16 (47.1%)	
	Disease Progression	16 (47.1%)	
	Death	0 (0.0%)	
Progression Free Survival (weeks)	Median (95% CI)	32.9	(14.7, -)
Progression Free Survival (months)	Median (95% CI)	7.6	(3.4, -)
Korea (N=12)			
Number of subjects, n (%)	Censored	4 (33.3%)	
	Last Tumor Assessment	4 (33.3%)	
	Any event	8 (66.7%)	
	Disease Progression	8 (66.7%)	
	Death	0 (0.0%)	
Progression Free Survival (weeks)	Median (95% CI)	12.7	(4.4, 31.3)
Progression Free Survival (months)	Median (95% CI)	2.9	(1.0, 7.2)

Source: Table 14.3.5.13 and Table 14.3.5.36 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set.
CI = confidence interval; PD = progressive disease.
Median of progression-free survival is estimated from Kaplan-Meier method.
95% CI is calculated based on log-log transformation.
Disease progression is defined as PD confirmed by Independent Overall Efficacy Review Committee.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-12 治験担当医師による評価に基づく無増悪生存期間（203 試験）（PPS）

	Event/Statistics	40 mg (N=46)	
Number of subjects, n (%)	Censored	21 (45.7%)	
	Last Tumor Assessment	21 (45.7%)	
	Any event	25 (54.3%)	
	Clinical PD	4 (8.7%)	
	Disease Progression	21 (45.7%)	
	Death	0 (0.0%)	
Progression Free Survival (weeks)	Median (95% CI)	24.1	(12.7, 48.1)
Progression Free Survival (months)	Median (95% CI)	5.6	(2.9, 11.1)

Source: Table 14.3.5.14 and Table 14.3.5.37 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
CI = confidence interval; PD = progressive disease.
Median of progression-free survival is estimated from Kaplan-Meier method.
95% CI is calculated based on log-log transformation.
Disease progression is defined as PD assessed by the investigator. Clinical PD is evaluated by investigator without imaging studies.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-13 再発、難治性及び不確定末梢性 T 細胞リンパ腫別の無増悪生存期間（203 試験）（PPS）

	Event/Statistics	40 mg	
Relapsed PTCL (N=28)			
Number of subjects, n (%)	Censored	15 (53.6%)	
	Last Tumor Assessment	15 (53.6%)	
	Any event	13 (46.4%)	
	Disease Progression	13 (46.4%)	
	Death	0 (0.0%)	
Progression Free Survival (weeks)	Median (95% CI)	24.1	(14.7, -)
Progression Free Survival (months)	Median (95% CI)	5.6	(3.4, -)
Refractory PTCL (N=18)			
Number of subjects, n (%)	Censored	7 (38.9%)	
	Last Tumor Assessment	7 (38.9%)	
	Any event	11 (61.1%)	
	Disease Progression	11 (61.1%)	
	Death	0 (0.0%)	
Progression Free Survival (weeks)	Median (95% CI)	9.6	(5.0, 58.1)
Progression Free Survival (months)	Median (95% CI)	2.2	(1.1, 13.4)
Undetermined PTCL (N=0)			
Number of subjects, n (%)	Censored	0 (0.0%)	
	Last Tumor Assessment	0 (0.0%)	
	Any event	0 (0.0%)	
	Disease Progression	0 (0.0%)	
	Death	0 (0.0%)	

Source: Table 14.3.5.15 and Table 14.3.5.38 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages are calculated based on the number of subjects in the PTCL category within the analysis set.
CI = confidence interval; PD = progressive disease; PTCL = peripheral T-cell lymphoma.
Median of progression-free survival is estimated from Kaplan-Meier method.
95% CI is calculated based on log-log transformation.
Disease progression is defined as PD confirmed by Independent Overall Efficacy Review Committee.
Subjects with relapsed, refractory, and undetermined PTCL are confirmed by Medical Expert.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-14 再発、難治性及び不確定末梢性 T 細胞リンパ腫別の治験担当医師による評価に基づく無増悪生存期間（203 試験）（PPS）

	Event/Statistics	40 mg	
Relapsed PTCL (N=28)			
Number of subjects, n (%)	Censored	15 (53.6%)	
	Last Tumor Assessment	15 (53.6%)	
	Any event	13 (46.4%)	
	Clinical PD	1 (3.6%)	
	Disease Progression	12 (42.9%)	
	Death	0 (0.0%)	
Progression Free Survival (weeks)	Median (95% CI)	24.1	(16.1, -)
Progression Free Survival (months)	Median (95% CI)	5.6	(3.7, -)
Refractory PTCL (N=18)			
Number of subjects, n (%)	Censored	6 (33.3%)	
	Last Tumor Assessment	6 (33.3%)	
	Any event	12 (66.7%)	
	Clinical PD	3 (16.7%)	
	Disease Progression	9 (50.0%)	
	Death	0 (0.0%)	
Progression Free Survival (weeks)	Median (95% CI)	11.6	(5.0, 58.1)
Progression Free Survival (months)	Median (95% CI)	2.7	(1.1, 13.4)
Undetermined PTCL (N=0)			
Number of subjects, n (%)	Censored	0 (0.0%)	
	Last Tumor Assessment	0 (0.0%)	
	Any event	0 (0.0%)	
	Clinical PD	0 (0.0%)	
	Disease Progression	0 (0.0%)	
	Death	0 (0.0%)	

Source: Table 14.3.5.16 and Table 14.3.5.39 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages are calculated based on the number of subjects in the PTCL category within the analysis set.
CI = confidence interval; PD = progressive disease; PTCL = peripheral T-cell lymphoma.
Median of progression-free survival is estimated from Kaplan-Meier method.
95% CI is calculated based on log-log transformation.
Disease progression is defined as PD assessed by the investigator. Clinical PD is evaluated by investigator without imaging studies.
Subjects with relapsed, refractory, and undetermined PTCL are confirmed by Medical Expert.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-15 治験担当医師による評価に基づく奏効期間（203 試験）（PPS）

	Event/Statistics	40 mg (N=46)	
The number of subjects with CR or PR, n (%)		24	
	Censored	15 (62.5%)	
	Any event	9 (37.5%)	
	Clinical PD	1 (4.2%)	
	Disease Progression	8 (33.3%)	
	Death	0 (0.0%)	
Duration of Response (weeks)	Median (95% CI)	40.3	(12.3, -)
Duration of Response (months)	Median (95% CI)	9.3	(2.8, -)

Source: Table 14.3.5.17 and Table 14.3.5.40 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects with either CR or PR in the analysis set.
CI = confidence interval; CR= complete response; PD = progressive disease; PR = partial response.
Median of duration of response is estimated from Kaplan-Meier method.
95% CI is calculated based on log-log transformation.
Disease progression is defined as PD assessed by the investigator. Clinical PD is evaluated by investigator without imaging studies.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-16 全生存期間（203 試験）（FAS）

	Event/Statistics	40 mg (N=49)	
Number of subjects, n(%)	Censored	33 (67.3%)	
	Death	16 (32.7%)	
Overall survival (weeks)	Median (95% CI)	99.1	(50.7, 99.1)
Overall survival (months)	Median (95% CI)	22.8	(11.7, 22.8)

Source: Table 14.3.5.1.2 and Table 14.3.5.33 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
CI = confidence interval.
Median of overall survival is estimated from Kaplan-Meier method.
95% CI is calculated based on log-log transformation.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-17 国別の全生存期間（203 試験）（PPS）

	Event/Statistics	40 mg	
Japan (N=34)			
Number of subjects, n(%)	Censored	23 (67.6%)	
	Death	11 (32.4%)	
Overall survival (weeks)	Median (95% CI)	99.1	(50.7, 99.1)
Overall survival (months)	Median (95% CI)	22.8	(11.7, 22.8)
Korea (N=12)			
Number of subjects, n(%)	Censored	9 (75.0%)	
	Death	3 (25.0%)	
Overall survival (weeks)	Median (95% CI)	71.7	(8.4, -)
Overall survival (months)	Median (95% CI)	16.5	(1.9, -)

Source: Table 14.3.5.2 and Table 14.3.5.35 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set.
CI = confidence interval.
Median of overall survival is estimated from Kaplan-Meier method.
95% CI is calculated based on log-log transformation.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-18 再発、難治性及び不確定末梢性 T 細胞リンパ腫別の全生存期間（203 試験）（PPS）

	Event/Statistics	40 mg	
Relapsed PTCL (N=28)			
Number of subjects, n (%)	Censored	20 (71.4%)	
	Death	8 (28.6%)	
Overall survival (weeks)	Median (95% CI)	99.1	(63.9, 99.1)
Overall survival (months)	Median (95% CI)	22.8	(14.7, 22.8)
Refractory PTCL (N=18)			
Number of subjects, n (%)	Censored	12 (66.7%)	
	Death	6 (33.3%)	
Overall survival (weeks)	Median (95% CI)	54.9	(14.3, -)
Overall survival (months)	Median (95% CI)	12.6	(3.3, -)
Undetermined PTCL (N=0)			
Number of subjects, n (%)	Censored	0 (0.0%)	
	Death	0 (0.0%)	

Source: Table 14.3.5.1.3 and Table 14.3.5.34 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages are calculated based on the number of subjects in the PTCL category within the analysis set.
CI = confidence interval; PTCL = peripheral T-cell lymphoma.
Median of overall survival is estimated from Kaplan-Meier method.
95% CI is calculated based on log-log transformation.
Subjects with relapsed, refractory, and undetermined PTCL are confirmed by Medical Expert.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-19 治験担当医師による評価に基づく完全奏効率（203 試験）（PPS）

		40 mg (N=46)	
Response	**Status/Response rate**	**n (%)**	**(95% CI)**
Best overall response	Complete Response rate (CR)	7 (15.2%)	(6.3, 28.9)
	Status		
	CR	7 (15.2%)	
	PR	17 (37.0%)	
	SD	11 (23.9%)	
	PD	11 (23.9%)	

Source: Table 14.3.5.12 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Complete response rate is defined as proportion of subjects with best overall response of CR.
For subjects who do not have overall response assessment of CR, PR, SD or PD, the investigator response assessments of Clinical PD may be included as the best overall response.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-20 治験担当医師による評価に基づく完全奏効期間（203 試験）（PPS）

	Event/Statistics	40 mg (N=46)	
The number of subjects with CR, n (%)		7	
	Censored	5 (71.4%)	
	Any event	2 (28.6%)	
	Clinical PD	0 (0.0%)	
	Disease Progression	2 (28.6%)	
	Death	0 (0.0%)	
Duration of Complete Response (weeks)	Median (95% CI)	-	(3.6, -)

Source: Table 14.3.5.19 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects with CR in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease.
Median of duration of complete response is estimated from Kaplan-Meier method.
Disease progression is defined as PD assessed by the investigator. Clinical PD is evaluated by investigator without imaging studies.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-21 治験担当医師による評価に基づく病勢コントロール率（203 試験）（PPS）

		40 mg (N=46)	
Response	**Status/Response rate**	**n (%)**	**(95% CI)**
Best overall response	Disease Control Rate (CR, PR or SD)	35 (76.1%)	(61.2, 87.4)
	Status		
	CR	7 (15.2%)	
	PR	17 (37.0%)	
	SD	11 (23.9%)	
	PD	11 (23.9%)	

Source: Table 14.3.5.21 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Disease control rate is defined as proportion of subjects with best overall response of CR, PR or SD.
For subjects who do not have overall response assessment of CR, PR, SD or PD, the investigator response assessments of Clinical PD may be included as the best overall response.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-22 治験担当医師による評価に基づく節性／節外性標的病変の総腫瘍サイズのベースラインからの最大変化（203 試験）（PPS）

Total Tumor Size of Nodal and Extranodal Target Lesion(mm^2)	**Statistic**	**40 mg (N=46)**
Baseline	n	44
	Mean	1568.3
	StD	1262.6
	Median	1091.5
	Minimum	187
	Maximum	5516
Best Tumor Size at post-baseline	n	44
	Mean	1081.4
	StD	1359.7
	Median	352.0
	Minimum	0
	Maximum	5387
The Best Change from Baseline	n	44
	Mean	-486.9
	StD	1160.3
	Median	-448.0
	Minimum	-5157
	Maximum	2440
The Best Percent Change from Baseline (%)	n	44
	Mean	-35.40
	StD	74.03
	Median	-54.23
	Minimum	-100.0
	Maximum	330.6

Source: Table 14.3.5.23 in CSR of Study HBI-8000-203
n = number of subjects.
StD = standard deviation.
Best change from baseline in tumor size is defined as the maximum reduction in the change of total tumor size of nodal and extranodal target lesions up to End of Treatment.
Only subjects with post baseline nodal and extranodal target lesion assessment are presented in this table.
Subjects [redacted] and [redacted] did not have post baseline assessment hence are not included in the analysis.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-23 治験担当医師による評価に基づく測定可能な節性／節外性標的病変及び皮膚病変における腫瘍縮小効果（203 試験）（PPS）

		40 mg	
Lesion	**Status/Response rate**	**n (%)**	**(95% CI)**
Measurable Nodal and Extranodal Target Lesion Response	Objective Response rate (CR or PR)	25 (58.1%)	(42.1, 73.0)
(N=43)	Status		
	CR	15 (34.9%)	
	PR	10 (23.3%)	
	SD	14 (32.6%)	
	PD	3 (7.0%)	
	NE	1 (2.3%)	
Skin Lesion Response (N=8)	Objective Response rate (CR or PR)	4 (50.0%)	(15.7, 84.3)
	Status		
	CR	2 (25.0%)	
	PR	2 (25.0%)	
	SD	3 (37.5%)	
	PD	1 (12.5%)	
	NE	0 (0.0%)	
	NA	0 (0.0%)	

Source: Table 14.3.5.26 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in each lesion category within the analysis set.
CI = confidence interval; CR = complete response; NA = not assessable; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.
95% exact binomial CI.
Objective response rate is defined as proportion of subjects with best overall response of CR or PR.
Three subjects are not included in the nodal and extranodal target lesion best overall response analysis; subjects [redacted], [redacted], and [redacted] did not have data collected for nodal and extranodal target lesion.
Data cut-off date: [redacted] 20[redacted]

表 2.7.3.6-24 治験担当医師による評価に基づく奏効までの期間（203 試験）（PPS）

	Event/Statistics	40 mg (N=46)	
Number of subjects, n (%)	CR or PR	24 (52.2%)	
Time to response (weeks)	Median (95% CI)	8.1	(8.1, 9.1)

Source: Table 14.3.5.29 in CSR of Study HBI-8000-203
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects with either CR or PR in the analysis set.
CI = confidence interval; CR = complete response; PR = partial response.
Median of time to response is estimated from Kaplan-Meier method.
95% CI is calculated based on log-log transformation.
Data cut-off date: [redacted] 20[redacted]

2.7.3.6.2 付録 2 選択・除外基準の比較

203 試験及び 201 試験の主な選択・除外基準の比較を表 2.7.3.6-25 に示した。

表 2.7.3.6-25 主な選択・除外基準の比較

Study HBI-8000-203	Study HBI-8000-201
選択基準	
以下の PTCL サブタイプを有することが病理組織学的又は細胞学的に診断された患者 • 非特定型末梢性 T 細胞リンパ腫（PTCL-NOS） • 血管免疫芽球性 T 細胞リンパ腫（AITL） • 未分化リンパ腫キナーゼ（ALK）陽性未分化大細胞リンパ腫（ALCL） • ALK 陰性 ALCL • 腸管症関連 T 細胞リンパ腫（EATL） • 肝脾 T 細胞リンパ腫（HSTCL） • 皮下脂肪織炎様 T 細胞リンパ腫（SPTCL）	組織学的又は細胞学的に NHL と診断された患者
抗がん剤による全身療法を 1 レジメン以上施行した後の再発又は難治性の疾患であり、患者に適切と思われる他の標準的治療法がない患者	標準的治療法が適さない患者
20 歳以上の男性又は女性	（203 試験に同じ）
ECOG PS が 0～2 である患者	（203 試験に同じ）
なし	以前に受けた化学療法、抗体又は放射線療法に関連するすべての毒性が Grade 1 以下（CTCAE v4.03）まで回復している患者（例外として、継続的に脱毛症がみられる患者については、CTCAE グレードに関係なく本治験に参加可能）
除外基準	
スクリーニング時に中枢神経系リンパ腫が認められた患者	中枢神経系浸潤の合併又は既往を有する、もしくは臨床的に疑われる患者
スクリーニング時に QTcF が>450 msec の男性、又は、QTcF が>470 msec の女性 先天性 QT 延長症候群、臨床的に重大な不整脈を有する患者、うっ血性心不全（NYHA 分類 III 又は IV）の既往を有する患者、又は治験薬投与開始前 6 ヵ月以内に急性心筋梗塞を発症した患者	スクリーニング時に QTcF が>450 msec の男性、又は、QTcF が>470 msec の女性 QT 延長症候群、治験薬投与開始前 6 ヵ月以内に慢性うっ血性心不全（NYHA 分類 III 又は IV）を発症した患者、心室性頻脈、心室細動、第 2～3 度の心ブロック、不安定狭心症、冠動脈形成又はステント留置、心筋梗塞、心筋症を有する患者
治験対象疾患以外の悪性腫瘍の既往を有する患者。ただし、根治目的の治療を受け、過去 5 年間に再発の兆候がみられていない場合は組入れ可能（下記に記載されている疾患は除く）。また、以下の悪性腫瘍の既往を有する患者で、根治目的の治療を受け、過去 2 年間に再発の兆候がみられていない場合は組入れ可能。 • 皮膚基底細胞がん • 皮膚有棘細胞がん • 子宮頚部上皮内がん • 乳房上皮内がん • 組織検査で偶然見つかった前立腺がん（TNM 分類：T1a 又は T1b）	悪性腫瘍の既往歴又は合併症を有する患者。ただし、無病期間 5 年以上の患者は組入れ可能。また、以下の悪性腫瘍の既往を有する患者で、当該腫瘍が完全に切除されて治療が成功している場合も除外対象とはならない。 • 皮膚基底細胞がん • 皮膚有棘細胞がん • 子宮頚部上皮内がん • 乳房上皮内がん • 組織検査で偶然見つかった前立腺がん（TNM 分類：T1a 又は T1b） • 内視鏡的粘膜切除術又は内視鏡的粘膜下層剥離術が行われた早期胃がん

Study HBI-8000-203	Study HBI-8000-201
• 内視鏡的粘膜切除術又は内視鏡的粘膜下層剥離術が行われた早期胃がん • 根治目的の治療を受けた組織型が分化型の甲状腺がん（乳頭がん等）	
同種幹細胞移植を受けた患者	（203 試験に同じ）
臓器移植を受けた患者（自家造血幹細胞移植を除く）	臓器移植を受けた患者
治験薬投与開始前 12 週間（84 日間）以内に自家幹細胞移植を受けた患者	（203 試験に同じ）
なし	造血骨髄の≥30%に及ぶ広範囲を対象とする放射線療法歴を有する患者。ただし、自家幹細胞移植の前処置として行われた全身照射は除く。
コントロール不良の併発感染を有する患者	（203 試験に同じ）
HBs 抗原が陽性又は HCV 抗体が陽性の患者。 HBs 抗原が陰性であっても、B 型肝炎コア抗体、HBs 抗体が陽性の場合には HBV DNA 検査（リアルタイム PCR 法）を実施する。HBV DNA 検査で陽性の患者は除外する。	（203 試験に同じ）
HIV 検査陽性の既往。又は既知の後天性免疫不全症候群の既往を有する患者	HIV 抗体の血清陽性の患者

CTCAE = 有害事象共通用語規準; ECOG = 米国東海岸がん臨床試験グループ; HBs = B 型肝炎表面; HBV = B 型肝炎ウイルス; HCV = C 型肝炎ウイルス; HIV = ヒト免疫不全ウイルス; NHL = 非ホジキンリンパ腫; NYHA = ニューヨーク心臓協会; PCR = ポリメラーゼ連鎖反応; PS = パフォーマンスステータス; PTCL = 末梢性 T 細胞リンパ腫; QTcF = Fridericia 法の補正式を用いた心拍数の補正 QT 間隔; TNM =腫瘍-リンパ節-転移

2.7.3.6.3 付録 3 203 試験で用いた腫瘍縮小効果判定基準

203 試験で用いた腫瘍縮小効果判定基準を本項に記載した。

2.7.3.6.3.1 効果判定法

総合効果はスクリーニング時の評価及びそれ以降のサイクルの Day 1 の評価に基づき判定した。

節性病変及び節外性病変を評価する CT 等の画像検査を、8 週目の終了時、及びサイクル 1 の Day 1 以降は 8 週間（±1 週間）ごとに実施した。ただし、被験者に PD の臨床徴候及び症状を認めた場合、又は許容できない毒性が発現した場合は、必要に応じて早期に腫瘍縮小効果を評価した。PD が記録される前に治験薬の投与を中止する被験者で、かつ治療終了時来院の時点で直近の腫瘍評価から 30 日超が経過している場合、腫瘍評価は治療終了時に実施することとした。これらの被験者において、当該被験者が治験参加に対する同意を撤回しない限り、PD、又は新たながん治療の開始のいずれか早い方まで約 3 ヵ月ごと（±2 週間）にさらなる腫瘍評価を実施することとした。

2.7.3.6.3.1.1 スクリーニング時の評価

スクリーニング時の身体検査は、病変サイズの定量的評価とみなさないこととした。疾患の病変は、画像検査（CT 又は PET-CT）、骨髄検査（穿刺又は生検）及び皮膚の評価で判定した。消化管病変が疑われる場合、内視鏡検査を実施し、必要に応じて生検も実施することとした。

すべての病変を以下に分類した。

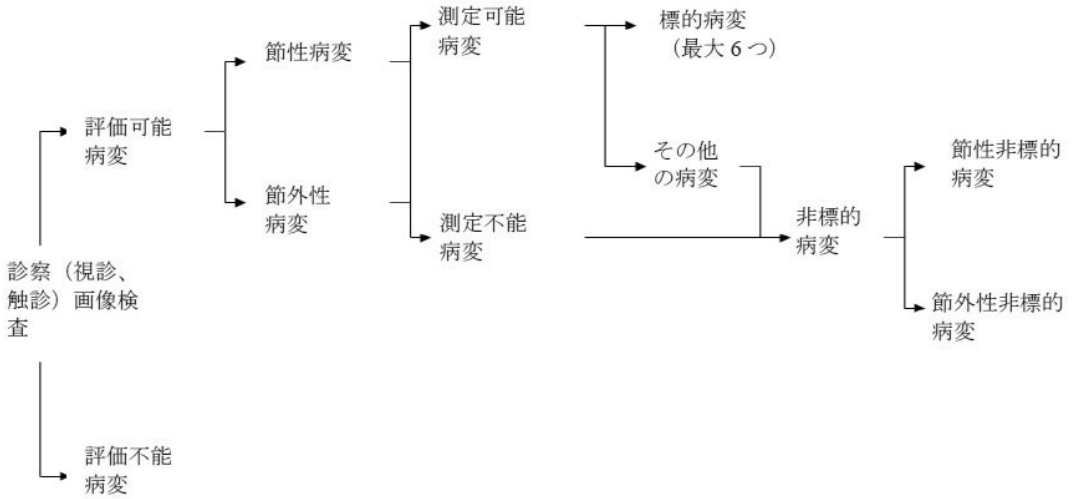
- 効果判定の対象となる病変（以下、評価可能病変）
- 効果判定の対象とならない病変（以下、評価不能病変）

さらに、評価可能病変を以下のいずれかに分類した。

- 測定可能病変
- 測定不能病変

測定可能病変のうち、標的病変として最大 6 つまでを選択した。標的病変として選択しなかった測定可能病変及び測定不能病変は非標的病変とした。

図 2.7.3.6-1 病変の選択



2.7.3.6.3.1.1.1 節性／節外性病変の評価

節性病変及び節外性病変は、リンパ腫に対する効果判定基準の改訂版［Cheson 2014］に従って評価した。

2.7.3.6.3.1.2 画像検査法

治験薬の投与開始前に、可能であれば 5 mm のスライス厚で（頸部画像については 2.5～5 mm のスライス厚が望ましい）で頸部、胸部、腹部及び骨盤の CT 画像による評価を行った。ベースライン時及び各評価時に同じ画像技術を使用することとした。PET-CT を推奨するが、必須とはしなかった。

2.7.3.6.3.1.2.1 効果判定の対象になる病変（評価可能病変）の定義

スクリーニング時の CT 断面像での横断方向の最大径が 1.5 cm を超える節性病変（リンパ節腫大等）及び画像検査で経過を追跡できる節外性病変を、評価可能病変と定義した。

2.7.3.6.3.1.2.2 効果判定の対象にならない病変（評価不能病変）の定義

スクリーニング時の CT 断面像で横断方向の最大径が 1.5 cm 以下の節性病変及び画像検査で経過を追跡できない節外性病変を、評価不能病変と定義した。

2.7.3.6.3.1.2.3 測定可能病変の定義（節性病変及び節外性病変）

評価可能病変のうち、以下の条件のいずれも満たす病変を測定可能病変とした。

- 節性病変については CT 断面像で横断方向の最大径が 1.5 cm を超える、また節外性病変では 1.0 cm を超える
- CT 断面像で 2 方向の径（横断方向の最大径及びその直交する径）が明らかに測定可能

2.7.3.6.3.1.2.4 測定不能病変の定義

評価可能病変のうち、以下の条件に該当する病変を測定不能病変とした。

- リンパ節腫大：CT 断面像で横断方向の最大径が 1.5 cm を超えるが、2 方向の径（横断方向の最大径及びその直交する径）が明らかに評価できない病変
- 節外性病変：画像検査で経過を追跡できるが、測定可能病変の定義を満たさないすべての病変

2.7.3.6.3.1.2.5 奏効中に複数の結節に分かれた節性病変又は節外性病変

融合した節性腫瘤が複数の個別の結節に分かれた場合、それらの結節のそれぞれ直交する径の積（PPD）を合計して分裂病変の PPD とし、腫瘍縮小効果を測定するために残りの病変の PPD の和にこの PPD を加算することとした。これらの個々の結節のいずれか又はすべてがその後増大した場合、進行を特定するためにそれぞれの結節の最低値を用いることとした。

2.7.3.6.3.1.2.6 進行中に複数の結節が融合した節性病変又は節外性病変

複数の標的リンパ節が融合した場合、現在融合している腫瘤の PPD を各結節の PPD の和と比較し、融合腫瘤の PPD が個々の結節の和と比較して 50%を超えて増加している場合は、病勢進行を指摘する必要があることとした。横断方向の最大径及び短軸径は進行の特定には必要ないこと

とした。

2.7.3.6.3.1.3 標的病変の選択

標的病変は、節性病変か節外性病変かを問わず、以下に従って測定可能病変から選択した。

- 同一の測定方法で継続して正確に測定することに適している病変
- CT 断面像で横断方向の最大径が大きい順に選択された最大 6 つの病変。測定可能病変の数が 6 つ未満の場合、すべての測定可能病変を選択した。
- 結節は体の異なる部位のものが望ましく、該当する場合、縦隔膜及び後腹膜を含むこと。

横断方向の最大径（cm）とその最大径に対して直交する短軸径（cm）を測定した。その 2 つの径の積（PPD）は、その病変の横断方向の最大径とその直交する径の交差積である。すべての標的病変の PPD の和［二方向積和（SPD)］をスクリーニング時に算出した。

2.7.3.6.3.1.4 非標的病変の定義及び選択

測定可能病変のうち標的病変として選択されなかった病変及び測定不能病変を非標的病変とした。

非標的病変は節性の非標的病変及び節外性の非標的病変に分けて評価した。消化管の内視鏡検査で腫瘍病変が特定された場合、当該病変を節外性の非標的病変として評価することとした。

2.7.3.6.3.1.5 皮膚病変の評価

皮膚に腫瘍病変を認めた場合、当該病変は非標的病変とみなした。有効性をモニタリングすることのできる皮膚病変は追跡することとした。治験担当医師は必要に応じて治験実施医療機関の皮膚科専門医に助言を求めてもよいこととした。

皮膚病変の有無を視診で判断することが難しい場合は、生検を実施して病理組織学的に診断を行うこととした。

皮膚病変は Severity-Weighted Assessment Tool［Stevens 2002］改訂版（mSWAT）に準じて評価した。

2.7.3.6.3.1.6 Modified Severity-Weighted Assessment Tool（mSWAT）による評価

人体の体表面積（BSA）全体を 100 とした場合の各部位の体表面積（%BSA）の総計を表 2.7.3.6-26 と図 2.7.3.6-2 に規定した（例：頭部 7、頸部 2、及び躯幹前部 13)。

部位ごとに、各病変タイプ（Patch、Plaque、腫瘤又は潰瘍）及び正常皮膚が占める%BSA を判定した後、病変タイプごとの全体表面積に占める割合（%TBSA）を算出した。さらに、病変タイプごとの%TBSA にそれぞれ重み付け係数を乗じ、これらの積を合計したもの（0～400）を mSWAT スコアとした（下式参照)。

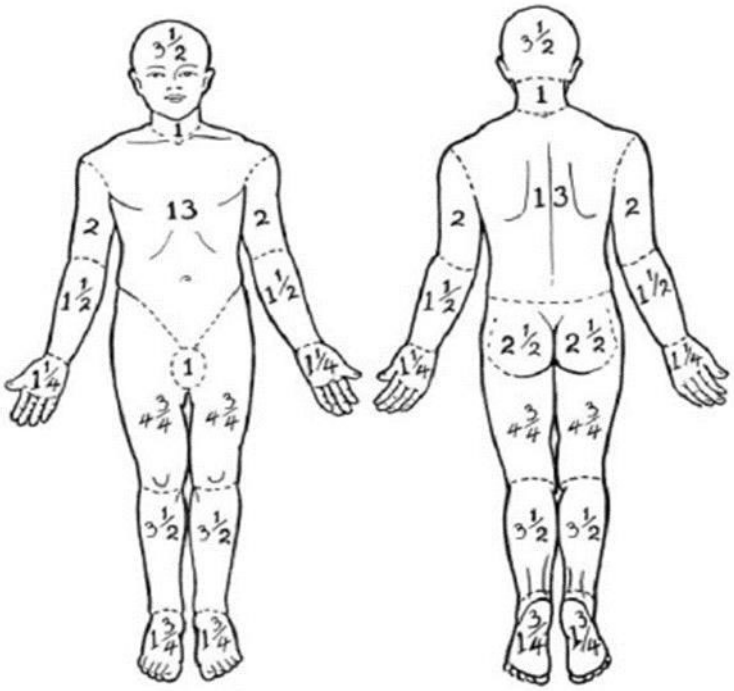
mSWAT スコア ＝（Patch の%TBSA × 1）＋（Plaque の%TBSA × 2）＋（腫瘤及び潰瘍の%TBSA × 4）

表 2.7.3.6-26 Modified Severity-Weighted Assessment Tool (mSWAT)

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch*	Plaque**	Tumor***
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion %BSA				
Weighting factor				
Subtotal lesion BSA × weighting factor				

BSA = body surface area; mSWAT = modified Severity-Weighted Assessment Tool
NOTE. mSWAT score equals summation of each column line.
*Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.
**Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
***Any solid or nodular lesion >1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

図 2.7.3.6-2 人体各部位の%BSA



2.7.3.6.3.1.7 脾腫の有無

リンパ球の浸潤によって引き起こされると考えられる脾腫の発現の有無を CT で評価した。陽性と判断するには、脾臓の縦方向の長さが CT にて 13 cm を超えていなければならないこととした。

2.7.3.6.3.1.8 骨髄浸潤の評価

骨髄浸潤を PET-CT、骨髄穿刺又は生検で評価した。骨髄評価を選択する際は、結果を以下に分類した。

- 陽性：明らかな異常リンパ球浸潤又は構築異常等の悪性所見がある
- 不確定：異常リンパ球浸潤又は構築異常を伴わないリンパ球集簇の増加が認められる
- 陰性：リンパ球集簇の所見がない又はあってもごく少数である

2.7.3.6.3.1.9 治験薬投与後の評価

スクリーニングと同じ方法で画像検査を行った。

2.7.3.6.3.1.9.1 標的病変の評価

標的病変の SPD の縮小率（A）と増大率（B）を以下の式により算出し、腫瘍縮小効果を判定した。

$$（A）= \frac{スクリーニング時の（C）- 評価時の（C）}{スクリーニング時の（C）} \times 100$$

$$（B）= \frac{評価時の（C）- （C）の最低値\ ^{*1}}{（C）の最低値\ ^{*1}} \times 100$$

*1：治験期間中（スクリーニングを含む）に得られた（C）の最低値

（C）= SPD

2.7.3.6.3.1.9.2 効果判定基準

表 2.7.3.6-27 効果判定基準の要約（Cheson 基準 2014）

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to <1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Response and Site	PET-CT-Based Response	CT-Based Response
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. When a lesion is too small to measure on CT, assign 5 × 5 mm as the default value When no longer visible, 0 × 0 mm For a node >5 × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following PPD progression:
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions <2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be

Response and Site	PET-CT-Based Response	CT-Based Response
	of new lesions, biopsy or interval scan may be considered	unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron-emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.
*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease, and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., gastrointestinal tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).
†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.
[Cheson 2014]

2.7.3.6.3.1.9.3 mSWAT による皮膚病変の評価

mSWAT を用いた皮膚病変に対する腫瘍縮小効果の判定は以下に従って実施した。

- CR：皮膚病変が 100%消失*
- PR：皮膚疾患がベースラインから 50～99%の割合で減少し、新たな病変が認められない
- SD：皮膚疾患がベースラインから 25%未満の割合で増加～50%未満の割合で減少し、新たな病変が認められない
- PD：ベースラインから 25%以上の mSWAT スコアの増加又は新たな皮膚腫瘤**又は効果減弱、CR 又は PR の患者で、mSWAT スコアが、最小値とベースラインスコアの 50%の合計値よりも増加している

* 残存病変と正常皮膚組織との区別が困難な場合には、生検を行い皮膚病変の消失を確認後に CR を判定した

** 皮膚腫瘤：≥1 cm、深達性又は垂直方向への増殖を示す結節性病変

ツシジノスタット
ハイヤスタ錠 10mg

第 2 部 CTD の概要

2.7 臨床概要
2.7.4 臨床的安全性の概要

Huya Japan 合同会社

略号一覧表

略語・用語	内容
AITL	angioimmunoblastic T-cell lymphoma 血管免疫芽球性 T 細胞リンパ腫
ALT	alanine aminotransferase アラニンアミノトランスフェラーゼ
ALP	alkaline phosphatase アルカリホスファターゼ
AST	aspartate aminotransferase アスパラギン酸アミノトランスフェラーゼ
ATC	Anatomical Therapeutic Chemical 解剖治療化学分類
ATL	adult T-cell lymphoma 成人 T 細胞白血病リンパ腫
BMI	body mass index 体格指数
CR	complete response 完全奏効
CSR	clinical study report 治験総括報告書
CT	computerised tomography コンピュータ断層撮影
CTCAE	Common Terminology Criteria for Adverse Events 有害事象共通用語規準
CTD	コモン・テクニカル・ドキュメント Common Technical Document
CYP	cytochrome P450 チトクロム P450
DLT	dose-limiting toxicity 用量制限毒性
DSUR	development safety update report 治験安全性最新報告
EBV	Epstein-Barr virus エプスタイン・バーウイルス
EBER	EBV-encoded small RNA EBV 小分子 RNA
ECOG	Eastern Cooperative Oncology Group 米国東海岸がん臨床試験グループ
G-CSF	granulocyte-colony stimulating factor 顆粒球コロニー形成刺激因子
GGT	gamma-glutamyl transpeptidase γ-グルタミルトランスフェラーゼ
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use 医薬品規制調和国際会議
LDH	lactate dehydrogenase 乳酸脱水素酵素
MedDRA	Medical Dictionary for Regulatory Activities ICH 国際医薬用語集
NCI	National Cancer Institute 米国国立がん研究所
NHL	non-Hodgkin's lymphoma 非ホジキンリンパ腫
NOS	not otherwise specified 非特定型

略語・用語	内容
PD	progressive disease 進行
PK	pharmacokinetic(s) 薬物動態
PS	performance status パフォーマンスステータス
PSUR	periodic safety update report 定期的安全性最新報告
PR	partial response 部分奏効
PT	preferred term 基本語
PTCL	peripheral T-cell lymphoma 末梢性 T 細胞リンパ腫
PTCL-NOS	peripheral T-cell lymphoma, not otherwise specified 非特定型末梢性 T 細胞リンパ腫
QTc	QT interval corrected for heart rate 心拍数で補正した QT 間隔
QTcF	QT interval corrected for heart rate using Fridericia's method Fridericia 法の補正式を用いた心拍数の補正 QT 間隔
SD	stable disease 安定
SMQ	Standard MedDRA Query 標準 MedDRA 検索式
SOC	system organ class 器官別大分類

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2.7.4 臨床的安全性の概要

2.7.4.1 医薬品への曝露

2.7.4.1.1 総括的安全性評価計画及び安全性試験の記述

2.7.4.1.1.1 安全性データを供する試験の概要

本項では、ツシジノスタット（HBI-8000 又は中国では chidamide）（以下、本薬）の安全性を要約する。本薬の安全性の評価には、再発又は難治性の末梢性 T 細胞リンパ腫（PTCL）患者を対象に、本薬の有効性、安全性及び薬物動態（PK）を評価した日本人／韓国人第 2b 相試験（HBI-8000-203 試験、以下 203 試験）（5.3.5.2-1）、並びに PTCL を含む非ホジキンリンパ腫（NHL）患者を対象に、本薬の安全性、忍容性、PK 及び予備的な有効性を評価した日本人第 1 相試験（HBI-8000-201 試験、以下 201 試験）（5.3.3.2-1）から得られた安全性データを評価資料として用いた。203 試験では、28 日の投与サイクルで本薬 40 mg を週 2 回経口投与した。201 試験では、28 日の投与サイクルで本薬 30 又は 40 mg を週 2 回経口投与した。

そのほか、安全性データの応用可能性を判断した主な点は、人種［日本人第 2b 相試験（HBI-8000-210 試験、以下 210 試験）］、疾患の種類［中国人第 2 相試験（TG0902CDM 試験、以下 902 試験）］は PTCL、210 試験は PTCL の一病型である成人 T 細胞白血病リンパ腫（ATL）が対象疾患］、及び用法（これらの試験すべてで本薬を単剤投与）であった。

902 試験（5.3.5.4-1/TG0902CDM p2a、5.3.5.4-2/TG0902CDM p2b）は、安全性の結果が評価試験の安全性プロファイルの評価に応用可能と考えられることから、参考資料として本薬の安全性評価に用いた。また、210 試験は日本人を対象に本薬の臨床推奨用量で実施した試験であり、再発又は難治性の ATL を適応症とした本薬の初回申請で既に提出済みである（初回申請資料 5.3.5.2-1）。210 試験は本申請のデータパッケージには含まれないが、その安全性の結果もその他の参考として本項に再掲した。

本薬の全般的な安全性評価は、個々の試験から得られた安全性データに基づいて評価した。

本薬の安全性評価に用いた試験を表 2.7.4.1-1 に示す。

表 2.7.4.1-1 安全性評価に用いた臨床試験

試験番号	試験の相	実施国	目的	試験デザイン	対象	計画した用法・用量	施設数／安全性評価対象被験者数	試験期間	CTD 番号
評価試験									
HBI-8000-203	2b	日本／韓国	PK 有効性 安全性	非盲検、単一群	再発又は難治性 PTCL 患者	40 mg を週 2 回経口投与 1 サイクル 28 日	31 施設／55 例 （日本人 39 例、韓国人 16 例）	2017 年 3 月 [redacted] 日～20[redacted] 年 [redacted] 月 [redacted] 日（主解析のデータカットオフ日、試験継続中）	5.3.5.2-1
HBI-8000-201	1	日本	PK 安全性	非盲検、用量漸増	標準的治療法が適さない NHL 患者（PTCL 患者を含む）	30、40 又は 50 mg を週 2 回経口投与 1 サイクル 28 日	8 施設／14 例 （30 mg：7 例、40 mg：7 例）	2014 年 6 月 [redacted] 日～2016 年 10 月 [redacted] 日	5.3.3.2-1
参考試験									
TG0902CDM	2	中国	PK 有効性 安全性	探索的試験： 非盲検、無作為化、多施設 ピボタル試験： 非盲検、非無作為化、単一群、多施設	再発又は難治性 PTCL 患者	探索的試験： 30 又は 50 mg 週 2 回経口投与を 2 週間連続投与後 1 週間休薬 1 サイクル 6 週間 ピボタル試験： 30 mg 週 2 回経口投与（休薬期間なし） 1 サイクル 6 週間	探索的試験： 13 施設／19 例 （30 mg：9 例、50 mg：10 例） ピボタル試験： 15 施設／83 例	2009 年 3 月 [redacted] 日～2012 年 9 月 [redacted] 日（最後に組み入れた被験者のデータカットオフ日）	探索的試験 5.3.5.4-1 ピボタル試験 5.3.5.4-2

CTD = コモン・テクニカル・ドキュメント; NHL = 非ホジキンリンパ腫; PK = 薬物動態; PTCL = 末梢性 T 細胞リンパ腫

2.7.4.1.1.1.1 日本人／韓国人第 2b 相試験（203 試験）（評価試験）

本試験は、日本人及び韓国人の再発又は難治性 PTCL 患者を対象に本薬の安全性、有効性及び PK を評価した第 2b 相、非盲検、単一群試験である。本試験では、通常の食事から約 30 分後に本薬 40 mg を週 2 回経口投与した。試験デザインの詳細は 2.7.3.1.1 項に示した。

2.7.4.1.1.1.2 日本人第 1 相試験（201 試験）（評価試験）

本試験は、日本人の NHL 患者（ATL 患者を含む）を対象に本薬の安全性、忍容性、PK 及び予備的な有効性を評価した第 1 相、非盲検、用量漸増試験である。本試験では、28 日の投与サイクルで、朝食後、本薬を 30 mg、40 mg 又は 50 mg の用量で週 2 回経口投与するものとした。試験デザインの詳細は 2.7.3.1.2 項に示した。

2.7.4.1.1.1.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

本試験は、日本人の再発又は難治性 ATL 患者を対象に本薬の有効性及び安全性を評価した第 2b 相、非盲検、単一群試験である。本試験では、通常の食事から約 30 分後に本薬 40 mg を週 2 回経口投与した。投与の間隔は 3～4 日、28 日の投与サイクルとした。許容できない有害事象が発現した場合、用量減量を 2 回まで可能とした。病勢進行が確認されるか、治験薬の適切な休薬、減量又は最適な支持療法の実施にかかわらず許容できない毒性が認められるまで、被験者は治験薬の投与を継続するものとした。

2.7.4.1.1.1.4 中国人第 2 相試験（902 試験）（参考試験）

本試験は、中国の Chipscreen 社が、中国人の再発又は難治性 PTCL 患者を対象に本薬の安全性、有効性及び PK を評価した第 2 相、非盲検、多施設共同試験であり、探索的試験及びピボタル試験の 2 つのステージから成る。

探索的試験は次のステージであるピボタル試験の推奨用法・用量を決定するためにデザインされた試験であった。探索的試験では、被験者を 30 mg 投与又は 50 mg 投与に無作為に割り付け、本薬を週 2 回 2 週間連続で経口投与した後、1 週間休薬した。探索的試験の安全性、忍容性及び有効性の結果を総合的に検証し、ピボタル試験では推奨用法・用量を本薬 30 mg の週 2 回投与、休薬期間なし、デザインを単一群、非無作為化試験として本薬の有効性及び安全性を評価した。探索的試験、ピボタル試験ともに投与サイクルは 6 週とした。病勢進行が認められるか、安全性上の懸念から試験を中止するまで、被験者は治験薬投与を継続した。

2.7.4.1.1.2 安全性データの収集及び評価方法

本薬を 1 回以上投与されたすべての被験者を安全性解析対象集団に含めた。本項以降、評価試験の 203 試験及び 201 試験、並びに参考試験の 902 試験から得られた安全性データを安全性評価の主要なデータとして提示する。また、210 試験は再発又は難治性の ATL を対象とした本薬の初回申請で既に提出済みであり本申請の臨床データパッケージには含まれないが、その安全性の結果も本薬投与時の安全性評価のその他の参考として簡潔に示す。

201 試験については、本申請の推奨用量である本薬 40 mg の安全性を評価するため、全体の集計だけでなく 40 mg コホートのみ集計した結果についても提示した。203 試験では、日本人患者における安全性を評価するため、全被験者を対象とした全体集団に加え、日本人集団の安全性デ

ータも提示した。902 試験では、各ステージ、すなわち探索的試験及びピボタル試験の安全性データをそれぞれ提示した。

2.7.4.1.1.2.1 有害事象

2.7.4.1.1.2.1.1 有害事象の定義

有害事象とは、医薬品の投与又は治療法と時間的に関連する、あらゆる好ましくない意図せぬ徴候（臨床検査値の異常等）、症状又は疾病を指す。医薬品の投与又は治療法との因果関係は問わない。

203 試験及び 210 試験では、医薬品規制調和国際会議（ICH）国際医薬用語集（MedDRA）version 21.1、201 試験では version 19.1 を用いて有害事象を分類し、同 version の日本語版（MedDRA/J）で日本語に読み替えた。

902 試験では、MedDRA/J version 21.1 及び米国国立がん研究所（NCI）有害事象共通用語規準（CTCAE）version 3.00 を用いて有害事象を日本語に読み替えた。

2.7.4.1.1.2.1.2 有害事象の収集

203 試験及び 201 試験（並びに 210 試験）では、同意取得から治療終了評価時まで有害事象を収集することとした。治験治療下で発現した有害事象を評価するため、安全性の解析には、治験薬の初回投与から治療終了評価時まで又はデータカットオフ日までに新たに発現又は悪化した有害事象を用いた。本薬の投与を中止し別の抗がん剤治療を開始した後に発現した有害事象は、安全性の解析から除外した。ただし、201 試験では本薬投与中止後に他の抗がん剤による治療開始の報告が漏れていた被験者がいたため（5.3.3.2-1/HBI-8000-201/CSR/11.2.5.3 項）、これらの被験者から収集した有害事象には他の抗がん剤開始後に発現したものが含まれた。これらの事象は、有害事象一覧（Listing）に治験薬と関連性のない事象として記載されている。

203 試験（及び 210 試験）では、電子症例報告書の有害事象の「治験薬に対する措置」及び「転帰」の情報はデータベースロックまで施設での更新が許容されていたため、有害事象一覧（Listing）はデータカットオフ日以降のデータを含んでいる（5.3.5.2-1/HBI-8000-203/CSR/11.4.2.3 項、初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/11.4.2.3 項）。

902 試験では、投与期間中、すなわち、治験薬の初回投与後から最終来院日までの有害事象を収集し、これらすべてを安全性解析の対象とした。本試験では、休薬に至った有害事象を集計しておらず、用量調整に至った有害事象の集計結果のみ評価に含めた。

有害事象を発現した被験者の割合を器官別大分類（SOC）別及び基本語（PT）別に要約した。また、治験薬と関連性のある有害事象、重症度別（最悪 NCI CTCAE Grade 3 以上）の有害事象、治験薬の投与中止もしくは休薬又は減量に至った有害事象、重篤な有害事象、及び死亡例についても要約した。203 試験（及び 210 試験）では、本薬投与期間中の有害事象を発現日に基づき、投与開始後 4 週未満、4 週から 16 週未満まで 4 週ごと、16 週以上に要約し、発現時期別に評価した。

血液学的有害事象の評価では、同じ血液学的有害事象を表す異なる PT をグループ化して検討した。例えば、血小板数減少は血小板減少症に含めた。203 試験（及び 210 試験）の有害事象（注目すべき有害事象を除く）の集計表では、表 2.7.4.1-2 に示すように、同じ血液学的有害事象を表す PT を、SOC「血液およびリンパ系障害」の中の 1 つの PT にまとめて集計した。なお、有害事象の一覧表では、そのようなグループ化した PT ではなく、報告事象名に基づき MedDRA でコー

ディングした PT をそのまま掲載している。201 試験では、血液学的有害事象（注目すべき有害事象）の集計表のみ表 2.7.4.1-3 に示すように同じ血液学的有害事象を表す異なる PT をグループ化して集計した。なお、本概要ではグループ化した血液学的有害事象には星印（*）を付記した。

表 2.7.4.1-2 グループ化した血液学的有害事象（203 試験及び 210 試験）

グループ化した血液学的有害事象	グループに含まれる PT		
血小板減少症*	血小板減少症	血小板数減少	-
好中球減少症*	好中球減少症	好中球数減少	顆粒球減少症
白血球減少症*	白血球減少症	白血球数減少	-
リンパ球減少症*	リンパ球減少症	リンパ球数減少	-
貧血*	貧血	ヘモグロビン減少	-

表 2.7.4.1-3 グループ化した血液学的有害事象（201 試験）

グループ化した血液学的有害事象	グループに含まれる PT	
血小板減少症*	血小板減少症	血小板数減少
好中球減少症*	好中球減少症	好中球数減少
白血球減少症*	白血球減少症	白血球数減少
貧血*	貧血	ヘモグロビン減少

2.7.4.1.1.2.1.3 有害事象の重症度

有害事象の重症度は、203 試験及び 201 試験（並びに 210 試験）では NCI CTCAE の version 4.03、902 試験では version 3.00 に従って判定した。

2.7.4.1.1.2.1.4 治験薬との因果関係

治験薬と有害事象の因果関係は、203 試験及び 201 試験（並びに 210 試験）では「明らかに関連あり」、「おそらく関連あり」、「関連があるかもしれない」、「おそらく関連なし」又は「関連なし」に分類し、902 試験では「明らかに関連あり」、「関連があるかもしれない」、「おそらく関連なし」、「関連なし」又は「判定不能」に分類した。

203 試験及び 201 試験（並びに 210 試験）では、「明らかに関連あり」、「おそらく関連あり」又は「関連があるかもしれない」と判定された事象は、治験薬との因果関係が否定できないため、「治験薬と関連性のある有害事象」とみなした。902 試験では、「明らかに関連あり」、「関連があるかもしれない」又は「判定不能」と判定された事象を副作用（ADR）、すなわち「治験薬と関連性のある有害事象」とみなした。

2.7.4.1.1.2.1.5 許容できない毒性（有害事象）に対する管理及び用量変更

203 試験（及び 210 試験）では、各治験実施計画書で許容できない毒性を定義した。各治験実施計画書には、許容できない毒性を血液学的事象及び非血液学的事象に分けて設定した用量調整ガイドライン（表 2.7.4.1-4）を示し、それに従って本薬を休薬又は減量することによって許容できない毒性を管理した。用量の減量は 2 回までとした（40 mg から 30 mg、その後 30 mg から 20 mg への減量）。用量を 2 回減量したにもかかわらず、許容できない毒性が再発した場合、治験薬の投与を完全に中止し、投与終了後の追跡調査を実施した。合併症のない血液学的有害事象など、治験薬の休薬を要する毒性が 2 回発現した場合、治験薬投与の再開時に減量することとした。

201 試験及び 902 試験では、それぞれ表 2.7.4.1-5 及び表 2.7.4.1-6 に示した各治験実施計画書

の規定に従い、用量調整及び休薬を実施した。201 試験及び 902 試験のピボタル試験では用量の減量は 1 回までとした。902 試験の探索的試験では用量の減量は 2 回まで可能とした（開始用量から 25 mg、その後 25 mg から 20 mg への減量）。

表 2.7.4.1-4 用量調整ガイドライン（203 試験及び 210 試験）

	有害事象の詳細	休薬と用量減量の有無
血液学的有害事象 - 合併症なし	• 観察時に Grade 3 又は Grade 4 の好中球減少症	治験薬の投与を中断し、G-CSF の投与を開始する。2 週間以内に Grade 1 以下に回復した場合は同用量で投与を再開する。
	• 観察時に Grade 3 又は Grade 4 の血小板減少症	治験薬の投与を中断する。2 週間以内に Grade 1 以下に回復した場合は同用量で投与を再開する。 2 週間以内に回復が認められない場合、治験薬の投与を中止する。
血液学的有害事象 - 合併症あり	• 増殖因子の最適な支持的投与を受けたにもかかわらず、7 日間を超えて持続する Grade 4 の無熱性好中球減少症 • Grade 3 以上の発熱性好中球減少症又は好中球減少性感染 • 臨床的に重大な出血を伴う Grade 3 以上の血小板減少症、又は血小板輸血を要する Grade 3 以上の血小板減少症	治験薬の投与を中断する。2 週間以内に Grade 1 以下に回復した場合は用量を減量して投与を再開する（40 mg から 30 mg、又は 30 mg から 20 mg への減量）。 2 週間以内に回復が認められない場合、治験薬の投与を中止する。
非血液学的有害事象（臨床検査値の評価が臨床的に重大でないものを除く）	Grade 3	治験薬の投与を中断する。2 週間以内に Grade 1 以下に回復した場合は用量を減量して投与を再開する（40 mg から 30 mg、又は 30 mg から 20 mg への減量）。該当する場合は適切な予防措置を取る。 2 週間以内に回復が認められない場合、治験薬の投与を中止する。
	Grade 4	治験薬の投与を中止する。

G-CSF = 顆粒球コロニー形成刺激因子

表 2.7.4.1-5 用量調整及び休薬（201 試験）

サイクル	有害事象の詳細	用量調整及び休薬
すべてのサイクル	• Grade 4 の血液毒性 [a] • Grade 3 の発熱性好中球減少症 • 臨床的に重大な出血を伴う Grade 3 の血小板減少症 • Grade 3 以上の非血液毒性 [b]	毒性が Grade 1 以下のレベルに回復するまで治験薬の投与を中断する。 2 週間以内に Grade 1 以下に回復した場合は用量を減量して投与を再開する。 2 週間以内に回復が認められない場合、治験薬の投与を中止する。
	• Grade 3 の QTcF 延長	用量減量又は投与中断を行うことなく、当該被験者の治験を中止する。
サイクル 1	• 3 日間継続して Grade 1 の心筋トロポニン I（又はトロポニン T）増加	トロポニン I（又はトロポニン T）が基準値の範囲に回復するまで治験薬の投与を中断する。 投与中断後 3 日間以内にトロポニン I（又はトロポニン T）が基準値の範囲に回復した場合は用量を減量して投与を再開する。 3 日間以内に回復が認められない場合、治験薬の投与を中止する。

サイクル	有害事象の詳細	用量調整及び休薬
サイクル 2 以降	• Grade 1 の心筋トロポニン I(又はトロポニン T）増加	トロポニン I（又はトロポニン T）が基準値の範囲に回復するまで治験薬の投与を中断／スキップする。

QTcF = Fridericia 法の補正式を用いた心拍数の補正 QT 間隔
a: Grade 4 の好中球減少症及び Grade 4 の血小板減少症を含む
b: 以下に該当する場合は除く。(1）適切な下痢治療を行う前に発現した Grade 3 の下痢、(2）適切な制吐治療を行う前に発現した Grade 3 の悪心又は嘔吐、(3）適切な治療を行う前に発現した Grade 3 の無症候性の血清カリウム、マグネシウム、又はリン酸などの臨床検査値異常で、関連する心電図変化を伴わないもの、(4）降圧剤 2 剤以下の追加で良好にコントロールされている Grade 3 の高血圧、(5）脱毛症

表 2.7.4.1-6 用量調整及び休薬（902 試験）

有害事象の詳細	用量調整及び休薬
• Grade 3 以上の非血液毒性（脱毛症を除く） • 38.5 度以上の発熱を伴う Grade 3 の好中球減少症 • Grade 4 の血液毒性	治験薬の投与を中断し、対症療法を開始する。2 週間以内に Grade 1 以下に回復した場合は用量を減量して投与を再開する（探索的試験では開始用量から 25 mg、又は 25 mg から 20 mg への減量、ピボタル試験では 30 mg から 20 mg への減量)。 2 週間以内に回復が認められない場合、治験薬の投与を中止する。

2.7.4.1.1.2.1.6 注目すべき有害事象

203 試験（及び 210 試験）では、注目すべき有害事象として、MedDRA の PT 及び標準 MedDRA 検索式 (SMQ) に基づいてグループ化した「血小板減少症」、「好中球減少症」、「リンパ球減少症」、「貧血」、「感染症」、「ウイルス再活性化」、「ウイルス再活性化を除く肝障害」、「間質性肺疾患」、「心臓障害」、「トルサード ド ポアント／QT 延長」、「過敏症」を集計した。注目すべき有害事象の定義は付録表 2.7.4.7-1 に示す。その他の試験でも、同様の定義を用いて注目すべき有害事象に該当する事象を特定し、発現状況を評価した。なお、グループ化した注目すべき有害事象名は、かぎ括弧付きで示した。

2.7.4.1.1.2.1.7 部分集団解析

203 試験（及び 210 試験）では、認められた有害事象を以下の因子で層別化し、試験ごとに部分集団解析を実施した。

- 性別：男性、女性
- 年齢：65 歳未満、65 歳以上 75 歳未満、75 歳以上
- 人種：日本人、韓国人（203 試験のみ）
- PTCL サブセット：再発、難治性（203 試験のみ）
- ベースライン時の米国東海岸がん臨床試験グループ（ECOG）パフォーマンスステータス（PS）：0、1、2
- 前治療のレジメン数：3 レジメン未満、3 レジメン以上
- 直近のがん治療からの期間：3 ヵ月未満、3 ヵ月以上

2.7.4.1.1.2.2 臨床検査及びその他の安全性評価

2.7.4.1.1.2.2.1 臨床検査

203 試験及び 201 試験（並びに 210 試験）では、規定の評価時点での測定値及びベースラインからの変化量を要約した。NCI CTCAE version 4.03 に従って異常値を Grade 化し、ベースライン

後の血液学的検査値及び血液生化学検査値の異常を最悪 Grade 別に集計した。また、Grade のベースラインからの変化を集計し、評価に含めた。

902 試験では、血液学的検査及び血液生化学検査の治験薬投与前後の正常値及び異常値への変化を集計表に示した。NCI CTCAE version 3.00 に従って検査値を Grade 化し、Grade 1 以上を異常値とした。また、治験担当医師により臨床的に重大であると判定された異常値を臨床的に重大な異常値として集計した。

2.7.4.1.1.2.2.2 バイタルサイン

203 試験及び 201 試験（並びに 210 試験）のバイタルサインの評価には、収縮期血圧、拡張期血圧、及び体重を用い、規定の評価時点における測定値及びベースラインからの臨床的に重大な変化量を要約した。各パラメータの臨床的に重大な異常の基準を次のように定義した。

収縮期血圧
- 血圧低下 = ベースラインから 20 mm Hg 以上の低下を伴う 90 mm Hg 以下の低血圧
- 血圧上昇 = ベースラインから 20 mm Hg 以上の上昇を伴う 180 mm Hg 以上の高血圧

拡張期血圧
- 血圧低下 = ベースラインから 15 mm Hg 以上の低下を伴う 50 mm Hg 以下の低血圧
- 血圧上昇 = ベースラインから 15 mm Hg 以上の上昇を伴う 105 mm Hg 以上の高血圧

体重
- 体重減少 = ベースラインから 7%以上の減少
- 体重増加 = ベースラインから 7%以上の増加

902 試験のバイタルサインの評価には血圧を用い、治験薬投与前後の正常値及び異常値の変化を集計表に示した。血圧の異常値の基準を次のように定義した。

血圧
- 低血圧 = 拡張期血圧が 60 mm Hg 未満
- 高血圧 = 収縮期血圧が 140 mm Hg 超又は拡張期血圧が 90 mm Hg 超

2.7.4.1.1.2.2.3 心電図

203 試験及び 201 試験（210 試験）では、本薬の心臓への潜在的な影響をモニターするため、規定の評価時点で連続 12-誘導心電図を triplicate 又は single で測定した。Fridericia 法の補正式を用いた心拍数の補正 QT 間隔（QTcF）の絶対値が 450 msec を超えた場合及び QTcF の変化量がベースライン時から 30 msec を超えた場合を臨床的に重大な心電図の異常として集計し、評価した。

902 試験では、規定の評価時点で標準 12-誘導心電図を測定し、心電図及び QTc の治験薬投与前後の正常及び異常の変化を集計表に示した。心電図の変化は、正常又は異常を治験担当医師が判断した。QTc は NCI CTCAE version 3.00 に従って Grade 化し、Grade 1 以上を異常とした。

なお、QTc サブスタディを実施した 302 試験の心電図データは再発又は難治性の ATL を対象とした本薬の初回申請で既に提出済みである。

2.7.4.1.1.2.2.4 ECOG PS

203 試験及び 201 試験（並びに 210 試験）では、ECOG PS のベースラインからの変化を要約し、評価した。

902 試験では、投与開始後の ECOG PS を収集しておらず、ECOG PS の変化は検討していない。

2.7.4.1.2 全般的な曝露状況

2.7.4.1.2.1 曝露状況

2.7.4.1.2.1.1 日本人／韓国人第 2b 相試験（203 試験）

曝露状況の概要を表 2.7.4.1-7 に示す。

全体集団では、安全性対象集団 55 例の曝露期間［中央値（最小値～最大値）、以降同様］は 80.0 日（10～580 日）、投与サイクル数は 2.857 サイクル（0.36～20.71 サイクル）、治験薬の累積曝露量は 600.0 mg（110～6560 mg）であった。相対用量強度は 0.854（0.42～1.05）であった。

26 例（47.3%）が治験薬を減量し、このうち 20 例（36.4%）が 40 mg から 30 mg に減量（1 回減量）し、6 例（10.9%）が 40 mg から 30 mg に減量した後、更に 20 mg に減量（2 回減量）した。初回の減量までの期間は 32.5 日（11～127 日）であった。合計 37 例（67.3%）が休薬し、休薬したサイクル数は 40%を超える被験者で 1 サイクルのみ又は 2 サイクル以内であった。投与開始から初回の休薬までの期間は 15.0 日（4～366 日）であった。

日本人集団の 39 例では、曝露期間［中央値（最小値～最大値）、以降同様］は 80.0 日（10～580 日）、投与サイクル数は 2.857 サイクル（0.36～20.71 サイクル）、治験薬の累積曝露量は 640 mg（110～6560 mg）であった。相対用量強度は 0.741（0.42～1.05）であった。

21 例（53.8%）が治験薬を減量し、このうち 15 例（38.5%）が 40 mg から 30 mg に減量（1 回減量）し、6 例（15.4%）が 40 mg から 30 mg、更に 20 mg に減量（2 回減量）した。初回の減量までの期間は 36.0 日（11～127 日）であった。27 例（69.2%）が休薬し、休薬したサイクル数は約 40%の被験者で 1 サイクルのみ又は 2 サイクル以内であった。投与開始から初回の休薬までの期間は 15.0 日（4～366 日）であった。

表 2.7.4.1-7 曝露状況の概要（203 試験）（安全性解析対象集団）

Variable (unit)	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Duration of exposure (days)	n	39	16	55
	Mean	125.2	111.7	121.3
	SD	132.3	133.0	131.4
	Median	80.0	54.0	80.0
	Minimum	10	22	10
	Maximum	580	486	580
Number of times study drug is administered	n	39	16	55
	Mean	31.4	29.2	30.7
	SD	36.3	37.8	36.4
	Median	16.0	14.0	16.0
	Minimum	3	6	3
	Maximum	164	139	164

Variable (unit)	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Number of cycles	n	39	16	55
	Mean	4.473	3.989	4.332
	SD	4.724	4.749	4.692
	Median	2.857	1.929	2.857
	Minimum	0.36	0.79	0.36
	Maximum	20.71	17.36	20.71
Cumulative exposure (mg)	n	39	16	55
	Mean	1087.9	1112.5	1095.1
	SD	1256.6	1490.0	1314.5
	Median	640.0	540.0	600.0
	Minimum	110	220	110
	Maximum	6560	5560	6560
Dose intensity (mg/cycle)	n	39	16	55
	Mean	247.7	271.4	254.6
	SD	65.4	58.3	63.8
	Median	237.0	291.6	273.2
	Minimum	133	166	133
	Maximum	336	332	336
Relative dose intensity	n	39	16	55
	Mean	0.774	0.848	0.796
	SD	0.204	0.182	0.199
	Median	0.741	0.911	0.854
	Minimum	0.42	0.52	0.42
	Maximum	1.05	1.04	1.05
Number of subjects who had dose reduction	n (%)	21 (53.8)	5 (31.3)	26 (47.3)
40mg to 30mg (only 1 dose reduction)	n (%)	15 (38.5)	5 (31.3)	20 (36.4)
40mg to 30mg to 20mg (2 dose reductions excluding 1 dose reduction)	n (%)	6 (15.4)	0 (0.0)	6 (10.9)
Number of subjects who had at least one dose interruptions	n (%)	27 (69.2)	10 (62.5)	37 (67.3)
Cycles with dose interruptions				
Number of subjects where dose interruption occurred only at 1 cycle	n (%)	7 (17.9)	6 (37.5)	13 (23.6)
Number of subjects where dose interruption occurred at a maximum 2 cycles	n (%)	9 (23.1)	2 (12.5)	11 (20.0)
Number of subjects where dose interruption occurred at a maximum 3 cycles	n (%)	7 (17.9)	1 (6.3)	8 (14.5)
Number of subjects where dose interruption occurred at a maximum 4 cycles	n (%)	1 (2.6)	0 (0.0)	1 (1.8)
Number of subjects where dose interruption occurred more than 5 cycles	n (%)	3 (7.7)	1 (6.3)	4 (7.3)
Time to first dose interruption (days)	n	27	10	37
	Mean	39.1	43.9	40.4
	SD	70.3	65.6	68.2
	Median	15.0	21.5	15.0
	Minimum	4	7	4
	Maximum	366	224	366
Time to first dose reduction (days)	n	21	5	26
	Mean	50.7	34.6	47.6
	SD	35.5	20.9	33.5
	Median	36.0	31.0	32.5
	Minimum	11	15	11
	Maximum	127	70	127
Time of administration from last meal (minutes)	n*	1216	467	1683
	Mean	32.8	33.2	32.9
	SD	9.8	14.9	11.4

Variable (unit)	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
	Median	30.0	30.0	30.0
	Minimum	5	20	5
	Maximum	180	150	180
Number of subjects who had at least one overdose	n (%)	1 (2.6)	4 (25.0)	5 (9.1)

Source: Appendix Table 2.7.4.7-2
SD = standard deviation
Duration of exposure (days) = (Date of last study drug – Date of first study drug + 3), if date of last study drug minus date of first study drug is multiple of 7. Else, Duration of exposure (days) = (Date of last study drug – Date of first study drug + 4).
Number of times study drug is administered = the number of study drug administration where dose is greater than 0 mg.
Number of cycles = (Date of last study drug – Date of first study drug + 3) / 28, if date of last study drug minus date of first study drug is multiple of 7. Else, number of cycles = (Date of last study drug – Date of first study drug + 4) / 28.
Last study drug date is the date of last study drug administered as collected in case report form.
% = percentages of subjects are calculated relative to the number of subjects in the respective country within the analysis set.
Dose intensity (mg/cycle) = Cumulative Exposure (mg) / Number of cycles.
Relative dose intensity = dose intensity (mg/cycle) / plan dose intensity. Where plan dose intensity is 320 mg/cycle.
Dose interruption is defined as the subject who did not have dose administered at a scheduled timepoint, and this is captured up to the last dose administered as collected in case report form.
Dose intensity and relative dose intensity are calculated based on the last dose administered as collected in case report form.
* denoted the total number of regular meals consumed prior to study drug administration by subjects in the analysis set.
Time to first dose interruption (days) = date of the last dose administered prior to dose interruption + 3 – date of first dose + 1.
Time to first dose reduction (days) = date of the 1st dose administered that is less than 40 mg – date of first dose + 1.
Time of administration from last meal (minutes) = Datetime of study drug – Datetime of most recent ingestion of food before study drug. Meal time is calculated for any regular meal consumed prior to study drug administration.
Overdose is defined as subjects who took more than 320 mg in a 28 days cycle. Particularly for this overdose calculation, 28 days cycle is calculated from Cycle 1 Day 1.
Data cut-off date: [redacted] 20[redacted]

2.7.4.1.2.1.2 日本人第 1 相試験（201 試験）

曝露状況の概要を表 2.7.4.1-8 に示す。

全体では、安全性解析対象集団の 14 例の曝露期間［中央値（最小値～最大値）、以降同様］は 59.0 日（4～239 日）、投与サイクル数は 2.107 サイクル（0.14～8.54 サイクル）であった。治験薬の累積曝露量は 455.0 mg（30～1630 mg）であり、用量強度は 53.64 mg/体重/週（43.6～80.0 mg/体重/週）であった。6 例（42.9%）が治験薬を減量し、予定投与回数に対する実投与回数の割合は 87.50%（74.8～100.0%）であった。

40 mg コホートの 7 例では、曝露期間［中央値（最小値～最大値）、以降同様］は 56.0 日（24～239 日）、投与サイクル数は 2.000 サイクル（0.86～8.54 サイクル）であった。治験薬の累積曝露量は 610.0 mg（220～1630 mg）であり、用量強度は 53.75 mg/体重/週（43.6～80.0 mg/体重/週）であった。5 例（71.4%）が治験薬を減量し、予定投与回数に対する実投与回数の割合は 81.25%（74.8～100.0%）であった。

本試験では、40 mg コホートの 2 例が用量制限毒性（DLT）を発現したため、治験実施計画書で予定していた 50 mg の投与は実施されなかった。

表 2.7.4.1-8 曝露状況の概要（201 試験）（安全性解析対象集団）

Variable (unit)	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
Duration of exposure (day)	n	7	7	14
	Mean	58.4	103.0	80.7
	SD	42.04	89.90	71.28
	Median	62.0	56.0	59.0
	Minimum	4	24	4
	Maximum	119	239	239
Number of times study drug administered	n	7	7	14
	Mean	15.0	23.3	19.1
	SD	11.09	18.63	15.35
	Median	14.0	16.0	15.0
	Minimum	1	6	1
	Maximum	34	52	52
Number of cycles	n	7	7	14
	Mean	2.087	3.679	2.883
	SD	1.5014	3.2108	2.5457
	Median	2.214	2.000	2.107
	Minimum	0.14	0.86	0.14
	Maximum	4.25	8.54	8.54
Cumulative exposure (mg)	n	7	7	14
	Mean	434.3	762.9	598.6
	SD	302.54	565.79	468.04
	Median	420.0	610.0	455.0
	Minimum	30	220	30
	Maximum	910	1630	1630
Number of patients who had dose reduction	n (%)	1 (14.3%)	5 (71.4%)	6 (42.9%)
Percentages of planned dose received	n	7	7	14
	Mean	90.74	84.95	87.84
	SD	9.733	11.204	10.520
	Median	90.32	81.25	87.50
	Minimum	76.6	74.8	74.8
	Maximum	100.0	100.0	100.0
Dose intensity (mg/body/week)	n	7	7	14
	Mean	53.52	59.52	56.52
	SD	5.300	15.457	11.530
	Median	53.53	53.75	53.64
	Minimum	45.9	43.6	43.6
	Maximum	60.0	80.0	80.0

Source: Appendix Table 2.7.4.7-3
SD = standard deviation
Duration of exposure = (Date of last study drug - Date of first study drug + 3), if date of last study drug minus date of first study drug is multiple of 7. Else, duration of exposure = (Date of last study drug - Date of first study drug + 4).
Number of times study drug administered = the number of study drug administration where dose was greater than 0mg.
Number of cycles = (Date of last study drug - Date of first study drug + 3) / 28, if date of last study drug minus date of first study drug is multiple of 7. Else, number of cycles = (Date of last study drug - Date of first study drug + 4) / 28.
% = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Percentages of planned dose received = [(Number of times study drug administered)/(Number of times planned dose administered)] * 100.
Number of times planned dose administered: Number of Cycles *8
Dose intensity (mg/body/week) = Cumulative Exposure / (Number of cycles *4)

2.7.4.1.2.1.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

曝露状況の概要を表 2.7.4.1-9 に示す。

安全性解析対象集団 23 例の曝露期間［中央値（最小値～最大値）、以降同様］は 35.0 日（7～388 日）、投与サイクル数は 1.250 サイクル（0.25～13.86 サイクル）、治験薬の累積曝露量は 310.0 mg（80～2260 mg）であった。相対用量強度は 0.810（0.43～1.04）であった。10 例（43.5%）が治験薬を減量し、このうち 7 例（30.4%）が 40 mg から 30 mg に減量（1 回減量）、3 例（13.0%）が 40 mg から 30 mg に減量した後、更に 20 mg に減量（2 回減量）した。投与開始から初回の減量までの期間は 38.0 日（25～78 日）であった。

合計 13 例（56.5%）が休薬し、休薬したサイクル数はその多くが 1 サイクルのみ又は 2 サイクル以内であった。投与開始から初回の休薬までの期間は 18.0 日（7～40 日）であった。

表 2.7.4.1-9 曝露状況の概要（210 試験）（安全性解析対象集団）

Variable (unit)	Statistic	40 mg (N=23)
Duration of exposure (days)	n	23
	Mean	65.9
	SD	95.3
	Median	35.0
	Minimum	7
	Maximum	388
Number of times study drug is administered	n	23
	Mean	15.6
	SD	23.4
	Median	8.0
	Minimum	2
	Maximum	96
Number of cycles	n	23
	Mean	2.355
	SD	3.402
	Median	1.250
	Minimum	0.25
	Maximum	13.86
Cumulative exposure (mg)	n	23
	Mean	480.4
	SD	592.4
	Median	310.0
	Minimum	80
	Maximum	2260
Dose intensity (mg/cycle)	n	23
	Mean	254.591
	SD	61.446
	Median	260.000
	Minimum	138.51
	Maximum	333.33
Relative dose intensity	n	23
	Mean	0.796
	SD	0.192
	Median	0.810
	Minimum	0.43
	Maximum	1.04

Variable (unit)	Statistic	40 mg (N=23)
Number of subjects who had dose reduction	n (%)	10 (43.5%)
40mg to 30mg (only 1 dose reduction)	n (%)	7 (30.4%)
40mg to 30mg to 20mg (2 dose reductions excluding 1 dose reduction)	n (%)	3 (13.0%)
Number of subjects who had at least one dose interruptions	n (%)	13 (56.5%)
Cycles with dose interruptions		
Number of subjects where dose interruption occurred only at 1 cycle	n (%)	6 (26.1%)
Number of subjects where dose interruption occurred at a maximum 2 cycles	n (%)	3 (13.0%)
Number of subjects where dose interruption occurred at a maximum 3 cycles	n (%)	2 (8.7%)
Number of subjects where dose interruption occurred at a maximum 4 cycles	n (%)	0 (0.0%)
Number of subjects where dose interruption occurred more than 5 cycles	n (%)	2 (8.7%)
Time to first dose interruption (days)	n	13
	Mean	19.2
	SD	8.3
	Median	18.0
	Minimum	7
	Maximum	40
Time to first dose reduction (days)	n	10
	Mean	42.0
	SD	16.2
	Median	38.0
	Minimum	25
	Maximum	78
Time of administration from last meal (minutes)	n *	354
	Mean	40.9
	SD	28.5
	Median	30.0
	Minimum	5
	Maximum	250
Number of subjects who had at least one overdose	n (%)	0 (0.0%)

Source: Appendix Table 2.7.4.7-4 (cited from the new drug application for relapsed or refractory ATL)
SD = standard deviation
Duration of exposure (days) = (Date of last study drug – Date of first study drug + 3), if date of last study drug minus date of first study drug is multiple of 7. Else, Duration of exposure (days) = (Date of last study drug – Date of first study drug + 4).
Number of times study drug is administered = the number of study drug administration where dose was greater than 0 mg.
Number of cycles = (Date of last study drug – Date of first study drug + 3) / 28, if date of last study drug minus date of first study drug is multiple of 7. Else, number of cycles = (Date of last study drug – Date of first study drug + 4) / 28.
Last study drug date is the date of last study drug administered as collected in case report form
% = percentages of subjects were calculated relative to the total number of subjects in the analysis set.
Dose intensity (mg/cycle) = Cumulative Exposure (mg) / Number of cycles.
Relative dose intensity = dose intensity (mg/cycle) / plan dose intensity. Where plan dose intensity is 320 mg/cycle.
Dose interruption is defined as the subject who did not have dose administered at a scheduled timepoint, and this is captured up to the last dose administered as collected in case report form.
Dose intensity and relative dose intensity are calculated based on the last dose administered as collected in case report form.
Time to first dose interruption (days) = date of the last dose administered prior to dose interruption + 3 – date of first dose + 1.
Time to first dose reduction (days) = date of the 1st dose administered that is less than 40 mg – date of first dose + 1.
* denoted the total number of regular meals consumed prior to study drug administration by subjects in the analysis set.
Time of administration from last meal (minutes) = Datetime of study drug – Datetime of most recent ingestion of food before study drug. Meal time is calculated for any regular meal consumed prior to study drug administration.
Overdose is defined as subjects who took more than 320 mg in a 28 days cycle. Particularly for this overdose calculation, 28 days cycle is calculated from Cycle 1 Day 1.
Data cut-off date: [redacted] 20[redacted]

2.7.4.1.2.1.4 中国人第 2 相試験（902 試験）

探索的試験の被験者の投与サイクル数を表 2.7.4.1-10 に、ピボタル試験の被験者の曝露量及び投与サイクル数をそれぞれ表 2.7.4.1-11 及び表 2.7.4.1-12 に示す。

探索的試験では、安全性解析対象集団 19 例の投与サイクル数［中央値（最小値～最大値)］は 1.0 サイクル（0～8 サイクル）であった。14 例（73.7%）が 1 サイクル（6 週間）の投与を完了し、9 例（47.4%）が 2 サイクル、5 例（26.3%）が 3 サイクルの投与を完了した。

ピボタル試験では、安全性解析対象集団 83 例の投与サイクル数［中央値（最小値～最大値)］は 1.0 サイクル（0～13 サイクル）であった。59 例（71.1%）が 1 サイクル（6 週間）（6 週間)、30 例（36.1%）が 2 サイクル、21 例（25.3%）が 3 サイクル、12 例（14.5%）が 4 サイクルの投与を完了した。治験薬の累積曝露量は 360.0 mg（30～4860 mg）であった。

表 2.7.4.1-10 探索的試験の投与サイクル数（902 試験）（安全性解析対象集団）

	Statistical Magnitude	All Subjects
Completed treatment cycles	One cycle	14 (73.7%)
	Two cycles	9 (47.4%)
	Three cycles	5 (26.3%)
	Four cycles	1 (5.3%)
	Five cycles	1 (5.3%)
	Six cycles	1 (5.3%)
	Seven cycles	1 (5.3%)
	Eight cycles	1 (5.3%)
The total number of treatment cycles	N (Nmiss)	19 (0)
	Mean (SD)	1.7 (1.88)
	Median	1.0
	Min, Max	0, 8

Source: Module 5, 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.12.2
Nmiss = The number of subjects with missing data; SD = standard deviation

表 2.7.4.1-11 ピボタル試験の被験者の曝露量（902 試験）（安全性解析対象集団）

	Statistical Magnitude	30mg
Total times of administration	N (Nmiss)	83 (0)
	Mean (SD)	26.7 (32.26)
	Median	12.0
	Min, Max	1, 165
Total dosage in the entire study period (mg)	N (Nmiss)	83 (0)
	Mean (SD)	773.4 (920.57)
	Median	360.0
	Min, Max	30, 4860

Source: Module 5, 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.12.1
Nmiss = The number of subjects with missing data; SD = standard deviation

表 2.7.4.1-12 ピボタル試験の投与サイクル数（902 試験）（安全性解析対象集団）

	Statistical Magnitude	30mg
Completed treatment cycles	1 cycle	59 (71.1%)
	2 cycles	30 (36.1%)
	3 cycles	21 (25.3%)
	4 cycles	12 (14.5%)
	7 cycles	6 (7.2%)
	9 cycles	4 (4.8%)
	11 cycles	3 (3.6%)
	13 cycles	2 (2.4%)
Total number of treatment cycles	N (Nmiss)	83 (0)
	Mean (SD)	1.9 (2.66)
	Median	1.0
	Min, Max	0, 13

Source: Module 5, 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.12.2
Nmiss = The number of subjects with missing data; SD = standard deviation

2.7.4.1.2.2 被験者の内訳

2.7.4.1.2.2.1 日本人／韓国人第 2b 相試験（203 試験）

被験者の内訳を表 2.7.4.1-13 に示す。

全体集団では、同意取得した被験者 74 例のうち、19 例がスクリーニングで脱落し、55 例が本薬の投与を 1 回以上受けた。20■ 年■ 月■ 日のデータカットオフ時点で 55 例中 47 例（85.5%）が治験薬投与を中止した。投与を中止した 47 例の主な中止理由は、病勢進行が 24 例（51.1%）、許容できない毒性（有害事象）が 17 例（36.2%）、同意撤回が 5 例（10.6%）及び被験者の複数回にわたる治験実施計画書不遵守が 1 例（2.1%）であった。

日本人集団では、同意取得した被験者 52 例のうち、13 例がスクリーニングで脱落し、39 例が本薬の投与を 1 回以上受けた。カットオフ日時点で 39 例中 32 例（82.1%）が治験薬投与を中止した。投与を中止した 32 例の主な中止理由は、病勢進行及び許容できない毒性（有害事象）が各 15 例（46.9%）、同意撤回が 2 例（6.3%）であった。

表 2.7.4.1-13 被験者の内訳（203 試験）（全同意取得例）

Description	Japan (N=52) n (%)	Korea (N=22) n (%)	40 mg (N=74) n (%)
Consented	52	22	74
Screening failure	13	6	19
Treated with at least one dose of HBI-8000 (Safety Analysis Set)	39 (100.0%)	16 (100.0%)	55 (100.0%)
Full Analysis Set (FAS)	37 (94.9%)	12 (75.0%)	49 (89.1%)
Per Protocol Set	34 (87.2%)	12 (75.0%)	46 (83.6%)
Subjects who are on study drug treatment	7 (17.9%)	1 (6.3%)	8 (14.5%)
Subjects who had study drug treatment discontinuation	32 (82.1%)	15 (93.8%)	47 (85.5%)
Primary reason for study drug treatment discontinuation			
Unacceptable toxicity (adverse event)	15 (46.9%)	2 (13.3%)	17 (36.2%)
Progression disease	15 (46.9%)	9 (60.0%)	24 (51.1%)
Repeated subject noncompliance	0 (0.0%)	1 (6.7%)	1 (2.1%)
Withdrew consent	2 (6.3%)	3 (20.0%)	5 (10.6%)

Description	Japan (N=52) n (%)	Korea (N=22) n (%)	40 mg (N=74) n (%)
Subjects in FAS who completed 1 cycle of treatment (including subjects discontinued before C2D1 with >=75% protocol specified dose of 320mg)	31 (83.8%)	12 (100.0%)	43 (87.8%)
Subjects in FAS who did not complete 1 cycle of treatment (where study medication taken within cycle 1 is <75% protocol specified dose of 320mg)	6 (16.2%)	0 (0.0%)	6 (12.2%)
Subjects completed the study participation	14 (35.9%)	13 (81.3%)	27 (49.1%)
Primary reason for completing the study participation			
Lost to follow-up	0 (0.0%)	1 (7.7%)	1 (3.7%)
Death	14 (100.0%)	4 (30.8%)	18 (66.7%)
Withdrew consent	0 (0.0%)	8 (61.5%)	8 (29.6%)

Source: Appendix Table 2.7.4.7-5
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the Safety Analysis set;
Percentages for study drug treatment discontinuation reasons are calculated based on the number of subjects in the Safety Analysis set who discontinued.
Progression disease in primary reason for study drug treatment discontinuation is defined as progression of the disease under study, which also included clinical progression disease, except for isolated progression in skin lesion
Percentages for subjects who did or did not complete 1 cycle of treatment are calculated based on the number of subjects in the Full Analysis Set.
Percentages for primary reason for completing the study participation are calculated based on the number of subjects who completed study participation in the Safety Analysis set.
Data cut-off date: [redacted] 20[redacted]

2.7.4.1.2.2.2 日本人第 1 相試験（201 試験）

被験者の内訳を表 2.7.4.1-14 に示す。

全体では、22 例から同意取得し、そのうち 14 例が本薬の投与を 1 回以上受け、14 例全例が試験を中止した。中止の主な理由は、有害事象（許容できない毒性を発現した被験者を含む）が 6 例（42.9%）、病勢進行が 4 例（28.6%）、及び被験者による同意撤回が 1 例（7.1%）であった。3 例（21.4%）がその他の理由（治療継続の条件を満たしていない）で中止した。

40 mg コホートでは、7 例から同意取得し、7 例全例が本薬の投与を 1 回以上受け、7 例全例が試験を中止した。中止の主な理由は、有害事象（許容できない毒性を発現した被験者を含む）が 4 例（57.1%）、病勢進行、被験者による同意撤回及びその他（治療継続の条件を満たしていない）が各 1 例（14.3%）であった。

許容できない毒性のため中止した被験者（被験者[redacted]）は、DLT である Grade 4 の血液学的有害事象（好中球減少症）を発現し休薬及び減量したが、その後、同事象を再度発現した。本試験の治験実施計画書では DLT 発現後は減量することとしているが、減量は 1 回までと規定されていたことから、本被験者は許容できない毒性により治験中止となった。

表 2.7.4.1-14 被験者の内訳（201 試験）（全同意取得例）

Description	30 mg (N=15) n (%)	40 mg (N=7) n (%)	Total (N=22) n (%)
Enrolled	15	7	22
Screening Failure	8	0	8
Treated with at least one dose of HBI-8000 (Safety Analysis Set)	7 (46.7%)	7 (100.0%)	14 (63.6%)
Treated with 2 or more dose of HBI-8000 and have valid efficacy assessment at screening and post-dose (Efficacy Analysis Set)	6 (40.0%)	7 (100.0%)	13 (59.1%)
Discontinued	7 (46.7%)	7 (100.0%)	14 (63.6%)
Primary reason for discontinuation			
Adverse event	2 (28.6%)	3 (42.9%)	5 (35.7%)
Tumor progression	3 (42.9%)	1 (14.3%)	4 (28.6%)
Unacceptable toxicity including: QTc prolongation >= Grade 3	0 (0.0%)	1 (14.3%)	1 (7.1%)
Patient request to withdraw informed consent	0 (0.0%)	1 (14.3%)	1 (7.1%)
Other	2 (28.6%)	1 (14.3%)	3 (21.4%)

Source: Appendix Table 2.7.4.7-6
n = number of patients; % = percentage of patients calculated relative to the total number of enrolled patients in each cohort.
Percentage for discontinuation reasons was calculated based on the number of patients who had discontinuation in each cohort of the analysis set.

2.7.4.1.2.2.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

被験者の内訳を表 2.7.4.1-15 に示す。

本試験で同意取得した被験者 29 例のうち、6 例がスクリーニング時に脱落し、23 例が本薬の投与を 1 回以上受けた。23 例全例が治験薬の投与を中止した。中止の主な理由は、病勢進行が 12 例（52.2%）、許容できない毒性（有害事象）が 8 例（34.8%）、及び同意撤回（他の治療を希望した被験者を含む）が 3 例（13.0%）であった。

表 2.7.4.1-15 被験者の内訳（210 試験）（全同意取得例）

Description	40 mg (N=29) n (%)
Consented	29
Screening failure	6
Treated with at least one dose of HBI-8000 (Safety Analysis Set)	23 (100.0%)
Full Analysis Set (FAS)	23 (100.0%)
Per Protocol Set	23 (100.0%)
Subjects who had study drug treatment discontinuation	23 (100.0%)
Primary reason for study drug treatment discontinuation	
Unacceptable toxicity (adverse event)	8 (34.8%)
Progression disease	12 (52.2%)
Withdrew consent	2 (8.7%)
Other	1 (4.3%)
Subjects in FAS who completed 1 cycle of treatment (including subjects discontinued before C2D1 with >=75% protocol specified dose of 320mg)	16 (69.6%)
Subjects in FAS who did not complete 1 cycle of treatment (where study medication taken within cycle 1 is <75% protocol specified dose of 320mg)	7 (30.4%)
Subjects completed the study participation	13 (56.5%)
Primary reason for completing the study participation	
Death	12 (92.3%)
Withdrew consent	1 (7.7%)

Source: Appendix Table 2.7.4.7-7 (cited from the new drug application for relapsed or refractory ATL)
n = number of subjects; % = percentages of subjects were calculated relative to the total number of subjects in the Safety Analysis set;
Percentages for study treatment discontinuation reasons were calculated based on the number of subjects in the Safety Analysis set who discontinued.
Progression disease in primary reason for study treatment discontinuation is defined as progression of the disease under study, which also

included clinical progression disease, except for isolated progression in skin lesion.
Percentages for subjects who did or did not complete 1 cycle of treatment are calculated based on the number of subjects in the Full Analysis Set.
Percentages for primary reason for completing the study were calculated based on the number of subjects who completed study participation in the Safety Analysis set.
Data cut-off date: [redacted] 20[redacted]

2.7.4.1.2.2.4 中国人第 2 相試験（902 試験）

探索的試験及びピボタル試験の被験者の内訳を表 2.7.4.1-16 及び表 2.7.4.1-17 にそれぞれ示す。

探索的試験では、本試験に組み入れた被験者 19 例のうち、1 例（5.3%）が治療の継続を拒否し（被験者による治療不遵守）、試験を中止した。

ピボタル試験では、本試験に組み入れた被験者 83 例のうち、8 例（9.6%）が試験を中止した。5 例（6.0%）が治療の継続を拒否し（被験者による治療不遵守）、3 例（3.6%）が追跡不能となった。

表 2.7.4.1-16 探索的試験における被験者の内訳（902 試験）（安全性解析対象集団）

	Number of subjects (%)
Enrolled subjects	19
Subjects who completed the study	18 (94.7%)
Subjects who did not complete the study	1 (5.3%)
Reason for not completing the study	
Patient refused participation	1 (5.3%)

Source: Module 5, 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.1.1

表 2.7.4.1-17 ピボタル試験における被験者の内訳（902 試験）（安全性解析対象集団）

	Number of subjects (%)
Enrolled Subjects	83
Subjects who completed the trial according to protocol	75 (90.4%)
Subjects who did not complete the trial according to protocol	8 (9.6%)
Reasons for not completing treatment according to protocol	
Lost to follow-up	3 (3.6%)
Patient refused participation	5 (6.0%)

Source: Module 5, 5.3.5.4-2TG0902CDM p2b/Statistical Analysis Report/Table 7.1.1

2.7.4.1.3 人口統計学的及びその他のベースライン特性

2.7.4.1.3.1 人口統計学的特性及び疾患特性

2.7.4.1.3.1.1 日本人／韓国人第 2b 相試験（203 試験）

主な人口統計学的特性を表 2.7.4.1-18 及び表 2.7.4.1-19 に示す。

全体集団では、安全性解析対象集団 55 例のうち、70.9%（39 例）が日本人で、29.1%（16 例）が韓国人であった。被験者の年齢の平均値（標準偏差）及び中央値（最小値～最大値）はそれぞれ 67.7 歳（11.7 歳）［日本人 68.9 歳（12.1 歳）、韓国人 64.7 歳（10.7 歳）］及び 71.0 歳（38～87 歳）［日本人 73.0 歳（38～87 歳）、韓国人 67.0 歳（44～79 歳）］で、63.6%（35 例）が男性であった。被験者のほとんどで、ECOG PS が 0（28 例、50.9%）又は 1（25 例、45.5%）であった。身長［平均値（標準偏差）、以降同様］は 162.22 cm（9.18 cm）、体重は 58.05 kg（11.03 kg）、体格指数（BMI）は 21.960 kg/m^2（3.071 kg/m^2）であった。

日本人集団では、年齢の平均値（標準偏差）及び中央値（最小値～最大値）はそれぞれ 68.9 歳

（12.1 歳）及び 73.0 歳（38～87 歳）であり、75 歳以上が 35.9%（14 例）であった。日本人集団 39 例のうち、71.8%（28 例）が男性であった。被験者のほとんどで、ECOG PS が 0（26 例、66.7%）又は 1（12 例、30.8%）であった。身長［平均値（標準偏差）、以降同様］は 163.18 cm（8.96 cm）、体重は 58.52 kg（11.59 kg）、BMI は 21.842 kg/m^2（3.062 kg/m^2）であった。

表 2.7.4.1-18 人口統計学的特性及びその他のベースライン特性 －1（203 試験）（安全性解析対象集団）

Characteristic (unit)	Category	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Age (years)		n	39	16	55
		Mean	68.9	64.7	67.7
		SD	12.1	10.7	11.7
		Median	73.0	67.0	71.0
		Minimum	38	44	38
		Maximum	87	79	87
	<65	n (%)	8 (20.5%)	7 (43.8%)	15 (27.3%)
	>=65 to <75	n (%)	17 (43.6%)	6 (37.5%)	23 (41.8%)
	>=75	n (%)	14 (35.9%)	3 (18.8%)	17 (30.9%)
Sex	Male	n (%)	28 (71.8%)	7 (43.8%)	35 (63.6%)
	Female	n (%)	11 (28.2%)	9 (56.3%)	20 (36.4%)
Race	Asian	n (%)	39 (100.0%)	16 (100.0%)	55 (100.0%)
Ethnicity	Japanese	n (%)	39 (100.0%)	0 (0.0%)	39 (70.9%)
	Korea	n (%)	0 (0.0%)	16 (100.0%)	16 (29.1%)
ECOG Performance Status at baseline	0	n (%)	26 (66.7%)	2 (12.5%)	28 (50.9%)
	1	n (%)	12 (30.8%)	13 (81.3%)	25 (45.5%)
	2	n (%)	1 (2.6%)	1 (6.3%)	2 (3.6%)
Height (cm)		n	39	16	55
		Mean	163.18	159.88	162.22
		SD	8.96	9.55	9.18
		Median	162.00	160.10	162.00
		Minimum	148.0	142.5	142.5
		Maximum	189.6	177.7	189.6
Weight (kg)		n	39	16	55
		Mean	58.52	56.93	58.05
		SD	11.59	9.79	11.03
		Median	57.10	58.50	57.40
		Minimum	36.4	41.3	36.4
		Maximum	88.2	69.3	88.2
BMI (kg/m^2)		n	39	16	55
		Mean	21.842	22.248	21.960
		SD	3.062	3.176	3.071
		Median	22.281	22.309	22.281
		Minimum	14.47	15.54	14.47
		Maximum	29.00	27.09	29.00

Source: Appendix Table 2.7.4.7-8
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; SD = standard deviation.
Data cut-off date: [redacted] 20[redacted]

全体集団 55 例のうち、ベースライン時に中央病理評価委員会により PTCL と判定された被験者は 52 例（94.5%）であった。サブタイプは、非特定型末梢性 T 細胞リンパ腫（PTCL-NOS）が

最も多く 37 例（67.3%）で、次いで血管免疫芽球性 T 細胞リンパ腫（AITL）が 10 例（18.2%）であった。初診時からの罹病期間の中央値（最小値～最大値、以降同様）は 1.339 年（0.06～12.88 年）であり、被験者の多く（42 例、76.4%）の罹病期間は 5 年以下であった。直近の病勢進行から本薬の初回投与までの期間の中央値は 27.0 日（7～605 日）であった。

日本人集団39例のうち、PTCLと判定された被験者は38例(97.4%)で、サブタイプは、PTCL-NOSが最も多く 27 例（69.2%）で、次いで AITL が 8 例（20.5%）であった。初診時からの罹病期間の中央値（最小値～最大値、以降同様）は 1.202 年（0.06～10.95 年）であり、被験者の多く（29 例、74.4%）の罹病期間は 5 年以下であった。直近の病勢進行から本薬の初回投与までの期間の中央値は 27.0 日（9～605 日）であった。

表 2.7.4.1-19 人口統計学的特性及びその他のベースライン特性 －2（203 試験）（安全性解析対象集団）

Description	Subtype/Category	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Diagnosis at screening and confirmed by Central Pathology Review	Peripheral T-cell Lymphoma (PTCL):	38 (97.4%)	14 (87.5%)	52 (94.5%)
	Peripheral T-Cell Lymphoma Not Otherwise Specified (PTCL-NOS)	27 (69.2%)	10 (62.5%)	37 (67.3%)
	Angioimmunoblastic T-Cell Lymphoma (AITL)	8 (20.5%)	2 (12.5%)	10 (18.2%)
	Anaplastic Large-Cell Lymphoma (ALCL), ALK-	2 (5.1%)	1 (6.3%)	3 (5.5%)
	Enteropathy-Type T-Cell Lymphoma (EATL)	1 (2.6%)	1 (6.3%)	2 (3.6%)
	Non-PTCL	1 (2.6%)	1 (6.3%)	2 (3.6%)
Diagnosis at screening assessed by Investigator	Peripheral T-cell Lymphoma (PTCL):	39 (100.0%)	16 (100.0%)	55 (100.0%)
	Peripheral T-Cell Lymphoma Not Otherwise Specified (PTCL-NOS)	22 (56.4%)	6 (37.5%)	28 (50.9%)
	Angioimmunoblastic T-Cell Lymphoma (AITL)	14 (35.9%)	7 (43.8%)	21 (38.2%)
	Anaplastic Large-Cell Lymphoma (ALCL), ALK-	2 (5.1%)	2 (12.5%)	4 (7.3%)
	Enteropathy-Type T-Cell Lymphoma (EATL)	1 (2.6%)	1 (6.3%)	2 (3.6%)
Duration since initial diagnosis (years)	n	39	16	55
	Mean	3.133	2.576	2.971
	SD	3.190	3.262	3.191
	Median	1.202	1.392	1.339
	Minimum	0.06	0.35	0.06
	Maximum	10.95	12.88	12.88
Duration since initial diagnosis by category	> 5 years	10 (25.6%)	3 (18.8%)	13 (23.6%)
	<= 5 years	29 (74.4%)	13 (81.3%)	42 (76.4%)
Duration from most recent progression (days)	n	39	16	55
	Mean	53.0	50.3	52.2
	SD	99.7	54.8	88.5
	Median	27.0	26.0	27.0
	Minimum	9	7	7
	Maximum	605	205	605
Duration from most recent progression by category	> 1 months	17 (43.6%)	7 (43.8%)	24 (43.6%)
	<= 1 months	22 (56.4%)	9 (56.3%)	31 (56.4%)

Source: Appendix Table 2.7.4.7-9

n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;
SD = standard deviation
Duration since initial diagnosis (years)= (informed consent date - date of 1st diagnosis + 1)/365.25.
Duration from most recent progression (days) = (first study drug date - date of most recent progression + 1).
Duration from most recent progression (months) = (first study drug date - date of most recent progression + 1)/ 30.4375.
Central pathology reviewer could not confirm subject [redacted] disease subtype, due to the reason that subject's tumor slides were not submitted for central pathology review
Data cut-off date: [redacted] 20[redacted]

2.7.4.1.3.1.2 日本人第 1 相試験（201 試験）

主な人口統計学的特性を表 2.7.4.1-20 及び表 2.7.4.1-21 に示す。

全体では、安全性解析対象集団の 14 例の年齢の平均値（標準偏差）及び中央値（最小値～最大値）はそれぞれ 68.0 歳（8.35 歳）及び 69.0 歳（53～81 歳）で、50.0%（7 例）が男性であった。ベースライン時の ECOG PS は、すべての被験者が 0（9 例、64.3%）又は 1（5 例、35.7%）であった。身長の平均値（標準偏差、以降同様）は 158.17 cm（9.746 cm）、体重は 61.14 kg（11.730 kg）、BMI は 24.33 kg/m^2（3.578 kg/m^2）であった。

40 mg コホートでは、年齢の平均値（標準偏差）及び中央値（最小値～最大値）はそれぞれ 65.1 歳（6.54 歳）及び 63.0 歳（57～76 歳）であった。40 mg コホート 7 例のうち、男性は 3 例（42.9%）であった。ベースライン時の ECOG PS は、すべての被験者が 0（5 例、71.4%）又は 1（2 例、28.6%）であった。身長［平均値（標準偏差）、以降同様］は 156.04 cm（7.703 cm）、体重は 63.31 kg（12.257 kg）、BMI は 25.84 kg/m^2（3.579 kg/m^2）であった。

表 2.7.4.1-20 人口統計学的特性及びその他のベースライン特性 －1（201 試験）（安全性解析対象集団）

Characteristic (unit)	Category	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
Age (years)		n	7	7	14
		Mean	70.9	65.1	68.0
		SD	9.44	6.54	8.35
		Median	72.0	63.0	69.0
		Minimum	53	57	53
		Maximum	81	76	81
Sex	Male	n (%)	4 (57.1%)	3 (42.9%)	7 (50.0%)
	Female	n (%)	3 (42.9%)	4 (57.1%)	7 (50.0%)
Race	Asian	n (%)	7 (100.0%)	7 (100.0%)	14 (100.0%)
Ethnicity	Japanese	n (%)	7 (100.0%)	7 (100.0%)	14 (100.0%)
ECOG Performance Status	0	n (%)	4 (57.1%)	5 (71.4%)	9 (64.3%)
	1	n (%)	3 (42.9%)	2 (28.6%)	5 (35.7%)
Height (cm)		n	7	7	14
		Mean	160.30	156.04	158.17
		SD	11.657	7.703	9.746
		Median	161.10	158.80	159.90
		Minimum	138.3	146.6	138.3
		Maximum	171.1	167.4	171.1
Weight (kg)		n	7	7	14
		Mean	58.97	63.31	61.14
		SD	11.700	12.257	11.730
		Median	62.00	66.50	62.90
		Minimum	41.6	44.1	41.6
		Maximum	75.9	77.8	77.8

Characteristic (unit)	Category	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
BMI (kg/m^2)		n	7	7	14
		Mean	22.83	25.84	24.33
		SD	3.108	3.579	3.578
		Median	22.20	25.68	24.21
		Minimum	17.7	19.7	17.7
		Maximum	27.3	29.8	29.8

Source: Appendix Table 2.7.4.7-10
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set with data.
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; SD = standard deviation.

初診時の NHL の種類（2 例以上）は、全体では ATL（5 例）、非特定型（NOS）びまん性大細胞型 B 細胞リンパ腫（3 例）、並びに濾胞性リンパ腫及び PTCL（各 2 例）であり、40 mg コホートでは ATL（4 例）及び濾胞性リンパ腫（2 例）であった。

安全性解析対象集団 14 例中 13 例（30 mg コホート 7 例、40 mg コホート 6 例）が直近の再発診断時に画像による疾患診断を受けており、いずれの被験者も直近で再発と診断された疾患は初診時と同じ疾患であった。

直近の再発疾患の Ann Arbor 分類（2 例以上）は、全体では IV 期（14 例中 5 例、35.7%）及び II 期（4 例、28.6%）であり、40 mg コホートでは II 期（7 例中 3 例、42.9%）であった。再発 ATL 患者 1 例は直近の再発部位が血液のみであったため Ann Arbor 分類は適用されなかった。

表 2.7.4.1-21 人口統計学的特性及びその他のベースライン特性 －2（201 試験）（安全性解析対象集団）

Description	Category	Type	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Initial diagnosis	Mature B-cell neoplasm	Follicular lymphoma	0 (0.0%)	2 (28.6%)	2 (14.3%)
		Extranodal marginal zone B-cell lymphoma of mucosa-associated	1 (14.3%)	0 (0.0%)	1 (7.1%)
		Diffuse large B-cell lymphoma NOS	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Mature T-cell and NK-cell neoplasm	N	3	4	7
		Adult T-cell leukaemia/lymphoma	1 (33.3%)	4 (100.0%)	5 (71.4%)
		Peripheral T-cell lymphoma	2 (66.7%)	0 (0.0%)	2 (28.6%)
	Other		1 (14.3%)	0 (0.0%)	1 (7.1%)
Most recent relapse	Mature B-cell neoplasm	Follicular lymphoma	0 (0.0%)	2 (28.6%)	2 (14.3%)
		Extranodal marginal zone B-cell lymphoma of mucosa-associated	1 (14.3%)	0 (0.0%)	1 (7.1%)
		Diffuse large B-cell lymphoma NOS	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Mature T-cell and NK-cell neoplasm	N	3	3	6
		Adult T-cell leukaemia/lymphoma	1 (33.3%)	3 (100.0%)	4 (66.7%)
		Peripheral T-cell lymphoma	2 (66.7%)	0 (0.0%)	2 (33.3%)
	Other		1 (14.3%)	0 (0.0%)	1 (7.1%)

Description	Category	Type	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Stage	Ann Arbor	I	1 (14.3%)	0 (0.0%)	1 (7.1%)
		II	1 (14.3%)	3 (42.9%)	4 (28.6%)
		IIa	1 (14.3%)	0 (0.0%)	1 (7.1%)
		III	0 (0.0%)	1 (14.3%)	1 (7.1%)
		IV	4 (57.1%)	1 (14.3%)	5 (35.7%)
	Other	Not applicable	0 (0.0%)	1 (14.3%)	1 (7.1%)

Source: Appendix Table 2.7.4.7-11
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Percentage of mature T-cell and NK-cell neoplasm results was calculated based on the number of patients with mature T-cell and NK-cell neoplasm in each cohort of the analysis set with data.
Subject [redacted] had initial diagnosis of ADULT T-CELL LEUKEMIA/LYMPHOMA, however there was no data available for relapse.

2.7.4.1.3.1.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

主な人口統計学的特性を表 2.7.4.1-22 及び表 2.7.4.1-23 に示す。

安全性解析対象集団 23 例の年齢の平均値（標準偏差）及び中央値（最小値～最大値）はそれぞれ 73.4 歳（7.1 歳）及び 72.0 歳（60～89 歳）で、75 歳以上が 39.1%（9 例）であった。また、65.2%（15 例）が男性であった。被験者のほとんどで、ECOG PS が 0（12 例、52.2%）又は 1（10 例、43.5%）であった。身長［平均値（標準偏差）、以降同様］は 158.47 cm（8.68 cm）、体重は 54.04 kg（10.35 kg）、BMI は 21.440 kg/m^2（3.348 kg/m^2）であった。

表 2.7.4.1-22 人口統計学的特性及びその他のベースライン特性 －1（210 試験）（安全性解析対象集団）

Characteristic (unit)	Category	Statistic	40 mg (N=23)
Age (years)		n	23
		Mean	73.4
		SD	7.1
		Median	72.0
		Minimum	60
		Maximum	89
	<65	n (%)	1 (4.3%)
	>=65 to <75	n (%)	13 (56.5%)
	>=75	n (%)	9 (39.1%)
Sex	Male	n (%)	15 (65.2%)
	Female	n (%)	8 (34.8%)
Race	Asian	n (%)	23 (100.0%)
Ethnicity	Japanese	n (%)	23 (100.0%)
ECOG Performance Status	0	n (%)	12 (52.2%)
	1	n (%)	10 (43.5%)
	2	n (%)	1 (4.3%)
Height (cm)		n	23
		Mean	158.47
		SD	8.68
		Median	158.00
		Minimum	143.0
		Maximum	176.0

Characteristic (unit)	Category	Statistic	40 mg (N=23)
Weight (kg)		n	23
		Mean	54.04
		SD	10.35
		Median	52.70
		Minimum	34.4
		Maximum	70.7
BMI (kg/m^2)		n	23
		Mean	21.440
		SD	3.348
		Median	21.290
		Minimum	15.88
		Maximum	29.60

Source: Appendix Table 2.7.4.7-12 (cited from the new drug application for relapsed or refractory ATL)
n = number of subjects; % = percentages of subjects were calculated relative to the total number of subjects in the analysis set with data; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; SD = standard deviation
Data cut-off date: [redacted]

スクリーニング時（本試験参加前の直近の病勢進行時）に確認された ATL の臨床病型（サブタイプ）は、23 例中、急性型が 13 例（56.5%）、リンパ腫型が 8 例（34.8%）、予後不良因子を有する慢性型が 2 例（8.7%）であった。初診時からの罹病期間の中央値（最小値～最大値、以降同様）は 1.500 年（0.31～21.95 年）であり、被験者の多く（20 例、87.0%）の罹病期間は 5 年以下であった。本試験参加前の直近の病勢進行から本薬の初回投与までの期間の中央値は 26.0 日（3～371 日）であった。

表 2.7.4.1-23 人口統計学的特性及びその他のベースライン特性 －2（210 試験）（安全性解析対象集団）

Description	Subtype/Category	40 mg (N=23) n (%)
Diagnosis at screening	Adult T-cell Lymphoma:	23 (100.0%)
	Acute	13 (56.5%)
	Lymphoma	8 (34.8%)
	Unfavorable Chronic	2 (8.7%)
Duration since initial diagnosis(years)	n	23
	Mean	3.019
	SD	4.838
	Median	1.500
	Minimum	0.31
	Maximum	21.95
Duration since initial diagnosis by category	> 5 years	3 (13.0%)
	<= 5 years	20 (87.0%)
Duration from most recent progression (days)	n	23
	Mean	47.6
	SD	80.4
	Median	26.0
	Minimum	3
	Maximum	371

Description	Subtype/Category	40 mg (N=23) n (%)
Duration from most recent progression by category	> 1 month	8 (34.8%)
	<= 1 month	15 (65.2%)

Source: Appendix Table 2.7.4.7-13 (cited from the new drug application for relapsed or refractory ATL)
n = number of subjects; % = percentages of subjects were calculated relative to the total number of subjects in the analysis set.
SD = standard deviation
Duration since initial diagnosis (years)= (informed consent date - date of 1st diagnosis + 1)/365.25.
Duration from most recent progression (days) = (first study drug date - date of most recent progression + 1).
Duration from most recent progression (months) = (first study drug date - date of most recent progression + 1)/ 30.4375.
Data cut-off date: [redacted] 20[redacted]

2.7.4.1.3.1.4 中国人第 2 相試験（902 試験）

主な人口統計学的特性を、探索的試験は表 2.7.4.1-24 及び表 2.7.4.1-25 に、ピボタル試験は表 2.7.4.1-26 及び表 2.7.4.1-27 にそれぞれ示す。

探索的試験の 19 例では、年齢の平均値（標準偏差）及び中央値（最小値～最大値）はそれぞれ 52.5 歳（12.52 歳）及び 51.0 歳（29～77 歳）で、73.7%（14 例）が男性であった。ECOG PS は、すべての被験者が 0（11 例、57.9%）又は 1（8 例、42.1%）であった。身長［平均値（標準偏差）、以降同様］は 165.16 cm（6.543 cm）、体重は 67.63 kg（9.651 kg）、BMI は 24.61 kg/m^2（2.730 kg/m^2）であった。

表 2.7.4.1-24 探索的試験の人口統計学的特性及びその他のベースライン特性 －1（902 試験）（最大の解析対象集団）

Parameter		All subjects (N=19)
Age (years)	N(Nmiss)	19 (0)
	Mean(SD)	52.5 (12.52)
	Median	51.0
	Min,Max	29, 77
Gender	Female	5 (26.3%)
	Male	14 (73.7%)
	Total	19 (100.0%)
Body Weight (kg)	N(Nmiss)	19 (0)
	Mean(SD)	67.63 (9.651)
	Median	68.00
	Min,Max	47.0, 83.0
Height (cm)	N(Nmiss)	19 (0)
	Mean(SD)	165.16 (6.543)
	Median	168.00
	Min,Max	147.0, 172.0
Body Mass Index (kg/m^2)	N(Nmiss)	19(0)
	Mean(SD)	24.61 (2.730)
	Median	24.00
	Min,Max	20.0, 31.2
ECOG Score	0	11 (57.9%)
	1	8 (42.1%)
	Total	19 (100.0%)

Source: Module 5, 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.2.1, Table 7.2.8
ECOG = Eastern Cooperative Oncology Group; Nmiss = The number of subjects with missing data; SD = standard deviation

初診時の PTCL の罹病期間の中央値（最小値～最大値）は 1.41 年（0.2～8.1 年）であった。19 例中 18 例（94.7%）が再発しており、再発回数の中央値は 2.00 回（0.0～4.0 回）であった。

PTCL の病期分類は IV 期が最も多く、判定結果が得られた 18 例中 11 例で報告された。その内訳は、IVA 期が 7 例（38.9%）、IVB 期が 4 例（22.2%）であった。次いで III 期が合計 4 例で報告され、内訳は IIIA 期が 3 例（16.7%）、IIIB 期が 1 例（5.6%）であった。

表 2.7.4.1-25 探索的試験の人口統計学的特性及びその他のベースライン特性 －2（902 試験）（最大の解析対象集団）

Parameter		All subjects (N=19)
Initial Disease Course (Year)	N(Nmiss)	19 (0)
	Mean(SD)	1.83 (1.883)
	Median	1.41
	Min,Max	0.2, 8.1
Relapse	Yes	18 (94.7%)
	No	1 (5.3%)
	Total	19 (100.0%)
Current Disease Course (Months)	N(Nmiss)	18 (0)
	Mean(SD)	2.962 (6.1785)
	Median	1.018
	Min,Max	0.03, 25.03
Number of Relapses	N(Nmiss)	19 (0)
	Mean(SD)	1.84 (1.167)
	Median	2.00
	Min,Max	0.0, 4.0
Clinical Stages	IIA	2 (11.1%)
	IIB	1 (5.6%)
	IIIA	3 (16.7%)
	IIIB	1 (5.6%)
	IVA	7 (38.9%)
	IVB	4 (22.2%)
	Total	18 (100.0%)
	Missing	1

Source: Module 5, 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.2.2, Table 7.2.3
Note: Initial disease course (years) = (the date of informed consent – the date of first diagnosis +1)/ 365.25; Current disease course (months) = (the date of informed consent – the date of relapse +1) / 365.25 * 12
Nmiss = The number of subjects with missing data; SD = standard deviation

ピボタル試験の 79 例では、年齢の平均値（標準偏差）及び中央値（最小値～最大値）はそれぞれ 49.6 歳（13.73 歳）及び 53.0 歳（20～77 歳）で、67.1%（53 例）が男性であった。ECOG PS は、ほとんどの被験者で 0（28 例、35.4%）又は 1（50 例、63.3%）であった。身長［平均値（標準偏差）、以降同様］は 167.56 cm（7.080 cm）、体重は 65.34 kg（11.686 kg）であり、BMI は 23.17 kg/m^2（3.492 kg/m^2）であった。

表 2.7.4.1-26 ピボタル試験の人口統計学的特性及びその他のベースライン特性 －1
（902 試験）（最大の解析対象集団）

Parameter		30 mg (N=79)
Age (years)	N(Nmiss)	79 (0)
	Mean(SD)	49.6 (13.73)
	Median	53.0
	Min,Max	20, 77
Gender	Female	26 (32.9%)
	Male	53 (67.1%)
	Total	79 (100.0%)
Body Weight (kg)	N(Nmiss)	79 (0)
	Mean(SD)	65.34 (11.686)
	Median	65.00
	Min,Max	44.0, 96.0
Height (cm)	N(Nmiss)	79 (0)
	Mean(SD)	167.56 (7.080)
	Median	168.00
	Min,Max	150.0, 183.0
Body Mass Index (Kg/m^2)	N(Nmiss)	76 (0)
	Mean(SD)	23.17 (3.492)
	Median	23.00
	Min,Max	15.0, 32.0
ECOG Score	0	28 (35.4%)
	1	50 (63.3%)
	2	1 (1.3%)
	Total	79 (100.0%)

Source: Module 5, 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.2.1, Table 7.2.8
ECOG = Eastern Cooperative Oncology Group ; Nmiss = The number of subjects with missing data; SD = standard deviation

初診時の PTCL の罹病期間の中央値（最小値～最大値）は 1.06 年（0.1～9.1 年）であった。79 例中 63 例（79.7%）が再発しており、再発回数の中央値は 1.00 回（0.0～4.0 回）であった。

PTCL の病期分類は IV 期が最も多く、次いで III 期が多かった。判定結果が得られた 74 例中、IV 期は 34 例（45.9%）であり、その内訳は IVA 期が 18 例（24.3%）、IVB 期が 16 例（21.6%）であった。III 期は 26 例（35.1%）であり、内訳は IIIA 期及び IIIB 期が各 13 例（17.6%）であった。II 期は 11 例（14.9%）、I 期は 3 例（4.1%）で報告された。

表 2.7.4.1-27 ピボタル試験の人口統計学的特性及びその他のベースライン特性 －2（902 試験）（最大の解析対象集団）

Parameter		30 mg (N=79)
Initial Disease Course(Year)	N(Nmiss)	79 (0)
	Mean(SD)	1.69 (1.932)
	Median	1.06
	Min,Max	0.1, 9.1
Relapse in current disease course	Yes	63 (79.7%)
	No	16 (20.3%)
	Total	79 (100.0%)
Current Disease Course(Months)	N(Nmiss)	63 (0)
	Mean(SD)	3.466 (8.7006)
	Median	0.953
	Min,Max	0.03, 60.35
Number of Relapses	N(Nmiss)	75 (4)
	Mean(SD)	1.09 (1.055)
	Median	1.00
	Min,Max	0.0, 4.0
Clinical Stages	IA	1 (1.4%)
	IB	2 (2.7%)
	IIA	7 (9.5%)
	IIB	4 (5.4%)
	IIIA	13 (17.6%)
	IIIB	13 (17.6%)
	IVA	18 (24.3%)
	IVB	16 (21.6%)
	Total	74 (100.0%)
	Missing	5

Source: Module 5, 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.2.2, Table 7.2.3
Note: Initial disease course (years) = (the date of informed consent – the date of first diagnosis +1)/ 365.25; Current disease course (months) = (the date of informed consent – the date of relapse +1) / 365.25 * 12
Nmiss = The number of subjects with missing data; SD = standard deviation

2.7.4.1.3.2 がんに対する前治療

2.7.4.1.3.2.1 日本人／韓国人第 2b 相試験（203 試験）

がんに対する前治療の要約を表 2.7.4.1-28 に示す。

全体集団では、安全性解析対象集団 55 例全例が、がんに対する前治療を 1 回以上受けており、全例が前治療として化学療法を受けていた。化学療法以外のがんに対する前治療としてダリナパルシンを 8 例（14.5%）が、フォロデシンを 6 例（10.9%）が受けていた。また、自家移植及び放射線療法を受けていた被験者が各 6 例（10.9%）であった。また、2 レジメン以上のがんに対する前治療を受けていた被験者は 38 例（69.1%）で、直近の化学療法の最良効果は完全奏効（CR）が 17 例（30.9%）、部分奏効（PR）が 13 例（23.6%）、安定（SD）が 12 例（21.8%）であった。前治療として放射線療法を受けていた被験者では、2 例（3.6%）が CR を達成した。

日本人集団では、39 例全例が、がんに対する前治療を 1 回以上受けており、全例が前治療として化学療法を受けていた。化学療法以外のがんに対する前治療として 7 例（17.9%）がダリナパルシン、6 例（15.4%）がフォロデシンの投与を受けていた。また、2 例（5.1%）が自家移植、4 例（10.3%）が放射線療法を受けていた。また、2 レジメン以上のがんに対する前治療を受けていた被験者は 24 例（61.5%）で、直近の化学療法の最良効果は CR が 13 例（33.3%）、SD が 11 例

（28.2%）、PR が 10 例（25.6%）であった。前治療として放射線療法を受けていた被験者では、2 例（5.1%）が CR を達成した。

表 2.7.4.1-28 がんに対する前治療（203 試験）（安全性解析対象集団）

Description	Category	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Number of subjects with at least one treatment agent type		n	39	16	55
Type of previous cancer therapy	Chemotherapy	n (%)	39 (100.0%)	16 (100.0%)	55 (100.0%)
	Other anticancer therapy	n (%)	14 (35.9%)	2 (12.5%)	16 (29.1%)
	Brentuximab vedotin	n (%)	1 (2.6%)	1 (6.3%)	2 (3.6%)
	Darinaparsin	n (%)	7 (17.9%)	1 (6.3%)	8 (14.5%)
	E7777[a]	n (%)	2 (5.1%)	0 (0.0%)	2 (3.6%)
	Forodesine	n (%)	6 (15.4%)	0 (0.0%)	6 (10.9%)
	Mogamulizumab	n (%)	1 (2.6%)	0 (0.0%)	1 (1.8%)
	Rituximab	n (%)	2 (5.1%)	0 (0.0%)	2 (3.6%)
	Romidepsin	n (%)	4 (10.3%)	0 (0.0%)	4 (7.3%)
	Radiotherapy	n (%)	4 (10.3%)	2 (12.5%)	6 (10.9%)
	Hematopoietic stem cell transplantation	n (%)	2 (5.1%)	4 (25.0%)	6 (10.9%)
	Other prior therapy	n (%)	1 (2.6%)	1 (6.3%)	2 (3.6%)
Total number of previous cancer therapy regimens	1 regimen	n (%)	15 (38.5%)	2 (12.5%)	17 (30.9%)
	2 regimens	n (%)	10 (25.6%)	8 (50.0%)	18 (32.7%)
	3 regimens	n (%)	7 (17.9%)	1 (6.3%)	8 (14.5%)
	4 regimens	n (%)	2 (5.1%)	2 (12.5%)	4 (7.3%)
	5 or more regimens	n (%)	5 (12.8%)	3 (18.8%)	8 (14.5%)
	2 or more regimens	n (%)	24 (61.5%)	14 (87.5%)	38 (69.1%)
		Median	2.0	2.0	2.0
Refractory, relapsed and undetermined PTCL based on last previous treatment	Refractory	n (%)	15 (38.5%)	8 (50.0%)	23 (41.8%)
	Relapsed	n (%)	24 (61.5%)	8 (50.0%)	32 (58.2%)
	Undetermined	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Days from end of the last immediate previous treatment	< 3 months	n (%)	20 (51.3%)	7 (43.8%)	27 (49.1%)
	>=3 months	n (%)	19 (48.7%)	9 (56.3%)	28 (50.9%)
Number of days from end of the last immediate previous treatment (days)		n	39	16	55
		Mean	344.6	253.2	318.0
		SD	724.1	516.5	667.0
		Median	88.0	110.5	97.0
		Minimum	29	30	29
		Maximum	3861	2154	3861
Chemotherapy	Total number of regimens				
	1 regimen	n (%)	17 (43.6%)	3 (18.8%)	20 (36.4%)
	2 regimens	n (%)	10 (25.6%)	7 (43.8%)	17 (30.9%)
	3 regimens	n (%)	6 (15.4%)	2 (12.5%)	8 (14.5%)
	4 regimens	n (%)	3 (7.7%)	2 (12.5%)	5 (9.1%)
	5 or more regimens	n (%)	3 (7.7%)	2 (12.5%)	5 (9.1%)
	2 or more regimens	n (%)	22 (56.4%)	13 (81.3%)	35 (63.6%)
		Median	2.0	2.0	2.0

Description	Category	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
The last immediate previous chemotherapy best response	Complete response (CR)	n (%)	13 (33.3%)	4 (25.0%)	17 (30.9%)
	Unconfirmed complete response (CRu)	n (%)	1 (2.6%)	0 (0.0%)	1 (1.8%)
	Partial response (PR)	n (%)	10 (25.6%)	3 (18.8%)	13 (23.6%)
	Stable disease (SD)	n (%)	11 (28.2%)	1 (6.3%)	12 (21.8%)
	Relapsed disease or progressive disease (PD)	n (%)	4 (10.3%)	6 (37.5%)	10 (18.2%)
	Not assessable	n	0	1	1
	Unknown	n	0	1	1
Type of transplantation	Autologous transplantation	n (%)	2 (5.1%)	4 (25.0%)	6 (10.9%)
	Allogeneic transplantation	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
The last immediate previous radiotherapy best response	Complete response (CR)	n (%)	2 (5.1%)	0 (0.0%)	2 (3.6%)
	Unconfirmed complete response (CRu)	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Partial response (PR)	n (%)	0 (0.0%)	1 (6.3%)	1 (1.8%)
	Stable disease (SD)	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Relapsed disease or progressive disease (PD)	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not assessable	n	0	0	0
	Unknown	n	2	1	3

Source: Appendix Table 2.7.4.7-14
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set.
PTCL = peripheral T-cell lymphoma; SD = standard deviation
a: development code for denileukin diftitox
Subjects may have had more than one type of treatment agent.
Previous cancer therapy regimens included other prior therapy, radiotherapy and chemotherapy.
Number of days from end of the last immediate previous treatment (days) = date of first study drug – end date of last immediate previous treatment + 1
Days from end of the last immediate previous treatment (months) = (date of first study drug – end date of last immediate previous treatment + 1)/30.4375.
Data cut-off date: [redacted] 20[redacted]

2.7.4.1.3.2.2 日本人第 1 相試験（201 試験）

がんに対する前治療の要約を表 2.7.4.1-29 に示す。

全体では、安全性解析対象集団の 14 例全例が前治療として化学療法を受けており、そのサイクル数［中央値（最小値～最大値）、以降同様］は、6.0 サイクル（2～10 サイクル）であった。前治療の化学療法の最良効果は CR（7 例、50.0%）が最も多く、次いで PR（3 例、21.4%）であった。化学療法以外では、放射線療法を受けていた被験者が 3 例（21.4%）、免疫療法及び UV 光療法が各 1 例（7.1%）であった。がんに対する前治療のレジメン数は 2.5 レジメン（1～9 レジメン）であった。

40 mg コホートの 7 例では、前治療の化学療法のサイクル数［中央値（最小値～最大値）、以降同様］は、6.0 サイクル（2～8 サイクル）であった。前治療の化学療法の最良効果は PR 及び CR（各 3 例、42.9%）が多かった。化学療法以外では、放射線療法、免疫療法及び UV 光療法を受けていた被験者が各 1 例（14.3%）であった。がんに対する前治療のレジメン数は 3.0 レジメン（1～8 レジメン）であった。

表 2.7.4.1-29 がんに対する前治療（201 試験）（安全性解析対象集団）

Description	Category	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
Number of patients with at least one treatment agent type		n	7	7	14
Previous Treatment agent type	Chemotherapy	n (%)	7 (100.0%)	7 (100.0%)	14 (100.0%)
	Radiation therapy	n (%)	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Immuno therapy	n (%)	0 (0.0%)	1 (14.3%)	1 (7.1%)
	UV light therapy	n (%)	0 (0.0%)	1 (14.3%)	1 (7.1%)
Previous Chemotherapy best response	Complete response	n (%)	4 (57.1%)	3 (42.9%)	7 (50.0%)
	Partial response	n (%)	0 (0.0%)	3 (42.9%)	3 (21.4%)
	Stable disease	n (%)	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Progressive disease	n (%)	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Unknown	n	1	0	1
Number of cycles	Chemotherapy	n	7	7	14
		Mean	6.4	5.9	6.1
		SD	1.62	2.48	2.03
		Median	6.0	6.0	6.0
		Minimum	5	2	2
		Maximum	10	8	10
Radiation source	X-ray	n (%)	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Electron ray	n (%)	1 (14.3%)	0 (0.0%)	1 (7.1%)
Type of UV light therapy	UVB	n (%)	0 (0.0%)	1 (14.3%)	1 (7.1%)
Total number of regimens		n	7	7	14
		Mean	3.0	3.1	3.1
		SD	2.89	2.27	2.50
		Median	2.0	3.0	2.5
		Minimum	1	1	1
		Maximum	9	8	9

Source: Appendix Table 2.7.4.7-15
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
SD = standard deviation
Patients may have had more than one type of treatment agent.
Percentage of best responses, radiation source and type of UV light therapy was calculated based on the number of patients with chemotherapy, radiation therapy and UV light therapy in each cohort of the analysis set, respectively.
If patients had more than one chemotherapy regimen, best response to any prior therapy is presented.
The number of cycles denotes the highest number of cycles given among all prior chemotherapy regimens.

2.7.4.1.3.2.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

がんに対する前治療の要約を表 2.7.4.1-30 に示す。

安全性解析対象集団の 23 例全例が、がんに対する前治療を 1 回以上受けていた。これらのうち、前治療として化学療法の単独治療を受けていた被験者は 17 例（73.9%）、モガムリズマブの単独療法は 12 例（52.2%）、モガムリズマブと化学療法の併用療法は 11 例（47.8%）であった。10 例（43.5%）はモガムリズマブ不耐性であった。前治療として放射線療法を受けていた被験者は 2 例（8.7%）であった。

また、2 レジメン以上のがんに対する前治療を受けていた被験者は 18 例（78.3%）であった。直近の化学療法の最良効果は PR が 8 例（34.8%）で最も多く、次いで疾患再発又は進行（PD）が 5 例（21.7%）、CR が 4 例（17.4%）であった。直近のモガムリズマブ治療の最良効果は、PR が 6 例（26.1%）で最も多く、次いで CR が 3 例（13.0%）であった。前治療として放射線療法を受け

ていた 1 例（4.3%）は CR を達成した。

表 2.7.4.1-30 がんに対する前治療（210 試験）（安全性解析対象集団）

Description	Category	Statistic	40 mg (N=23)
Number of subjects with at least one treatment agent type		n	23
Type of previous cancer therapy	Chemotherapy alone	n (%)	17 (73.9%)
	Chemotherapy plus Mogamulizumab Therapy	n (%)	11 (47.8%)
	Mogamulizumab Monotherapy	n (%)	12 (52.2%)
	Radiotherapy	n (%)	2 (8.7%)
	Hematopoietic stem cell transplantation	n (%)	0 (0.0%)
	Other prior therapy	n (%)	3 (13.0%)
Number of subjects with:	Mogamulizumab tolerance	n (%)	13 (56.5%)
	Mogamulizumab in-tolerance	n (%)	10 (43.5%)
Total number of previous cancer therapy regimens	1 regimen	n (%)	5 (21.7%)
	2 regimens	n (%)	6 (26.1%)
	3 regimens	n (%)	4 (17.4%)
	4 regimens	n (%)	4 (17.4%)
	5 or more regimens	n (%)	4 (17.4%)
	2 or more regimens	n (%)	18 (78.3%)
		Median	3.0
Relapsed, recurrent, refractory and undetermined ATL based on last previous treatment	Relapsed	n (%)	5 (21.7%)
	Recurrent	n (%)	13 (56.5%)
	Refractory	n (%)	5 (21.7%)
	Undetermined	n (%)	0 (0.0%)
Days from end of the last immediate previous treatment	< 3 months	n (%)	12 (52.2%)
	>=3 months	n (%)	11 (47.8%)
Number of days from end of the last immediate previous treatment (days)		n	23
		Mean	131.0
		SD	138.6
		Median	89.0
		Minimum	30
		Maximum	496
Chemotherapy	Total number of regimens		
	1 regimen	n (%)	6 (26.1%)
	2 regimens	n (%)	6 (26.1%)
	3 regimens	n (%)	3 (13.0%)
	4 regimens	n (%)	5 (21.7%)
	5 or more regimens	n (%)	3 (13.0%)
	2 or more regimens	n (%)	17 (73.9%)
		Median	2.0
The last immediate previous chemotherapy best response	Complete response (CR)	n (%)	4 (17.4%)
	Unconfirmed complete response (CRu)	n (%)	1 (4.3%)
	Partial response (PR)	n (%)	8 (34.8%)
	Stable disease (SD)	n (%)	3 (13.0%)
	Relapsed disease or progressive disease (PD)	n (%)	5 (21.7%)
	Not assessable	n	2
	Unknown	n	0
Type of transplantation	Autologous transplantation	n (%)	0 (0.0%)
	Allogeneic transplantation	n (%)	0 (0.0%)

Description	Category	Statistic	40 mg (N=23)
The last immediate previous radiotherapy best response	Complete response (CR)	n (%)	1 (4.3%)
	Unconfirmed complete response (CRu)	n (%)	0 (0.0%)
	Partial response (PR)	n (%)	0 (0.0%)
	Stable disease (SD)	n (%)	0 (0.0%)
	Relapsed disease or progressive disease (PD)	n (%)	0 (0.0%)
	Not assessable	n	0
	Unknown	n	1
The last immediate previous mogamulizumab therapy best response	Complete response (CR)	n (%)	3 (13.0%)
	Unconfirmed complete response (CRu)	n (%)	0 (0.0%)
	Partial response (PR)	n (%)	6 (26.1%)
	Stable disease (SD)	n (%)	2 (8.7%)
	Relapsed disease or progressive disease (PD)	n (%)	1 (4.3%)
	Not assessable	n	2
	Unknown	n	0
Number of days from end of the last immediate previous Mogamulizumab therapy (days)		n	14
		Mean	210.1
		SD	159.1
		Median	134.0
		Minimum	30
		Maximum	534

Source: Appendix Table 2.7.4.7-16 (cited from the new drug application for relapsed or refractory ATL)
n = number of subjects; % = percentages of subjects were calculated relative to the total number of subjects in the analysis set.
ATL = adult T-cell lymphoma; SD = standard deviation
Subjects may have had more than one type of cancer therapy. Data for mogamulizumab monotherapy and combination therapy were provided by Medical Reviewer.
Number of regimens were provided by Medical Reviewer. Previous cancer therapy regimens included other prior therapy, radiotherapy and chemotherapy.
Subjects with relapsed, recurrent, refractory and undetermined ATL are confirmed by Medical Expert.
Days from end of the last immediate previous treatment (months) = (date of first study drug – end date of last immediate previous treatment + 1)/30.4375
Number of days from end of the last immediate previous treatment (days) = date of first study drug – end date of last immediate previous treatment + 1
Data for total number of regimens was provided by Medical Reviewer.
Total number of regimens for chemotherapy and the last immediate previous chemotherapy best response included mogamulizumab therapy. Chemotherapy included molecular targeted therapy and others.
Best response for last immediate previous mogamulizumab therapy included monotherapy and combination therapy. In the event when combination therapy was used, best response from the mogamulizumab treatment is presented.
Last immediate previous mogamulizumab therapy applies to subjects who had mogamulizumab therapy (either monotherapy or combination therapy) as last immediate therapy before the administration of tucidinostat
Data cut-off date: [redacted] 20[redacted]

2.7.4.1.3.2.4 中国人第 2 相試験（902 試験）

探索的試験及びピボタル試験における PTCL に対する前治療の要約をそれぞれ表 2.7.4.1-31 及び表 2.7.4.1-32 に示す。

探索的試験では、被験者の大半（19 例中 14 例、73.7%）が前治療として 2 種類の化学療法を受けていた。

ピボタル試験では 79 例中 36 例（45.6%）が前治療として 3 種類以上の化学療法を受けており、24 例（30.4%）が 2 種類、18 例（22.8%）が 1 種類の化学療法を受けていた。残りの 1 例（1.3%）は前治療として化学療法を受けていたが、そのレジメン及び種類は不明であった。

表 2.7.4.1-31 探索的試験の PTCL に対する前治療（902 試験）（最大の解析対象集団）

Parameter	Number	All subjects (N=19)
Chemotherapy regimen before enrollment	1	4 (21.1%)
	2	14 (73.7%)
	>2	1 (5.3%)
	Total	19 (100.0%)

Source: Module 5, 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.2.6

表 2.7.4.1-32 ピボタル試験の PTCL に対する前治療（902 試験）（最大の解析対象集団）

Parameter	Number	30 mg (N=79)
Chemotherapy Regimen before Enrollment	NA	1 (1.3%)
	1	18 (22.8%)
	2	24 (30.4%)
	>2	36 (45.6%)
	Total	79 (100.0%)

Source: Module 5, 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.2.6
NA: The number of chemotherapy received prior to enrollment for patient [redacted] was presented as “NA”, with the name of drug used indicated as unknown.

2.7.4.1.3.3 併用薬／併用療法

2.7.4.1.3.3.1 日本人／韓国人第 2b 相試験（203 試験）

併用薬の要約を付録表 2.7.4.7-17 に示す。

全体集団では、安全性解析対象集団 55 例全例が併用薬を使用していた。解剖治療化学分類（ATC）別で最も多く使用された併用薬は「消化性潰瘍と胃食道逆流用薬」（37 例、67.3%）であり、次いで「その他の鎮痛薬と解熱薬」（26 例、47.3%）、「抗炎症及び抗リウマチ製剤、非ステロイド系」（23 例、41.8%）であった。

日本人集団の 39 例では、ATC 別で最も多く使用された併用薬は「消化性潰瘍と胃食道逆流用薬」（26 例、66.7%）であり、次いで「X 線造影剤、ヨウ化物」（21 例、53.8%）、「その他の鎮痛薬と解熱薬」（22 例、56.4%）、「スルホンアミドとトリメトプリム」（19 例、48.7%）、「便秘薬」（18 例、46.2%）であった。

2.7.4.1.3.3.2 日本人第 1 相試験（201 試験）

併用薬の要約を付録表 2.7.4.7-18 に示す。

全体では、安全性解析対象集団の 14 例全例が併用薬を使用していた。ATC 別で最も多く使用された併用薬は「消化性潰瘍と胃食道逆流用薬」（9 例、64.3%）であり、次いで「便秘薬」（6 例、42.9%）、「抗痛風製剤」及び「その他の鎮痛薬と解熱薬」（各 5 例、35.7%）であった。

40 mg コホートでは、7 例全例が併用薬を使用していた。ATC 分類別で最も多く使用された併用薬は、「消化性潰瘍と胃食道逆流用薬」（6 例、85.7%）であり、次いで「便秘薬」及び「抗炎症及び抗リウマチ製剤、非ステロイド系」（各 4 例、57.1%）であった。

2.7.4.1.3.3.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

併用薬の要約を付録表 2.7.4.7-19 に示す。

安全性解析対象集団の 23 例全例が併用薬を使用していた。ATC 別で最も多く使用された併用薬は「消化性潰瘍と胃食道逆流用薬」（20 例、87.0%）であり、次いで「スルホンアミドとトリメトプリム」（14 例、60.9%）、「皮膚軟化薬と保護薬」及び「睡眠薬と鎮静薬」（各 13 例、56.5%）、「便秘薬」（12 例、52.2%）、「抗痛風製剤」（10 例、43.5%）であった。

2.7.4.1.3.3.4 中国人第 2 相試験（902 試験）

探索的試験及びピボタル試験における併用薬の要約を 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.5 及び 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.5 に示す。

探索的試験では、安全性解析対象集団の 19 例中 11 例（57.9%）が疾患の状態により新規の併用薬を必要とした。ATC 別で最も多く使用された併用薬は「免疫賦活薬」（4 例、21.1%）であり、「全身用抗菌薬」（3 例、15.8%）がこれに次いで多かった。

ピボタル試験では、安全性解析対象集団の 83 例中 46 例（55.4%）の被験者が疾患の状態により新規の併用薬を必要とした。ATC 別で最も多く使用された併用薬は「免疫賦活薬」（27 例、32.5%）であり、次いで「全身用抗菌薬」（19 例、22.9%）、「胃酸関連疾患用薬」及び「代用血液と灌流液」（各 9 例、10.8%）であった。

2.7.4.2 有害事象

2.7.4.2.1 有害事象の解析

2.7.4.2.1.1 有害事象の要約

2.7.4.2.1.1.1 日本人／韓国人第 2b 相試験（203 試験）

有害事象の概要を表 2.7.4.2-1 に示す。

全体集団では、安全性解析対象集団 55 例全例に 1 件以上の有害事象が認められ、このうち 51 例（92.7%）で治験薬と関連性のある有害事象が認められた。重篤な有害事象が 14 例（25.5%）に認められ、このうち 10 例（18.2%）で治験薬と関連性のある重篤な有害事象が認められた。Grade 3 以上の有害事象は 46 例（83.6%）、治験薬の休薬又は減量に至った有害事象は 40 例（72.7%）、治験薬の投与中止に至った有害事象は 18 例（32.7%）に認められた。本試験では、1 例（1.8%）が有害事象により死亡した。

日本人集団では、39 例全例に 1 件以上の有害事象が認められ、全例で治験薬と関連性のある有害事象が認められた。重篤な有害事象が 11 例（28.2%）に認められ、このうち 8 例（20.5%）で治験薬と関連性のある重篤な有害事象が認められた。Grade 3 以上の有害事象は 34 例（87.2%）、治験薬の休薬又は減量に至った有害事象は 31 例（79.5%）、治験薬の投与中止に至った有害事象は 15 例（38.5%）に認められた。日本人集団では、死亡に至った有害事象は認められなかった。

表 2.7.4.2-1 有害事象の概要（203 試験）（安全性解析対象集団）

Description	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Number of subjects with			
At least one TEAE	39 (100.0%)	16 (100.0%)	55 (100.0%)
At least one TEAE related to the study drug	39 (100.0%)	12 (75.0%)	51 (92.7%)
At least one serious TEAE	11 (28.2%)	3 (18.8%)	14 (25.5%)
At least one serious TEAE related to the study drug	8 (20.5%)	2 (12.5%)	10 (18.2%)
At least one TEAE leading to dose reduction or interruption	31 (79.5%)	9 (56.3%)	40 (72.7%)
At least one TEAE leading to study drug discontinuation	15 (38.5%)	3 (18.8%)	18 (32.7%)
At least one TEAE leading to death	0 (0.0%)	1 (6.3%)	1 (1.8%)
At least one TEAE with grade 3 or higher	34 (87.2%)	12 (75.0%)	46 (83.6%)
At least one TEAE with grade 3 or higher and related to the study drug	33 (84.6%)	9 (56.3%)	42 (76.4%)

Source: Appendix Table 2.7.4.7-20
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Data cut-off date: [redacted] 20[redacted]

2.7.4.2.1.1.2 日本人第 1 相試験（201 試験）

有害事象の概要を表 2.7.4.2-2 に示す。

全体では、安全性解析対象集団の 14 例中 13 例（92.9%）に 1 件以上の有害事象が認められ、その 13 例全例で治験薬と関連性のある有害事象が認められた。なお、本試験の安全性解析対象集団には、本薬を 1 回投与した後に治験実施計画書不適格のため治験薬の投与を中止した 1 例（有害事象発現なし）が含まれている。重篤な有害事象が 2 例（14.3%）に認められ、このうち 1 例（7.1%）で治験薬と関連性のある重篤な有害事象が認められた。Grade 3 以上の有害事象は 11 例（78.6%）、治験薬の休薬又は減量に至った有害事象は 8 例（57.1%）、投与中止に至った有害事象は 6 例（42.9%）に認められた。本試験では死亡に至った有害事象は認められなかった。

40 mg コホートでは、7 例全例に 1 件以上の有害事象が認められ、その全例で治験薬と関連性のある有害事象が認められた。治験薬と関連性のある重篤な有害事象が 1 例（14.3%）に認められた。Grade 3 以上の有害事象は 6 例（85.7%）、治験薬の休薬又は減量に至った有害事象及び投与中止に至った有害事象は各 4 例（57.1%）に認められた。

表 2.7.4.2-2 有害事象の概要（201 試験）（安全性解析対象集団）

Description	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Number of patients with			
At least one TEAE	6 (85.7%)	7 (100.0%)	13 (92.9%)
At least one TEAE related to the study drug	6 (85.7%)	7 (100.0%)	13 (92.9%)
At least one serious TEAE	1 (14.3%)	1 (14.3%)	2 (14.3%)
At least one serious TEAE related to the study drug	0 (0.0%)	1 (14.3%)	1 (7.1%)
A TEAE leading to dose reduction or delay	4 (57.1%)	4 (57.1%)	8 (57.1%)
A TEAE leading to study drug discontinuation	2 (28.6%)	4 (57.1%)	6 (42.9%)
A TEAE leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity			
Grade 1: Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 2: Moderate	1 (14.3%)	1 (14.3%)	2 (14.3%)
Grade 3: Severe	5 (71.4%)	4 (57.1%)	9 (64.3%)
Grade 4: Life-Threatening	0 (0.0%)	2 (28.6%)	2 (14.3%)
Grade 5: Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 3 or higher	5 (71.4%)	6 (85.7%)	11 (78.6%)
Causal relationship			
Unrelated	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unlikely	0 (0.0%)	0 (0.0%)	0 (0.0%)
Possible	0 (0.0%)	1 (14.3%)	1 (7.1%)
Probable	4 (57.1%)	3 (42.9%)	7 (50.0%)
Definite	2 (28.6%)	3 (42.9%)	5 (35.7%)

Source: Appendix Table 2.7.4.7-21
Severities were graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients were calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE were counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

2.7.4.2.1.1.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

有害事象の概要を表 2.7.4.2-3 に示す。

安全性解析対象集団の 23 例全例に 1 件以上の有害事象が認められ、全例で治験薬と関連性のある有害事象が認められた。重篤な有害事象が 7 例（30.4%）に認められ、このうち 6 例（26.1%）で治験薬と関連性のある重篤な有害事象が認められた。Grade 3 以上の有害事象は 18 例（78.3%）、治験薬の休薬又は減量に至った有害事象は 16 例（69.6%）、投与中止に至った有害事象は 9 例（39.1%）に認められた。本試験では死亡に至った有害事象は認められなかった。

表 2.7.4.2-3 有害事象の概要（210 試験）（安全性解析対象集団）

Description	40 mg (N=23) n (%)
Number of subjects with	
At least one TEAE	23 (100.0%)
At least one TEAE related to the study drug	23 (100.0%)
At least one serious TEAE	7 (30.4%)
At least one serious TEAE related to the study drug	6 (26.1%)
At least one TEAE leading to dose reduction or interruption	16 (69.6%)
At least one TEAE leading to study drug discontinuation	9 (39.1%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	18 (78.3%)
At least one TEAE with grade 3 or higher and related to the study drug	18 (78.3%)

Source: Appendix Table 2.7.4.7-22 (cited from the new drug application for relapsed or refractory ATL)
Severities were graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects were calculated relative to the total number of subjects in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE were counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Data cut-off date: [redacted] 20[redacted]

2.7.4.2.1.1.4 中国人第 2 相試験（902 試験）

探索的試験及びピボタル試験における有害事象の概要を表 2.7.4.2-4 及び表 2.7.4.2-5 にそれぞれ示す。

探索的試験では、安全性解析対象集団 19 例中 14 例（73.7%）で 1 件以上の有害事象が認められた。このうち、11 例（57.9%）で治験薬と関連性のある有害事象が認められた。重篤な有害事象が 1 例（5.3%）に認められ、治験薬と関連性のある重篤な有害事象と判定された。投与中止に至った有害事象が 3 例（15.8%）に認められた。探索的試験では、死亡に至った有害事象は認められなかった。

表 2.7.4.2-4 探索的試験における有害事象の概要（902 試験）（安全性解析対象集団）

	Number of Cases (N=19)	Incident Rate (95% CI)
At least 1 AE	14	73.7% (48.8%, 90.9%)
At least 1 ADR	11	57.9% (33.5%, 79.7%)
At least 1 significant AE	11	57.9% (33.5%, 79.7%)
At least 1 SAE	1	5.3% (0.1%, 26.0%)
At least 1 SAE related to the study drug	1	5.3% (0.1%, 26.0%)
Death due to AE	0	0.0% (0.0%, 17.6%)
At least 1 AE that led to discontinuation of the study drug	3	15.8% (3.4%, 39.6%)

Source: Module 5, 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.1
ADR = adverse drug reaction; AE = adverse event; CI = confidence interval; SAE = serious adverse event
ADR: definitely study drug related, probably related, and cannot be determined.
Significant AE: Unexpected medical events that lead to discontinuation of the drug, or need medical intervention to resolve or prevent progression except for serious adverse events.

ピボタル試験では、安全性解析対象集団 83 例中 68 例（81.9%）に 1 件以上の有害事象が認められ、このうち 60 例（72.3%）で治験薬と関連性のある有害事象が認められた。重篤な有害事象

が 7 例（8.4%）に認められ、このうち 2 例（2.4%）で治験薬と関連性のある有害事象が認められた。投与中止に至った有害事象が 14 例（16.9%）に認められ、死亡に至った有害事象が 3 例（3.6%）に認められた。

表 2.7.4.2-5 ピボタル試験における有害事象の概要（902 試験）（安全性解析対象集団）

	Number of Cases (N=83)	Incident Rate (95% CI)
At least 1 AE	68	81.9% (72.0%, 89.5%)
At least 1 ADR	60	72.3% (61.4%, 81.6%)
At least 1 significant AE	50	60.2% (48.9%, 70.8%)
At least 1 SAE	7	8.4% (3.5%, 16.6%)
At least 1 SAE related to the study drug	2	2.4% (0.3%, 8.4%)
Death due to AE	3	3.6% (0.8%, 10.2%)
At least 1 AE that led to discontinuation of the study drug	14	16.9% (9.5%, 26.7%)

Source: Module 5, 5.3.5.4-2TG0902CDM p2b/Statistical Analysis Report/Table 7.4.1
ADR = adverse drug reaction; AE = adverse event; CI = confidence interval; SAE = serious adverse event
ADR: definitely study drug related, probably related, and cannot be determined.
Significant AE: adverse events that led to the exit of study, adjusted dosing regimen, or required drug intervention.

2.7.4.2.1.2 比較的よくみられる有害事象

2.7.4.2.1.2.1 日本人／韓国人第 2b 相試験（203 試験）

203 試験で 10%以上の被験者に認められた有害事象を SOC 別及び PT 別に表 2.7.4.2-6 に示す。

全体集団では、SOC 別の主な有害事象は「血液およびリンパ系障害」（55 例中 52 例、94.5%）が最も多く、「胃腸障害」（32 例、58.2%）及び「一般・全身障害および投与部位の状態」（27 例、49.1%）がこれに次いだ。PT 別の主な有害事象（発現割合 30%以上）は血小板減少症*（46 例、83.6%）、好中球減少症*（31 例、56.4%）、白血球減少症*（24 例、43.6%）、貧血*（18 例、32.7%）、下痢（17 例、30.9%）であった。

日本人集団で、SOC 別の主な有害事象は「血液およびリンパ系障害」（39 例中 38 例、97.4%）が最も多く、「胃腸障害」（25 例、64.1%）及び「臨床検査」（24 例、61.5%）がこれに次いだ。

PT 別の主な有害事象（発現割合 30%以上）は血小板減少症*（35 例、89.7.%）、好中球減少症*（28 例、71.8%）、白血球減少症*（24 例、61.5%）、リンパ球減少症*（16 例、41.0%）、貧血*及び下痢（各 14 例、35.9%）であった。

表 2.7.4.2-6 10%以上の被験者に認められた有害事象（203 試験）（安全性解析対象集団）

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Number of subjects with at least one TEAE	39 (100.0%)	16 (100.0%)	55 (100.0%)
血液およびリンパ系障害	38 (97.4%)	14 (87.5%)	52 (94.5%)
血小板減少症*	35 (89.7%)	11 (68.8%)	46 (83.6%)
好中球減少症*	28 (71.8%)	3 (18.8%)	31 (56.4%)
白血球減少症*	24 (61.5%)	0 (0.0%)	24 (43.6%)
貧血*	14 (35.9%)	4 (25.0%)	18 (32.7%)
リンパ球減少症*	16 (41.0%)	0 (0.0%)	16 (29.1%)
胃腸障害	25 (64.1%)	7 (43.8%)	32 (58.2%)
下痢	14 (35.9%)	3 (18.8%)	17 (30.9%)
悪心	9 (23.1%)	3 (18.8%)	12 (21.8%)
一般・全身障害および投与部位の状態	19 (48.7%)	8 (50.0%)	27 (49.1%)
発熱	5 (12.8%)	6 (37.5%)	11 (20.0%)
倦怠感	8 (20.5%)	0 (0.0%)	8 (14.5%)
疲労	4 (10.3%)	2 (12.5%)	6 (10.9%)
臨床検査	24 (61.5%)	1 (6.3%)	25 (45.5%)
血中アルカリホスファターゼ増加	8 (20.5%)	0 (0.0%)	8 (14.5%)
γ－グルタミルトランスフェラーゼ増加	8 (20.5%)	0 (0.0%)	8 (14.5%)
アスパラギン酸アミノトランスフェラーゼ増加	7 (17.9%)	0 (0.0%)	7 (12.7%)
体重減少	6 (15.4%)	0 (0.0%)	6 (10.9%)
代謝および栄養障害	16 (41.0%)	9 (56.3%)	25 (45.5%)
食欲減退	8 (20.5%)	5 (31.3%)	13 (23.6%)
神経系障害	7 (17.9%)	2 (12.5%)	9 (16.4%)
頭痛	4 (10.3%)	2 (12.5%)	6 (10.9%)
呼吸器、胸郭および縦隔障害	14 (35.9%)	7 (43.8%)	21 (38.2%)
咳嗽	2 (5.1%)	4 (25.0%)	6 (10.9%)

Source: Appendix Table 2.7.4.7-23
MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anaemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Preferred terms >= 10% is defined as the percentages of preferred terms based on number of subjects in the total column.
TEAE of overdose is not included in this analysis.
Data cut-off date: [redacted] 20[redacted]

2.7.4.2.1.2.2 日本人第 1 相試験（201 試験）

201 試験で 10%以上の被験者に認められた有害事象を SOC 別及び PT 別に表 2.7.4.2-7 に示す。

全体では、SOC 別の主な有害事象は「臨床検査」（14 例中 11 例、78.6%）、「血液およびリンパ系障害」及び「代謝および栄養障害」（各 10 例、71.4%）、並びに「一般・全身障害および投与部位の状態」及び「胃腸障害」（各 7 例、50.0%）であった。PT 別の主な有害事象（発現割合 30%以上）は血小板数減少及び血小板減少症（各 6 例、42.9%）、貧血（5 例、35.7%）であった。

グループ化した血液学的有害事象で最も発現割合が高かった事象は血小板減少症*（12 例、85.7%）で、貧血*、好中球減少症*及び白血球減少症*（各 5 例、35.7%）がこれに次いだ（付録表

2.7.4.7-51）。

40 mg コホートでは、SOC 別の主な有害事象は「臨床検査」（7 例中 7 例、100.0%）、「代謝および栄養障害」（6 例、85.7%）、「血液およびリンパ系障害」（5 例、71.4%）、「胃腸障害」（4 例、57.1%）、「一般・全身障害および投与部位の状態」及び「感染症および寄生虫症」（各 3 例、42.9%）であった。

PT 別の主な有害事象（発現割合 30%以上）は血小板減少症（4 例、57.1%）、血小板数減少及び低カルシウム血症（各 3 例、42.9%）であった。

グループ化した血液学的有害事象で最も発現割合が高かった事象は血小板減少症*（7 例、100.0%）で、好中球減少症*（2 例、28.6%）、白血球減少症*（1 例、14.3%）がこれに次いだ（付録表 2.7.4.7-51）。

表 2.7.4.2-7　10%以上の被験者に認められた有害事象（201 試験）（安全性解析対象集団）

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Number of patients with at least one TEAE	6 (85.7%)	7 (100.0%)	13 (92.9%)
血液およびリンパ系障害	5 (71.4%)	5 (71.4%)	10 (71.4%)
貧血	5 (71.4%)	0 (0.0%)	5 (35.7%)
好中球減少症	1 (14.3%)	2 (28.6%)	3 (21.4%)
血小板減少症	2 (28.6%)	4 (57.1%)	6 (42.9%)
胃腸障害	3 (42.9%)	4 (57.1%)	7 (50.0%)
腹痛	1 (14.3%)	1 (14.3%)	2 (14.3%)
下痢	3 (42.9%)	1 (14.3%)	4 (28.6%)
悪心	1 (14.3%)	2 (28.6%)	3 (21.4%)
一般・全身障害および投与部位の状態	4 (57.1%)	3 (42.9%)	7 (50.0%)
疲労	3 (42.9%)	1 (14.3%)	4 (28.6%)
発熱	1 (14.3%)	2 (28.6%)	3 (21.4%)
感染症および寄生虫症	2 (28.6%)	3 (42.9%)	5 (35.7%)
鼻咽頭炎	0 (0.0%)	2 (28.6%)	2 (14.3%)
臨床検査	4 (57.1%)	7 (100.0%)	11 (78.6%)
C-反応性蛋白増加	1 (14.3%)	1 (14.3%)	2 (14.3%)
好中球数減少	2 (28.6%)	0 (0.0%)	2 (14.3%)
血小板数減少	3 (42.9%)	3 (42.9%)	6 (42.9%)
体重減少	1 (14.3%)	2 (28.6%)	3 (21.4%)
白血球数減少	3 (42.9%)	1 (14.3%)	4 (28.6%)
代謝および栄養障害	4 (57.1%)	6 (85.7%)	10 (71.4%)
高トリグリセリド血症	1 (14.3%)	1 (14.3%)	2 (14.3%)
高尿酸血症	2 (28.6%)	0 (0.0%)	2 (14.3%)
低カルシウム血症	0 (0.0%)	3 (42.9%)	3 (21.4%)
低カリウム血症	2 (28.6%)	1 (14.3%)	3 (21.4%)
食欲減退	1 (14.3%)	2 (28.6%)	3 (21.4%)
筋骨格系および結合組織障害	1 (14.3%)	2 (28.6%)	3 (21.4%)
背部痛	0 (0.0%)	2 (28.6%)	2 (14.3%)
神経系障害	3 (42.9%)	1 (14.3%)	4 (28.6%)
味覚異常	2 (28.6%)	1 (14.3%)	3 (21.4%)
頭痛	1 (14.3%)	1 (14.3%)	2 (14.3%)

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
精神障害	1 (14.3%)	1 (14.3%)	2 (14.3%)
不眠症	1 (14.3%)	1 (14.3%)	2 (14.3%)

Source: Appendix Table 2.7.4.7-24
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

2.7.4.2.1.2.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

210 試験で 10%以上の被験者に認められた有害事象を SOC 別及び PT 別に表 2.7.4.2-8 に示す。

本試験の SOC 別の主な有害事象は「血液およびリンパ系障害」（23 例中 19 例、82.6%）が最も多く、「一般・全身障害および投与部位の状態」及び「代謝および栄養障害」（各 13 例、56.5%）がこれに次いだ。

PT 別の主な有害事象（発現割合 30%以上）は血小板減少症*（18 例、78.3%）が最も多く、次いで好中球減少症*（12 例、52.2%）、白血球減少症*（10 例、43.5%）、貧血*（9 例、39.1%）、食欲減退（8 例、34.8%）、及び倦怠感（7 例、30.4%）であった。

表 2.7.4.2-8 10%以上の被験者に認められた有害事象（210 試験）（安全性解析対象集団）

System organ class Preferred term	40 mg (N=23) n (%)
Number of subjects with at least one TEAE	23 (100.0%)
血液およびリンパ系障害	19 (82.6%)
血小板減少症*	18 (78.3%)
好中球減少症*	12 (52.2%)
白血球減少症*	10 (43.5%)
貧血*	9 (39.1%)
胃腸障害	9 (39.1%)
下痢	6 (26.1%)
腹痛	3 (13.0%)
悪心	3 (13.0%)
一般・全身障害および投与部位の状態	13 (56.5%)
倦怠感	7 (30.4%)
疲労	3 (13.0%)
発熱	3 (13.0%)
臨床検査	10 (43.5%)
体重減少	4 (17.4%)
代謝および栄養障害	13 (56.5%)
食欲減退	8 (34.8%)
低アルブミン血症	3 (13.0%)
筋骨格系および結合組織障害	7 (30.4%))
背部痛	4 (17.4%)
神経系障害	9 (39.1%)

System organ class Preferred term	40 mg (N=23) n (%)
味覚異常	4 (17.4%)

Source: Appendix Table 2.7.4.7-25 (cited from the new drug application for relapsed or refractory ATL)
MedDRA Version 21.1 was used to code adverse events
N = number of subjects in the Safety Analysis Set.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anaemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Preferred terms >= 10% is defined as the percentages of preferred terms based on number of subjects in the 40 mg column.
TEAE of overdose is not included in this analysis.
Data cut-off date: [redacted] 20[redacted]

2.7.4.2.1.2.4 中国人第 2 相試験（902 試験）

902 試験の探索的試験及びピボタル試験で 10%以上の被験者に認められた有害事象をそれぞれ表 2.7.4.2-9 及び表 2.7.4.2-10 に示す。

探索的試験では、大分類別の主な有害事象は、「臨床検査」（19 例中 10 例、52.6%）が最も多く、次いで「一般・全身障害および投与部位の状態」（7 例、36.8%）及び「胃腸障害」（4 例、21.1%）であった。

事象別の主な有害事象（発現割合 30%以上）は血小板数減少（9 例、47.4%）であった。

表 2.7.4.2-9 探索的試験における 10%以上の被験者に認められた重症度別有害事象（902 試験）（安全性解析対象集団）

	CTCAE Classification				Total
	Grade I	Grade II	Grade III	Grade IV	(N=19)
At least 1 AE	4 (21.1%)	4 (21.1%)	4 (21.1%)	2 (10.5%)	14 (73.7%)
臨床検査 (Investigations)	1 (5.3%)	3 (15.8%)	4 (21.1%)	2 (10.5%)	10 (52.6%)
血小板数減少 (Platelet count decreased)	1 (5.3%)	2 (10.5%)	4 (21.1%)	2 (10.5%)	9 (47.4%)
白血球数減少 (Leukocyte count decreased)	1 (5.3%)	2 (10.5%)	2 (10.5%)	0 (0.0%)	5 (26.3%)
ヘモグロビン減少 (Haemoglobin decreased)	1 (5.3%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	2 (10.5%)
一般・全身障害および投与部位の状態 (General disorders and administration site conditions)	5 (26.3%)	1 (5.3%)	1 (5.3%)	0 (0.0%)	7 (36.8%)
発熱 (Pyrexia)	4 (21.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (21.1%)
無力症 (Asthenia)	2 (10.5%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	3 (15.8%)
胃腸障害 (Gastrointestinal disorders)	2 (10.5%)	2 (10.5%)	0 (0.0%)	0 (0.0%)	4 (21.1%)
悪心 (Nausea)	1 (5.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	2 (10.5%)

Source: Module 5, 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2, modified

% = percentage of subjects was calculated relative to the total number of subjects in the analysis set.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events

ピボタル試験で認められた大分類別の主な有害事象は、「臨床検査値異常（laboratory abnormalities）」（83 例中 57 例、68.7%）が最も多く、次いで「全身障害および様々な投与部位の状態（systemic diseases and various administration site conditions）」（19 例、22.9%）及び「胃腸障害（gastrointestinal system diseases）」（18 例、21.7%）であった。

事象別の主な有害事象（発現割合 30%以上）は血小板減少症（42 例、50.6%）、白血球減少症（33 例、39.8%）であった。

大分類別の「全身障害および様々な投与部位の状態」及び「胃腸障害」に含まれる事象で、10%以上の被験者に認められた事象はなかった。

表 2.7.4.2-10 ピボタル試験における 10%以上の被験者に認められた重症度別有害事象（902 試験）（安全性解析対象集団）

	CTCAE Classification						
	Non-Assessable	Grade I	Grade II	Grade III	Grade IV	Grade V	Total (N=83)
At least 1 AE	0 (0.0%)	10 (12.0%)	26 (31.3%)	21 (25.3%)	8 (9.6%)	3 (3.6%)	68 (81.9%)
臨床検査値異常 (Laboratory abnormalities)	1 (1.2%)	7 (8.4%)	22 (26.5%)	19 (22.9%)	8 (9.6%)	0 (0.0%)	57 (68.7%)
血小板減少症 (Thrombocytopenia)	0 (0.0%)	11 (13.3%)	13 (15.7%)	13 (15.7%)	5 (6.0%)	0 (0.0%)	42 (50.6%)
白血球減少症 (Leukopenia)	0 (0.0%)	3 (3.6%)	19 (22.9%)	10 (12.0%)	1 (1.2%)	0 (0.0%)	33 (39.8%)
好中球減少症 (Neutropenia)	0 (0.0%)	2 (2.4%)	7 (8.4%)	7 (8.4%)	2 (2.4%)	0 (0.0%)	18 (21.7%)

Source: Module 5, 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2, modified
% = percentage of subjects was calculated relative to the total number of subjects in the analysis set.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events

2.7.4.2.1.3 治験薬と関連性のある有害事象

2.7.4.2.1.3.1 日本人／韓国人第 2b 相試験（203 試験）

203 試験の治験薬と関連性のある有害事象を付録表 2.7.4.7-26 に示す。

全体集団で発現割合が高かった治験薬と関連性のある有害事象（発現割合 30%以上）は、血小板減少症*（55 例中 42 例、76.4%）、好中球減少症*（31 例、56.4%）、及び白血球減少症*（21 例、38.2%）であった。

日本人集団で発現割合が高かった治験薬と関連性のある有害事象（発現割合 30%以上）は、血小板減少症*（39 例中 35 例、89.7%）、好中球減少症*（28 例、71.8%）、白血球減少症*（21 例、53.8%）、及びリンパ球減少症*（16 例、41.0%）であった。

2.7.4.2.1.3.2 日本人第 1 相試験（201 試験）

201 試験の治験薬と関連性のある有害事象を付録表 2.7.4.7-27 に示す。

全体で発現割合が高かった治験薬と関連性のある有害事象（発現割合 30%以上）は、血小板数減少及び血小板減少症（14 例中各 6 例、42.9%）、並びに貧血（5 例、35.7%）であった。グループ化した血液学的有害事象で治験薬と関連性のある事象では、血小板減少症*（12 例、85.7%）が最も多く、次いで貧血*、好中球減少症*、及び白血球減少症*（各 5 例、35.7%）であった（付録表 2.7.4.7-51）。

40 mg コホートで発現割合が高かった治験薬と関連性のある有害事象（発現割合 30%以上）は、血小板減少症（7 例中 4 例、57.1%）及び血小板数減少（3 例、42.9%）であった。グループ化した血液学的有害事象で治験薬と関連性のある事象では、血小板減少症*（7 例、100.0%）が最も多く、次いで好中球減少症*（2 例、28.6%）、白血球減少症*（1 例、14.3%）であった（付録表 2.7.4.7-51）。

2.7.4.2.1.3.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

210 試験の治験薬と関連性のある有害事象を付録表 2.7.4.7-28 に示す。

本試験で発現割合が高かった治験薬と関連性のある有害事象（発現割合 30%以上）は、血小板減少症*（23 例中 18 例、78.3%）、好中球減少症*（12 例、52.2%）、白血球減少症*（10 例、43.5%）、貧血*（9 例、39.1%）、食欲低下（8 例、34.8%）、及び倦怠感（7 例、30.4%）であった。

2.7.4.2.1.3.4 中国人第 2 相試験（902 試験）

902 試験の探索的試験及びピボタル試験における治験薬と関連性のある有害事象をそれぞれ 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.3 及び 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.3 に示す。

探索的試験で発現割合が高かった治験薬と関連性のある有害事象（発現割合 30%以上）は血小板数減少（19 例中 9 例、47.4%）であった。

ピボタル試験で発現割合が高かった治験薬と関連性のある有害事象（発現割合 30%以上）は血小板減少症（83 例中 39 例、47.0%）及び白血球減少症（31 例、37.3%）であった。

2.7.4.2.1.4 Grade 3 以上の有害事象

2.7.4.2.1.4.1 日本人／韓国人第 2b 相試験（203 試験）

重症度別の有害事象の発現割合を付録表 2.7.4.7-29 に示す。

全体集団では、安全性解析対象集団 55 例中 46 例（83.6%）に Grade 3 以上の有害事象が認められ、そのうち 15 例（27.3%）に Grade 4、1 例（1.8%）に Grade 5 の有害事象が認められた。治験薬と関連性のある有害事象は、Grade 3 以上の事象が 42 例（76.4%）、Grade 4 の事象が 12 例（21.8%）、Grade 5 の事象が 1 例（1.8%）で認められた。

2 例以上に認められた Grade 3 以上の有害事象は、血小板減少症*（28 例、50.9%）、好中球減少症*（20 例、36.4%）、リンパ球減少症*（12 例、21.8%）、白血球減少症*（11 例、20.0%）、貧血*（9 例、16.4%）、発熱性好中球減少症、γ-グルタミルトランスフェラーゼ（GGT）増加（各 3 例、5.5%）、C-反応性蛋白増加、食欲減退、低カリウム血症、低ナトリウム血症及び肺臓炎（各 2 例、3.6%）であった。2 例以上に認められた Grade 4 の有害事象は、血小板減少症*（9 例、16.4%）、好中球減少症*（5 例、9.1%）、リンパ球減少症*及び低カリウム血症（各 2 例、3.6%）であった。Grade 5 の有害事象は、1 例（1.8%）の被験者に報告された肺炎であった（Grade 5 の事象の詳細は 2.7.4.2.1.6.1 項を参照）。

治験薬と関連性のある有害事象では、2 例以上に認められた Grade 3 以上の事象は、血小板減少症*（24 例、43.6%）、好中球減少症*（20 例、36.4%）、リンパ球減少症*（12 例、21.8%）、白血球減少症*（10 例、18.2%）、貧血*（6 例、10.9%）、発熱性好中球減少症、GGT 増加（各 3 例、5.5%）、C-反応性蛋白増加、食欲減退、低ナトリウム血症、及び肺臓炎（各 2 例、3.6%）であった。2 例以上に認められた Grade 4 の事象は、血小板減少症*（7 例、12.7%）、好中球減少症*（5 例、9.1%）、及びリンパ球減少症*（2 例、3.6%）であった。1 例（1.8%）の被験者に報告された Grade 5 の肺炎は、発現時に Grade 3 と判断された際には治験薬と関連性があると判定され、転帰死亡（Grade 5）となった際に、治験薬との関連性はないと判断された（2.7.4.2.1.6.1 項）。

日本人集団では、39 例中 34 例（87.2%）に Grade 3 以上の有害事象が認められ、そのうち 12 例

（30.8%）に Grade 4 の有害事象が認められた。Grade 5 の有害事象は認められなかった。治験薬と関連性のある有害事象は、Grade 3 以上の事象が 33 例（84.6%）、Grade 4 の事象が 11 例（28.2%）で認められた。

日本人集団で 2 例以上に認められた Grade 3 以上の有害事象は、血小板減少症*（22 例、56.4%）、好中球減少症*（17 例、43.6%）、リンパ球減少症*（12 例、30.8%）、白血球減少症*（11 例、28.2%）、貧血*（7 例、17.9%）、GGT 増加（3 例、7.7%）、発熱性好中球減少症、食欲減退、及び低ナトリウム血症（各 2 例、5.1%）であった。2 例以上に認められた Grade 4 の有害事象は、血小板減少症*（8 例、20.5%）、好中球減少症*（4 例、10.3%）、リンパ球減少症*（2 例、5.1%）であった。

治験薬と関連性のある有害事象では、2 例以上に認められた Grade 3 以上の事象は、血小板減少症*（21 例、53.8%）、好中球減少症*（17 例、43.6%）、リンパ球減少症*（12 例、30.8%）、白血球減少症*（10 例、25.6%）、貧血*（5 例、12.8%）、GGT 増加（3 例、7.7%）、発熱性好中球減少症、食欲減退、及び低ナトリウム血症（各 2 例、5.1%）であった。2 例以上に認められた Grade 4 の事象は、血小板減少症*（7 例、17.9%）、好中球減少症*（4 例、10.3%）、及びリンパ球減少症*（2 例、5.1%）であった。

2.7.4.2.1.4.2 日本人第 1 相試験（201 試験）

重症度別の有害事象を付録表 2.7.4.7-30 に示す。

全体では、安全性解析対象集団 14 例中 11 例（78.6%）に Grade 3 以上の有害事象が認められ、そのうち Grade 4 の有害事象は 2 例（14.3%）に認められた（表 2.7.4.2-2）。治験薬と関連性のある有害事象は、Grade 3 以上の有害事象を発現した 11 例全例、Grade 4 の有害事象を発現した 2 例全例に認められた（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3）。

2 例以上に認められた Grade 3 以上の有害事象は、好中球減少症（3 例、21.4%）、血小板減少症、好中球数減少、白血球数減少（各 2 例、14.3%）であった。Grade 4 の有害事象は好中球減少症（2 例、14.3%）であった。

グループ化した血液学的有害事象では、Grade 3 以上の事象は好中球減少症*（5 例、35.7%）、血小板減少症*、白血球減少症*（各 2 例、14.3%）、及び貧血*（1 例、1.7%）であった（付録表 2.7.4.7-51）。

40 mg コホートでは、7 例中 6 例（85.7%）に Grade 3 以上の有害事象が認められ、そのうち Grade 4 の有害事象が 2 例（28.6%）に認められた（表 2.7.4.2-2）。治験薬と関連性のある有害事象は、Grade 3 以上の有害事象を発現した 6 例全例、Grade 4 の有害事象を発現した 2 例全例に認められた（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3）。

2 例以上に認められた Grade 3 以上の有害事象は、血小板減少症及び好中球減少症（各 2 例、28.6%）であった。Grade 4 の有害事象は好中球減少症（2 例、28.6%）であった。

グループ化した血液学的有害事象では、Grade 3 以上の事象は、血小板減少症*及び好中球減少症*（各 2 例、28.6%）であった（付録表 2.7.4.7-51）。

2 例以上に認められた Grade 3 以上の有害事象はいずれも治験薬と関連性があると判定された（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3）。

［201 試験で報告された用量制限毒性（DLT）］

201 試験では、DLT 評価期間に 2 例に DLT が認められ、その内訳は Grade 4 の好中球減少症（被験者 [redacted]）及び Grade 3 のアラニンアミノトランスフェラーゼ（ALT）増加（被験者 [redacted]）

であった。両事象とも治験薬と関連性があると判定された（詳細は 2.7.6.1 項を参照）。

2.7.4.2.1.4.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

重症度別の有害事象を付録表 2.7.4.7-31 に示す。

安全性解析対象集団 23 例中 18 例（78.3%）に Grade 3 以上の有害事象が認められ、そのうち Grade 4 の有害事象は 9 例（39.1%）に認められた。治験薬と関連性のある有害事象は Grade 3 以上の有害事象を発現した 18 例全例、Grade 4 の有害事象を発現した 9 例全例に認められた。

2 例以上に認められた Grade 3 以上の有害事象は、血小板減少症*（12 例、52.2%）、好中球減少症*（10 例、43.5%）、白血球減少症*（7 例、30.4%）、貧血*（5 例、21.7%）、及び疲労（2 例、8.7%）であった。2 例以上に認められた Grade 4 の有害事象は、血小板減少症*（6 例、26.1%）及び好中球減少症*（3 例、13.0%）であった。2 例以上に認められた Grade 3 以上の有害事象はいずれも治験薬と関連性があると判定された。

2.7.4.2.1.4.4 中国人第 2 相試験（902 試験）

902 試験の探索的試験及びピボタル試験における重症度別の有害事象をそれぞれ 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2 及び 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2 に、重症度別の治験薬と関連性のある有害事象をそれぞれ 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.3 及び 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.3 に示す。

探索的試験の 19 例では、Grade 3 及び Grade 4 の有害事象がそれぞれ 4 例（21.1%）及び 2 例（10.5%）に認められた。治験薬と関連性のある有害事象は Grade 3 及び Grade 4 の事象がそれぞれ 4 例（21.1%）及び 2 例（10.5%）で認められた。2 例以上に認められた Grade 3 の有害事象は血小板数減少（4 例、21.1%）及び白血球数減少（2 例、10.5%）であった。Grade 4 の有害事象は血小板数減少（2 例、10.5%）であった。2 例以上に認められた Grade 3 及び Grade 4 の有害事象はいずれも治験薬と関連性のある有害事象と判定された。

ピボタル試験の 83 例では、Grade 3、Grade 4 及び Grade 5 の有害事象がそれぞれ 21 例（25.3%）、8 例（9.6%）及び 3 例（3.6%）に認められた。治験薬と関連性のある有害事象は、Grade 3 の事象が 19 例（22.9%）、Grade 4 の事象が 8 例（9.6%）、Grade 5 の事象が 1 例（1.2%）で認められた。2 例以上の被験者に発現した Grade 3 の有害事象は、血小板減少症（13 例、15.7%）、白血球減少症（10 例、12.0%）、好中球減少症（7 例、8.4%）、ヘモグロビン減少（reduced haemoglobin）（3 例、3.6%）及び食欲減退（loss of appetite）（2 例、2.4%）であった。2 例以上に認められた Grade 4 の有害事象は、血小板減少症（5 例、6.0%）及び好中球減少症（2 例、2.4%）であった。Grade 5 の有害事象は、腸管穿孔（enterobrosis）、乳酸アシドーシス、及び心突然死（各 1 例、1.2%）であった（Grade 5 の事象の詳細は 2.7.4.2.1.6.4 項を参照）。

治験薬と関連性のある有害事象では、2 例以上の被験者に認められた Grade 3 の事象は、血小板減少症（12 例、14.5%）、白血球減少症（10 例、12.0%）、好中球減少症（7 例、8.4%）、ヘモグロビン減少（3 例、3.6%）及び食欲減退（2 例、2.4%）であった。2 例以上に認められた Grade 4 の有害事象は、血小板減少症（5 例、6.0%）及び好中球減少症（2 例、2.4%）であった。Grade 5 の治験薬と関連性のある有害事象は、心突然死（1 例、1.2%）であった（2.7.4.2.1.6.4 項）。

2.7.4.2.1.5 発現時期別の有害事象

2.7.4.2.1.5.1 日本人／韓国人第 2b 相試験（203 試験）

203 試験の 4 週ごとの有害事象の発現状況を付録表 2.7.4.7-32 に示す。

全体集団では、安全性解析対象症例 55 例中 52 例（94.5%）で治験薬の投与開始後最初の 4 週間に有害事象が認められた。投与開始後 4 週以上 8 週未満では、その間に治験薬の投与を受けていた 52 例中 46 例(88.5%)に有害事象が認められ、8 週以上 12 週未満では 39 例中 30 例(76.9%)、12 週以上 16 週未満では 29 例中 17 例（58.6%)、16 週以上では 22 例中 19 例（86.4%）で有害事象が認められた。

全体集団の投与開始後最初の 4 週間に認められた SOC 別の主な有害事象は、「血液およびリンパ系障害」(55 例中 48 例、87.3%)、「胃腸障害」(25 例、45.5%)、「一般・全身障害および投与部位の状態」(18 例、32.7%）であった。すべての投与週区分（4 週ごと）で「血液およびリンパ系障害」が最も多かった。投与開始後最初の 4 週間に認められた PT 別の主な有害事象（発現割合 30%以上）は血小板減少症*（38 例、69.1%)、好中球減少症*（22 例、40.0%)、白血球減少症*（17 例、30.9%）であった。投与週区分（4 週ごと）別の有害事象の発現状況は、投与期間中のすべての投与週区分で血液学的有害事象が最も多く認められた。

日本人集団では、39 例中 37 例（94.9%）で治験薬の投与開始後最初の 4 週間に有害事象が認められた。投与開始後 4 週以上 8 週未満では、その間に治験薬の投与を受けていた 37 例中 34 例（91.9%）に有害事象が認められ、8 週以上 12 週未満では 29 例中 26 例（89.7%)、12 週以上 16 週未満では 23 例中 16 例（69.6%)、16 週以上では 18 例中 15 例（83.3%）で有害事象が認められた。

日本人集団の投与開始後最初の 4 週間に認められた SOC 別の主な有害事象は、「血液およびリンパ系障害」(39 例中 37 例、94.9%)、「胃腸障害」(19 例、48.7%)、「一般・全身障害および投与部位の状態」(13 例、33.3%）であった。すべての投与週区分（4 週ごと）で「血液およびリンパ系障害」が最も多かった。投与開始後最初の 4 週間に認められた PT 別の主な有害事象（発現割合 30%以上）は血小板減少症*（29 例、74.4%)、好中球減少症*（20 例、51.3%)、白血球減少症*（17 例、43.6%）であった。投与週区分（4 週ごと）別の有害事象の発現状況は、全体集団と同様に、投与期間中のすべての投与週区分で血液学的有害事象が最も多く認められた。

投与期間に依存して発現割合が増加した有害事象は認められなかった。

2.7.4.2.1.5.2 日本人第 1 相試験（201 試験）

201 試験では本解析は実施していない。

2.7.4.2.1.5.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

210 試験の 4 週ごとの有害事象の発現状況を付録表 2.7.4.7-33 に示す。

安全性解析対象集団の 23 例全例で治験薬の投与開始後最初の 4 週間に有害事象が認められた。投与開始後 4 週以上 8 週未満では、その間に治験薬の投与を受けていた 17 例中 13 例（76.5%）に有害事象が認められ、8 週以上 12 週未満では 12 例中 8 例（66.7%)、12 週以上 16 週未満では 6 例中 6 例全例、16 週以上では 3 例中 3 例全例で有害事象が認められた。

本試験の投与開始後最初の 4 週間に認められた SOC 別の主な有害事象は、「血液およびリンパ系障害」(23 例中 19 例、82.6%)、「代謝および栄養障害」(13 例、56.5%)、「一般・全身障害および投与部位の状態」(10 例、43.5%）であった。すべての投与週区分（4 週ごと）で「血液および

リンパ系障害」が最も多かった。

投与開始後最初の 4 週間に認められた PT 別の主な有害事象（発現割合 30%以上）は血小板減少症*（18 例、78.3%）、好中球減少症*（10 例、43.5%）、白血球減少症*及び食欲減退（各 8 例、34.8%）であった。投与週区分（4 週ごと）別の有害事象の発現状況は、投与開始後最初の 4 週間に食欲減退が多く認められたことを除き、投与期間中のすべての投与週区分で血液学的有害事象が最も多く認められた。

投与期間に依存して発現割合が増加した有害事象は認められなかった。

2.7.4.2.1.5.4 中国人第 2 相試験（902 試験）

902 試験では本解析は実施していない。

2.7.4.2.1.6 死亡

2.7.4.2.1.6.1 日本人／韓国人第 2b 相試験（203 試験）

本試験では、データカットオフ日までに 18 例の被験者が死亡した（表 2.7.4.1-13）。多くの被験者は病勢進行による死亡であった（生存追跡調査では死因を収集していなかった）。1 例（1.8%）で転帰死亡の有害事象が認められた（付録表 2.7.4.7-34）。本症例は 7[redacted] 歳の韓国人男性被験者（被験者 [redacted]）で、治験薬投与開始から 48 日後に Grade 3 の肺炎を発現した。被験者は入院し、抗生物質による治療を受けたが、酸素飽和度の低下が回復せず、低血圧に陥った。本被験者の家族が蘇生措置を拒み、肺炎が悪化して転帰死亡（Grade 5）となった。死因は被験者の基礎疾患を考慮して治験薬との関連性はないと判断されたが、Grade 3 の肺炎は治験薬と関連性があると判定された（2.7.6.2.3 項参照）。

本試験期間中に、死亡に至った有害事象の一覧を表 2.7.4.2-11 に示す。

表 2.7.4.2-11 死亡に至った有害事象の一覧（203 試験）（安全性解析対象集団）

Subject ID	Age/Sex	Actual Dose	Sequence Number/ Derived TEAE Number	Start Date (Study Day) /End Date (Study Day)※	System Organ Class/ Preferred Term/ Reported Term	Seriousness	Severity/ Relationship	Action Taken with Study Drug	Outcome
[redacted]	7[redacted]/Male	40mg	6/6	20[redacted] (48)/ 20[redacted] (58)	感染症および寄生虫症/ 肺炎/ PNEUMONIA	Hospitalization	Grade 3/ Possible	Dose not changed	Not recovered/ Not resolved
		40mg	9/6	20[redacted] T22:41 (59)/ 20[redacted] (59)	感染症および寄生虫症/ 肺炎/ WORSENING OF PNEUMON.	Death	Grade 5/ Unrelated	Drug withdrawn	Fatal

Source: Listing 16.2.4.1, Listing 16.2.6.4 in CSR of Study HBI-8000-203
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration
MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
Actual dose is denoted as the dosage taken by subject prior to the occurrence of TEAE.
Derived AE numbers grouped the same AEs into one numbering. Multiple AEs with the same SOC and PT, where start date of the next AE is only one day apart from the end date of the previous AE are collapsed into one AE.
Data cut-off date: [redacted] 20[redacted]

※承認情報提供時に追記

2.7.4.2.1.6.2 日本人第 1 相試験（201 試験）

本試験では、試験期間中に死亡した被験者はなかった（表 2.7.4.2-2、付録表 2.7.4.7-35）。

2.7.4.2.1.6.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

本試験では、データカットオフ日までに 12 例の被験者が死亡した（表 2.7.4.1-15）。2 例が本試験での PD の判定後に死亡し、10 例が別のがん治療開始後に死亡した（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.1, Listing 16.2.5.6）。死亡に至った有害事象は報告されなかった（付録表 2.7.4.7-36）。

2.7.4.2.1.6.4 中国人第 2 相試験（902 試験）

902 試験の探索的試験では有害事象による死亡例はなかった（表 2.7.4.2-4）。ピボタル試験では、試験期間中に 3 例（3.6%）が有害事象により死亡した（表 2.7.4.2-5）。

- 5[redacted] 歳の男性被験者（被験者[redacted]）は、治験薬投与開始前に高熱及び両腕の腫脹を発現しており、治験薬を 3 回投与した後、高熱の継続及び腫脹の悪化により投与を中止した。治験薬の投与中止 2 日後に頻呼吸を発現し、心突然死した。治験担当医師は、治験薬との因果関係を「関連があるかもしれない」と判断したが、専門家で構成される独立委員会は、心突然死は被験者の病状のため、死亡と治験薬との因果関係は判定できないとした。
- 5[redacted] 歳の男性被験者（被験者[redacted]）は、治験薬を 3 回投与した後に腸管穿孔を発現した。当該被験者は腸管穿孔の既往を有していた。治験薬の投与を中止し、被験者は有害事象に対する治療を受けたが悪化し、治験薬投与開始から 16 日後に死亡した。治験担当医師は、腸管穿孔は病勢進行に起因するもので、治験薬との関連性はないと判断した。
- 4[redacted] 歳の男性被験者（被験者[redacted]）は治験薬の初回投与後に発熱し、翌日、治験薬の投与を中止した。治験薬の初回投与から 4 日後に乳酸アシドーシスを発現し、13 日後に死亡した。治験担当医師は、乳酸アシドーシスは病勢進行に起因するもので、治験薬と関連性はないと判断した。

ピボタル試験における死亡に至った有害事象の一覧を表 2.7.4.2-12 に示す。

表 2.7.4.2-12 ピボタル試験における死亡に至った有害事象の一覧（902 試験）（安全性解析対象集団）

Subject ID	Total dosage	Age/Sex	Start Date (Study Day)※ /End Date (Study Day)※	System Organ Class/ Preferred Term/ Reported Term	Seriousness	Severity/ Relationship	Action Taken with Study Drug	Outcome
[redacted]	90 mg	5[redacted]/Male	20[redacted] (10) /20[redacted] (10)	心臓障害 (Heart organ disorders) / 心突然死 (Sudden cardiac death) / Sudden cardiac death	Fatal	Grade 5/ Possibly Related	Not applicable	Death
[redacted]	90 mg	5[redacted]/Male	20[redacted] (10) /20[redacted] (17)	胃腸障害 (Gastrointestinal disorders) / 腸管穿孔 (Intestinal perforation) / Intestinal perforation	Fatal	Grade 5/ Unrelated	Withdrawal	Death
[redacted]	30 mg	4[redacted]/Male	20[redacted] (5) /20[redacted] (14)	代謝および栄養障害 (Metabolic and nutritic disorders) / 乳酸アシドーシス (Lactic acidosis)/ Lactic acidosis	Life-threatening	Grade 5/ Unrelated	Withdrawal	Death

Source: Module 5, 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.6.1, Table 7.6.8, Table 7.6.10, Table 7.6 14

※承認情報提供時に追記

2.7.4.2.1.7 その他の重篤な有害事象

2.7.4.2.1.7.1 日本人／韓国人第 2b 相試験（203 試験）

重篤な有害事象の発現割合を表 2.7.4.2-13 に示す。

全体集団では、安全性解析対象集団 55 例中 14 例（25.5%）に 17 件の重篤な有害事象が認められた。2 例以上に認められた重篤な有害事象は発熱性好中球減少症（2 例、3.6%）であった。

日本人集団では、39 例中 11 例（28.2%）に 13 件の重篤な有害事象が認められた。2 例以上に認められた重篤な有害事象はなかった。

表 2.7.4.2-13 重篤な有害事象の発現割合（203 試験）（安全性解析対象集団）

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Number of subjects with at least one serious TEAE	11 (28.2%)	3 (18.8%)	14 (25.5%)
血液およびリンパ系障害	2 (5.1%)	1 (6.3%)	3 (5.5%)
発熱性好中球減少症	1 (2.6%)	1 (6.3%)	2 (3.6%)
再生不良性貧血	1 (2.6%)	0 (0.0%)	1 (1.8%)
心臓障害	1 (2.6%)	0 (0.0%)	1 (1.8%)
不安定狭心症	1 (2.6%)	0 (0.0%)	1 (1.8%)
一般・全身障害および投与部位の状態	0 (0.0%)	2 (12.5%)	2 (3.6%)
疲労	0 (0.0%)	1 (6.3%)	1 (1.8%)
発熱	0 (0.0%)	1 (6.3%)	1 (1.8%)
感染症および寄生虫症	1 (2.6%)	1 (6.3%)	2 (3.6%)
咽頭炎	1 (2.6%)	0 (0.0%)	1 (1.8%)
ニューモシスチス・イロベチイ肺炎	1 (2.6%)	0 (0.0%)	1 (1.8%)
肺炎	0 (0.0%)	1 (6.3%)	1 (1.8%)
臨床検査	1 (2.6%)	0 (0.0%)	1 (1.8%)
C-反応性蛋白増加	1 (2.6%)	0 (0.0%)	1 (1.8%)
代謝および栄養障害	1 (2.6%)	0 (0.0%)	1 (1.8%)
低ナトリウム血症	1 (2.6%)	0 (0.0%)	1 (1.8%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (2.6%)	0 (0.0%)	1 (1.8%)
末梢性Ｔ細胞性リンパ腫、組織型不明	1 (2.6%)	0 (0.0%)	1 (1.8%)
腎および尿路障害	1 (2.6%)	0 (0.0%)	1 (1.8%)
急性腎障害	1 (2.6%)	0 (0.0%)	1 (1.8%)
呼吸器、胸郭および縦隔障害	3 (7.7%)	0 (0.0%)	3 (5.5%)
間質性肺疾患	1 (2.6%)	0 (0.0%)	1 (1.8%)
肺臓炎	1 (2.6%)	0 (0.0%)	1 (1.8%)
上気道の炎症	1 (2.6%)	0 (0.0%)	1 (1.8%)
血管障害	1 (2.6%)	0 (0.0%)	1 (1.8%)
末梢動脈閉塞性疾患	1 (2.6%)	0 (0.0%)	1 (1.8%)

Source: Appendix Table 2.7.4.7-37
MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
TEAE of overdose is not included in this analysis.
Data cut-off date: [redacted] 20[redacted]

重篤な有害事象（死亡を除く）の一覧を表 2.7.4.2-14 に示す。

不安定狭心症、疲労、発熱、咽頭炎、急性腎障害、上気道の炎症及び末梢動脈閉塞性疾患は、いずれも治験薬との関連性はないと判定された。再生不良性貧血、末梢性 T 細胞性リンパ腫 - 組織型不明、急性腎障害、及び間質性肺疾患の各 1 例は未回復であったが、その他の重篤な有害事象は治験薬の休薬、中止、及び／又は支持療法によっていずれも回復した。

表 2.7.4.2-14 重篤な有害事象（死亡を除く）の一覧（203 試験）（安全性解析対象集団）

Subject ID	Age/Sex/ Country	Actual Dose	TEAE Start Date (Study Day)	Serious Start Date (Study Day)	End Date (Study Day)※	System Organ Class/ Preferred Term/ Reported Term	Seriousness	Severity/ Relationship	Action Taken with Study Drug	Outcome
[redacted]	6[redacted]/Male/ Korea	40mg	20[redacted] (19)	20[redacted] (19)	20[redacted] (23)	血液およびリンパ系障害/ 発熱性好中球減少症/ FEBRILE NEUTROPENIA	Hospitalization	Grade 3/ Possible	Dose Reduced	Recovered/ Resolved
[redacted]	5[redacted]/Male/ Korea	40mg	20[redacted] (28)	20[redacted] (28)	20[redacted] (35)	一般・全身障害および投与部位の状態/ 発熱/ FEVER	Hospitalization	Grade 1/ Unlikely	Drug Interrupted	Recovered/ Resolved
[redacted]	7[redacted]/Male/ Korea	40mg	20[redacted] (2)	20[redacted] (2)	20[redacted] (8)	一般・全身障害および投与部位の状態/ 疲労/ FATIGUE AGGRAVATION	Hospitalization	Grade 2/ Unrelated	Dose Not Changed	Recovered/ Resolved
[redacted]	6[redacted]/Female/ Japan	30mg	20[redacted] (59)	20[redacted] (59)	-	血液およびリンパ系障害/ 再生不良性貧血/ SECONDARY APLASTIC ANEMIA	Life-threatening; Hospitalization; Important Medical Event	Grade 4/ Definite	Not Applicable	Not Recovered/ Not Resolved
[redacted]	7[redacted]/Male/ Japan	40mg	20[redacted] (227)	20[redacted] (245)	20[redacted] (259)	血管障害/ 末梢動脈閉塞性疾患/ WORSENING OF ARTERIOSCLEROSIS OBLITERANS	Hospitalization; Important Medical Event	Grade 3/ Unrelated	Drug Interrupted	Recovered/ Resolved
[redacted]	6[redacted]/Male/ Japan	40mg	20[redacted] (29)	20[redacted] (29)	20[redacted] (34)	心臓障害/ 不安定狭心症/ ANGINA PECTORIS UNSTABLE	Hospitalization	Grade 3/ Unrelated	Drug Interrupted	Recovered/ Resolved
[redacted]	6[redacted]/Male/ Japan	30mg	20[redacted] (84)	20[redacted] (84)	20[redacted] (220)	呼吸器、胸郭および縦隔障害/ 肺臓炎/ PNEUMONITIS	Hospitalization	Grade 3/ Possible	Drug Withdrawn	Recovered/ Resolved
[redacted]	6[redacted]/Male/ Japan	40mg	20[redacted] (24)	20[redacted] (28)	20[redacted] (38)	感染症および寄生虫症/ 咽頭炎/ WORSENING OF PHARYNGITIS	Hospitalization	Grade 3/ Unlikely	Not Applicable	Recovered/ Resolved
		40mg	20[redacted] (29)	20[redacted] (29)	20[redacted] (51)	感染症および寄生虫症/ ニューモシスチス・イロベチイ肺炎/ PNEUMOCYSTIS PNEUMONIA	Hospitalization	Grade 3/ Probable	Drug Withdrawn	Recovered/ Resolved
[redacted]	7[redacted]/Male/ Japan	40mg	20[redacted] (23)	20[redacted] (27)	20[redacted] (233)	臨床検査/ Ｃ－反応性蛋白増加 CRP INCREASED	Hospitalization	Grade 3/ Possible	Not Applicable	Recovered/ Resolved
[redacted]	7[redacted]/Male/ Japan	40mg	20[redacted] (57)	20[redacted] (59)	-	呼吸器、胸郭および縦隔障害/ 間質性肺疾患/ INTERSTITIAL LUNG DISEASE	Hospitalization	Grade 3/ Possible	Drug Withdrawn	Not Recovered/ Not Resolved

Subject ID	Age/Sex/ Country	Actual Dose	TEAE Start Date (Study Day)	Serious Start Date (Study Day)	End Date (Study Day)※	System Organ Class/ Preferred Term/ Reported Term	Seriousness	Severity/ Relationship	Action Taken with Study Drug	Outcome
[redacted]	7[redacted]/Male/ Japan	40mg	20[redacted] (102)	20[redacted] (102)	-	良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）/ 末梢性T細胞性リンパ腫、組織型不明/ PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED (PTCL-NOS)	Important Medical Event	Grade 3/ Possible	Drug Withdrawn	Not Recovered/ Not Resolved
[redacted]	8[redacted]/Female/ Japan	40mg	20[redacted] (22)	20[redacted] (26)	20[redacted] (38)	呼吸器、胸郭および縦隔障害/ 上気道の炎症/ UPPER RESPIRATORY TRACT INFLAMMATION	Hospitalization	Grade 3/ Unrelated	Not Applicable	Recovered/ Resolved
[redacted]	7[redacted]/Male/ Japan	40mg	20[redacted] (15)	20[redacted] (15)	20[redacted] (26)	血液およびリンパ系障害/ 発熱性好中球減少症/ FEBRILE NEUTROPENIA	Important Medical Event	Grade 3/ Probable	Drug Interrupted	Recovered/ Resolved
		30mg	20[redacted] (57)	20[redacted] (57)	-	腎および尿路障害/ 急性腎障害/ ACUTE RENAL FAILURE	Hospitalization	Grade 2/ Unrelated	Not Applicable	Not Recovered/ Not Resolved
[redacted]	8[redacted]/Male/ Japan	40mg	20[redacted] (8)	20[redacted] (8)	20[redacted] (23)	代謝および栄養障害/ 低ナトリウム血症/ HYPONATREMIA	Hospitalization	Grade 3/ Probable	Dose Reduced	Recovered/ Resolved

Source: Listing 16 2.4.1, Listing 16.2.6.3 in CSR of Study HBI-8000-203
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration
MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
Actual dose is denoted as the dosage taken by subject prior to the occurrence of TEAE.
Data cut-off date: [redacted] 20[redacted]

※承認情報提供時に追記

2.7.4.2.1.7.2 日本人第 1 相試験（201 試験）

重篤な有害事象の発現割合を表 2.7.4.2-15 に示す。

全体では、安全性解析対象集団 14 例中 2 例（14.3%）に 3 件の重篤な有害事象が認められ、その内訳は腹痛、腸炎及びパーキンソニズム（各 1 例、7.1%）であった。

40 mg コホートでは、7 例中 1 例（14.3%）に重篤な有害事象が認められ、内訳は腹痛及び腸炎であった。

表 2.7.4.2-15 重篤な有害事象の発現割合（201 試験）（安全性解析対象集団）

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Number of patients with at least one serious TEAE	1 (14.3%)	1 (14.3%)	2 (14.3%)
胃腸障害	0 (0.0%)	1 (14.3%)	1 (7.1%)
腹痛	0 (0.0%)	1 (14.3%)	1 (7.1%)
腸炎	0 (0.0%)	1 (14.3%)	1 (7.1%)
神経系障害	1 (14.3%)	0 (0.0%)	1 (7.1%)
パーキンソニズム	1 (14.3%)	0 (0.0%)	1 (7.1%)

Source: Appendix Table 2.7.4.7-38
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration

重篤な有害事象の一覧を表 2.7.4.2-16 に示す。

Grade 3 の腹痛を除き、治験薬と関連性のある重篤な有害事象は認められなかった。Grade 3 のパーキンソニズムは、被験者が次サイクルの投与基準に適合せず、治験薬の投与を中止した後に認められた（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.1）。併用薬が投与されたが、追跡期間中、本事象は未回復のままであった。Grade 3 の腹痛は治験薬の投与中止に至り、本事象も治験終了時まで未回復のままであった。Grade 3 の腸炎は標準治療により回復した。

表 2.7.4.2-16 重篤な有害事象の一覧（201 試験）（安全性解析対象集団）

Dose Cohort	Patient ID	Age/ Sex	Actual Dose	TEAE Start Date (Study Day)	Serious Start Date (Study Day)	End Date (Study Day)※	System Organ Class/ Preferred Term/ Reported Term	Seriousness	Severity/ Relationship	Action taken with study drug	Outcome
30 mg	[redacted]	7[redacted]/ Male	30 mg	20[redacted] (106)	20[redacted] (128)	Ongoing	神経系障害/ パーキンソニズム/ PARKINSONISM	Hospitalization	Grade 3: Severe/ Unlikely	Not Applicable	Not Recovered/ Not Resolved
40 mg	[redacted]	7[redacted]/ Female	20 mg	20[redacted] (138)	20[redacted] (138)	20[redacted] (156)	胃腸障害/ 腸炎/ ACUTE ENTEROCOLITIS	Hospitalization	Grade 3: Severe/ Unrelated	Dose Not Changed	Recovered/ Resolved
			30 mg	20[redacted] (236)	20[redacted] (238)	Ongoing	胃腸障害/ 腹痛/ ABDOMINAL PAIN	Hospitalization	Grade 3: Severe/ Possible	Drug Withdrawn	Not Recovered/ Not Resolved

Source: Listing 16 2.4.1, Listing 16.2.6.5 in CSR of Study HBI-8000-201
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration
MedDRA Version 19.1 was used to code adverse events.
Severities were graded using NCI-CTCAE Version 4.03.
Actual dose was denoted as the dosage taken by patient prior to the occurrence of TEAE.

※承認情報提供時に追記

2.7.4.2.1.7.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

重篤な有害事象の発現割合を表 2.7.4.2-17 に示す。

安全性解析対象集団 23 例中 7 例（30.4%）に 8 件の重篤な有害事象が認められた。その内訳は、血小板減少症*が 2 例（8.7%）、好中球減少症*、動悸、ニューモシスチス・イロベチイ肺炎、尿路感染、急性呼吸不全及び間質性肺疾患が各 1 例（4.3%）であった。

表 2.7.4.2-17 重篤な有害事象の発現割合（210 試験）（安全性解析対象集団）

System organ class Preferred term	40 mg (N=23) n (%)
Number of subjects with at least one serious TEAE	7 (30.4%)
血液およびリンパ系障害	2 (8.7%)
血小板減少症*	2 (8.7%)
好中球減少症*	1 (4.3%)
心臓障害	1 (4.3%)
動悸	1 (4.3%)
感染症および寄生虫症	2 (8.7%)
ニューモシスチス・イロベチイ肺炎	1 (4.3%)
尿路感染	1 (4.3%)
呼吸器、胸郭および縦隔障害	2 (8.7%)
急性呼吸不全	1 (4.3%)
間質性肺疾患	1 (4.3%)

Source: Appendix Table 2.7.4.7-39 (cited from the new drug application for relapsed or refractory ATL)
MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects were calculated relative to the total number of subjects in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anaemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Data cut-off date: [redacted] 20[redacted]

重篤な有害事象の一覧を表 2.7.4.2-18 に示す。

輸血治療後に発現した Grade 4 の急性呼吸不全を除き、いずれの重篤な有害事象も治験薬と関連性のある事象であった。Grade 1 の動悸に対する治験薬の休薬又は減量や投与中止などは実施しておらず、本事象はデータカットオフ時点で未回復であったが、その他の重篤な有害事象は治験薬の休薬及び投与中止、又は支持療法によっていずれも回復した。

表 2.7.4.2-18 重篤な有害事象の一覧（210 試験）（安全性解析対象集団）

Subject ID	Age/ Sex	Actual Dose	TEAE Start Date (Study Day)	Serious Start Date (Study Day)	End Date (Study Day)※	System Organ Class/ Preferred Term/ Reported Term	Seriousness	Severity/ relationship	Action taken with study drug	Outcome
[redacted]	7[redacted]/ Female	30mg	20[redacted] (141)	20[redacted] (142)	20[redacted] (158)	感染症および寄生虫症/ 尿路感染/ URINARY TRACT INFECTION	Hospitalization	Grade 3/ Possible	Drug Interrupted, Dose Reduced	Recovered/ Resolved
[redacted]	6[redacted]/ Female	30mg	20[redacted] (73)	20[redacted] (73)	20[redacted] (100)	感染症および寄生虫症/ ニューモシスチス・イロベチイ肺炎/ PNEUMOCYSTIS PNEUMONIA	Hospitalization; Important Medical Event	Grade 3/ Probable	Drug Withdrawn	Recovered/ Resolved
[redacted]	7[redacted]/ Female	40mg	20[redacted] (2)	20[redacted] (7)	-	心臓障害/ 動悸/ PALPITATIONS	Hospitalization	Grade 1/ Possible	Dose Not Changed	Not Recovered/ Not Resolved
[redacted]	8[redacted]/ Female	30mg	20[redacted] (36)	20[redacted] (43)	20[redacted] (72)	臨床検査/ 血小板数減少/ PLATELET COUNT DECREASED	Hospitalization	Grade 4/ Probable	Drug Interrupted	Recovered/ Resolved
[redacted]	6[redacted]/ Female	40mg	20[redacted] (24)	20[redacted] (24)	20[redacted] (26)	呼吸器、胸郭および縦隔障害/ 急性呼吸不全/ ACUTE RESPIRATORY FAILURE	Hospitalization	Grade 4/ Unrelated	Not Applicable	Recovered/ Resolved
[redacted]	6[redacted]/ Male	40mg	20[redacted] (35)	20[redacted] (35)	20[redacted] (74)	呼吸器、胸郭および縦隔障害/ 間質性肺疾患/ INTERSTITIAL PNEUMONIA	Life-threatening; Hospitalization; Important Medical Event	Grade 4/ Definite	Drug Interrupted, Drug Withdrawn	Recovered/ Resolved
[redacted]	6[redacted]/ Female	40mg	20[redacted] (8)	20[redacted] (18)	20[redacted] (29)	臨床検査/ 血小板数減少/ PLATELET COUNT DECREASED	Hospitalization; Important Medical Event	Grade 3/ Probable	Drug Interrupted	Recovered/ Resolved
		40mg, 30mg	20[redacted] (8)	20[redacted] (18)	20[redacted] (43)	臨床検査/ 好中球数減少/ NEUTROPHIL COUNT DECREASED	Hospitalization; Important Medical Event	Grade 3/ Probable	Drug Interrupted, Dose Reduced	Recovered/ Resolved

Source: Listing 16.2.4 1, Listing 16.2.6.3 in CSR of Study HBI-8000-210 (cited from the new drug application for relapsed or refractory ATL)
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration
MedDRA Version 21.1 was used to code adverse events. Severities were graded using NCI-CTCAE Version 4.03.
Actual dose was denoted as the dosage taken by subject prior to the occurrence of TEAE.
Data cut-off date: [redacted] 20[redacted]

※承認情報提供時に追記

2.7.4.2.1.7.4 中国人第 2 相試験（902 試験）

探索的試験では、19 例中 1 例（5.3%）に重篤な有害事象が認められ、その事象は血小板数減少であった。

7[redacted] 歳の男性被験者（被験者[redacted]）は悪寒を伴う Grade 1 の発熱を発現し、入院した。その病院で行った血液学的検査の結果、Grade 2 の血小板数減少が認められ、1 週間後に Grade 4 に悪化した。治験薬の休薬及び感染症の治療、血小板輸血、栄養療法などの支持療法により回復した。被験者は治験薬を 25 mg に減量して投与を再開した。本事象は治験薬と関連性があると判定された。

ピボタル試験では、有害事象による死亡 3 例を含め、83 例中 7 例（8.4%）に重篤な有害事象が認められた。死亡以外の重篤な有害事象は血小板減少症、壊疽、白血球増加症、肺感染（pulmonary infection）及びリンパ節症（各 1 例）であった。死亡以外の重篤な有害事象はいずれも治験薬の休薬又は中止、及び支持療法後に回復した。Grade 4 の血小板減少症を除き、いずれも治験薬と関連性はないと判定された。

- 4[redacted] 歳の女性被験者（被験者[redacted]）は治験薬投与開始 17 日後に Grade 4 の血小板減少症を発現した。本被験者は治験薬の投与を中止し、インターロイキン-11 による治療を受け、本事象は回復した。本事象と治験薬の因果関係は「明らかに関連あり」と判定された。
- 5[redacted] 歳の女性被験者（被験者[redacted]）は治験薬投与開始 37 日後に Grade 2 の壊疽を発現した。本被験者は治験薬を休薬して手術を受け、本事象は回復した。本事象と治験薬との因果関係は「関連なし」と判定された。
- 4[redacted] 歳の男性被験者（被験者[redacted]）は、治験薬投与開始 56 日後に Grade 2 の白血球増加症を発現し、治験薬の投与を中止した。本被験者は入院加療を受け、本事象は回復した。本事象と治験薬の因果関係は「おそらく関連なし」と判定された。
- 2[redacted] 歳の女性被験者（被験者[redacted]）は治験薬投与開始 21 日後に Grade 1 の肺感染を発現した。治験薬を休薬し、抗感染症薬による治療を受けた後、本事象は回復した。本事象と治験薬の因果関係は「おそらく関連なし」と判定された。また、本被験者は治験薬投与開始 113 日後に Grade 3 のリンパ節症を発現した。本被験者は治験薬の投与を中止し、抗感染症薬による治療を受け、本事象は回復した。本事象と治験薬との因果関係は「関連なし」と判定された。

探索的試験及びピボタル試験における重篤な有害事象（死亡を除く）の一覧をそれぞれ表 2.7.4.2-19 及び表 2.7.4.2-20 に示す。

表 2.7.4.2-19 探索的試験における重篤な有害事象（死亡を除く）の一覧（902 試験）（安全性解析対象集団）

Subject ID	Total dosage	Age/Sex	Start Date (Study Day)※	End Date (Study Day)※	System Organ Class/ Preferred Term/ Reported Term	Seriousness	Severity/ Relationship	Action Taken with Study Drug	Outcome
[redacted]	800 mg	7[redacted]/Male	20[redacted] (65)	Ongoing	臨床検査(Investigations) / 血小板数減少 (Platelet count decreased) / Platelet drop	Requiring hospitalization or prolongation of hospitalization	Grade 4/ Definitely Related	Treatment interruption	Resolved without sequelae
			20[redacted] (66)	20[redacted] (76)	一般・全身障害および投与部位の状態 (General disorders and administration site conditions) / 発熱 (Pyrexia) / Pyrexia	Requiring hospitalization or prolongation of hospitalization	Grade 1/ Definitely Related	Treatment interruption	Resolved without sequelae

Source: Module 5, 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.6.1, Table 7.6.8, Table 7.6.10, Table 7.6.13

※承認情報提供時に追記

表 2.7.4.2-20 ピボタル試験における重篤な有害事象（死亡を除く）の一覧（902 試験）（安全性解析対象集団）

Subject ID	Total dosage	Age/Sex	Start Date (Study Day)※	End Date (Study Day)※	System Organ Class/ Preferred Term/ Reported Term	Seriousness	Severity/ Relationship	Action Taken with Study Drug	Outcome
[redacted]	190 mg	4[redacted]/Female	20[redacted] (17)	20[redacted] (30)	臨床検査 (Various examinations) / 血小板減少症 (Thrombocytopenia) / Thrombocytopenia	Life-threatening	Grade 4/ Definitely Related	Withdrawal	Resolved; without sequela
[redacted]	360 mg	5[redacted]/Female	20[redacted] (37)	20[redacted] (51)	感染症および病原性疾患(Infectious and pathogenic diseases) / 壊疽(Gangrene)/ Right toe gangrene	Required/prolonged hospitalization	Grade 2/ Unrelated	Temporary withdrawal	Resolved; without sequela
[redacted]	450 mg	4[redacted]/Male	20[redacted] (56)	20[redacted] (119)	臨床検査(Various examinations) / 白血球増加症 (Leukocytosis)/ Leukocytosis	Required/prolonged hospitalization	Grade 2/ Possibly Unrelated	Withdrawal	Resolved; without sequela
[redacted]	1590 mg	2[redacted]/Female	20[redacted] (21)	20[redacted] (24)	呼吸器、胸郭および縦隔障害(Respiratory, thoracic and mediastinal disorders) / 肺感染 (Pulmonary infection)/ Left lung pneumonia	Required/prolonged hospitalization	Grade 1/ Possibly Unrelated	Temporary withdrawal	Resolved; without sequela
			20[redacted] (113)	20[redacted] (118)	血液およびリンパ系障害(Blood and lymphatic system disorders)/ リンパ節症 (Lymphadenopathy)/ Right axillary lymph nodes enlargement	Required/prolonged hospitalization	Grade 3/ Unrelated	Temporary withdrawal	Resolved; without sequela

Source: Module 5, 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.6.1, Table 7.6.8, Table 7.6.10, Table 7.6.13

※承認情報提供時に追記

2.7.4.2.1.8 その他の重要な有害事象

2.7.4.2.1.8.1 投与中止に至った有害事象

2.7.4.2.1.8.1.1 日本人／韓国人第 2b 相試験（203 試験）

203 試験の治験薬の投与中止に至った有害事象を付録表 2.7.4.7-41 に示す。

全体集団では、安全性解析対象集団 55 例中 18 例（32.7%）に治験薬の投与中止に至った有害事象が認められた。2 例以上で認められた事象は好中球減少症*（5 例、9.1%）、血小板減少症*（4 例、7.3%）、リンパ球減少症*及び GGT 増加（各 2 例、3.6%）であった。それらの 2 例以上に認められた事象の重症度はいずれも Grade 3 以上であり、治験薬と関連性のある事象であった。治験薬の投与中止に至った有害事象のうち 13 件［血小板数減少及び好中球数減少各 2 件、血小板減少症、肺炎、肺臓炎、GGT 増加、血中アルカリホスファターゼ（ALP）増加、リンパ球数減少、白血球数減少、間質性肺疾患、及び末梢性 T 細胞性リンパ腫 - 組織型不明各 1 件］はデータカットオフ時点で回復しておらず、その他の有害事象は治験薬の投与中止後に軽快又は回復した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.2）。

日本人集団では、39 例中 15 例（38.5%）に治験薬の投与中止に至った有害事象が認められた。2 例以上で認められた事象は好中球減少症*、血小板減少症*（各 4 例、10.3%）、リンパ球減少症*及び GGT 増加（各 2 例、5.1%）であった。それらの 2 例以上に認められた事象の重症度はいずれも Grade 3 以上であり、治験薬と関連性のある事象であった。治験薬の投与中止に至った有害事象のうち 10 件（血小板数減少 2 件、好中球数減少、血小板減少症、GGT 増加、血中 ALP 増加、リンパ球数減少、白血球数減少、間質性肺疾患、及び末梢性 T 細胞性リンパ腫 - 組織型不明各 1 件）はデータカットオフ時点で回復しておらず、その他の有害事象は治験薬の投与中止後に軽快又は回復した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.1, Listing 16.2.6.2）。

2.7.4.2.1.8.1.2 日本人第 1 相試験（201 試験）

201 試験の治験薬の投与中止に至った有害事象を付録表 2.7.4.7-42 に示す。

全体では、安全性解析対象集団 14 例中 6 例（42.9%）に治験薬の投与中止に至った有害事象が認められた。それらの事象は好中球減少症、血管周囲細胞浸潤性皮膚炎、血中クレアチンホスホキナーゼ増加、腹痛、多形紅斑、及び胸部コンピュータ断層撮影異常（各 1 例、7.1%）であり、2 例以上に認められた事象はなかった。いずれも治験薬と関連性があると判定された。Grade 3 以上の治験薬の投与中止に至った有害事象は、好中球減少症、血中クレアチンホスホキナーゼ増加、腹痛、及び多形紅斑であった。血管周囲細胞浸潤性皮膚炎は治験薬の投与中止後に回復した（5.3.3.2-1 /HBI-8000-201/CSR/Listing 16.2.6.4）。

40 mg コホートでは、7 例中 4 例（57.1%）に治験薬の投与中止に至った有害事象が認められ、その内訳は好中球減少症、腹痛、多形紅斑、及び胸部コンピュータ断層撮影異常が各 1 例（14.3%）であった。いずれも治験薬と関連性があると判定された。重症度は、胸部コンピュータ断層撮影異常を除き、いずれも Grade 3 以上であった。

2.7.4.2.1.8.1.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

210 試験の治験薬の投与中止に至った有害事象を付録表 2.7.4.7-44 に示す。

安全性解析対象集団 23 例中 9 例（39.1%）に治験薬の投与中止に至った有害事象が認められた。1 件の事象を除き、いずれも Grade 3 以上で、9 例全例（39.1%）で治験薬と関連性のある事象が

認められた。2 例以上に認められた事象は、血小板減少症*（4 例、17.4%）及び好中球減少症*（3 例、13.0%）であった。治験薬の投与中止に至った有害事象のうち 5 件（血小板数減少 2 件、疲労、血小板減少症及び好中球数減少各 1 件）はデータカットオフ時点で回復しておらず、その他の有害事象は治験薬の投与中止後に回復した（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.6.2）。

2.7.4.2.1.8.1.4 中国人第 2 相試験（902 試験）

902 試験の探索的試験及びピボタル試験において治験薬の投与中止に至った有害事象をそれぞれ 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.6.16 及び 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.5 並びに Table 7.6.16 に示す。

探索的試験では、19 例中 3 例（15.8%）に治験薬の投与中止に至った有害事象が認められ、いずれも治験薬と関連性があると判定された。2 例以上に認められた事象は血小板数減少（2 例、10.5%）であった。

ピボタル試験では、複数の有害事象により治験薬の投与を中止した場合は、最も重症度の高い有害事象のみを集計に含めた。83 例中 14 例（16.9%）に治験薬の投与中止に至った有害事象が認められた。2 例以上に認められた事象は、血小板減少症（4 例、4.8%）、白血球減少症（3 例、3.6%）、及び肝機能障害（liver dysfunction）（2 例、2.4%）であり、それらの 2 例以上に認められた事象はいずれも治験薬と関連性があると判定された。

2.7.4.2.1.8.2 休薬又は減量に至った有害事象

2.7.4.2.1.8.2.1 日本人／韓国人第 2b 相試験（203 試験）

203 試験の治験薬の休薬又は減量に至った有害事象を付録表 2.7.4.7-46 に示す。

全体集団では、安全性解析対象集団 55 例中 40 例（72.7%）に治験薬の休薬又は減量に至った有害事象が認められた。2 例以上に認められた事象は、血小板減少症*（21 例、38.2%）、好中球減少症*（19 例、34.5%）、発熱性好中球減少症、食欲減退（各 3 例、5.5%）、白血球減少症*、発熱、C-反応性蛋白増加、及び低ナトリウム血症（各 2 例、3.6%）であった。Grade 3 以上の休薬又は減量に至った有害事象は 36 例（65.5%）に認められ、そのうち、治験薬と関連性のある事象は 35 例（63.6%）に認められた。2 例以上に認められた Grade 3 以上の治験薬と関連性のある休薬又は減量に至った有害事象は血小板減少症*、好中球減少症*（各 19 例、34.5%）、発熱性好中球減少症（3 例、5.5%）、白血球減少症*、食欲減退、及び低ナトリウム血症（各 2 例、3.6%）であった。

26 例が有害事象により治験薬を減量し、そのうち 6 例が 2 回減量した。1 例（被験者[redacted]）は 2 回目の減量後、約 3 週間投与を継続し、その後 PD により治験薬の投与を中止した。当該被験者の総曝露期間（休薬期間を含む、以降同様）は 225 日であった。1 例（被験者[redacted]）は、2 回目の減量後、1 回の休薬期間を含め約 3 ヵ月間投与を継続し、最終的に有害事象（Grade 3 の血小板数減少）により治験薬の投与を中止した。当該被験者の総曝露期間は 280 日であった。1 例（被験者[redacted]）は、2 回目の減量後、2 回の休薬期間を含め約 3 ヵ月間投与を継続し、有害事象（Grade 3 の好中球数減少）により治験薬の投与を中止した。当該被験者の総曝露期間は 196 日であった。1 例（被験者[redacted]）は、2 回目の減量後 2 回投与を受け、有害事象（Grade 3 の好中球数減少、Grade 3 の白血球数減少及び Grade 3 のリンパ球数減少）により治験薬の投与を中止した。当該被験者の総曝露期間は 80 日であった。1 例（被験者[redacted]）は、2 回目の減量後約 1 ヵ月間投与を継続し、その後臨床的 PD により治験薬の投与を中止した。当該被験者の総曝露期間は 70

日であった。1 例（被験者[redacted]）は 2 回目の減量後、途中休薬することなく 14 ヵ月以上投与を継続し、データカットオフ時点で投与継続中であった。当該被験者のデータカットオフ時点の総曝露期間は 532 日であった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.1, Listing 16.2.5.1, Listing 16.2.6.1）。

日本人集団では、39 例中 31 例（79.5%）で治験薬の休薬又は減量に至った有害事象が認められた。2 例以上に認められた事象は、血小板減少症*（18 例、46.2%）、好中球減少症*（16 例、41.0%）、食欲減退（3 例、7.7%）、発熱性好中球減少症、白血球減少症*、及び低ナトリウム血症（各 2 例、5.1%）であった。Grade 3 以上の休薬又は減量に至った有害事象は 28 例（71.8%）に認められ、そのうち、治験薬と関連性のある事象は 27 例（69.2%）に認められた。2 例以上に認められた Grade 3 以上の治験薬と関連性のある休薬又は減量に至った有害事象は、血小板減少症*、好中球減少症*（各 16 例、41.0%）、発熱性好中球減少症、白血球減少症*、食欲減退、及び低ナトリウム血症（各 2 例、5.1%）であった。

本試験で有害事象により治験薬を 2 回減量した被験者はいずれも日本人であった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.1, Listing 16.2.6.1）。

2.7.4.2.1.8.2.2 日本人第 1 相試験（201 試験）

201 試験の治験薬の休薬又は減量に至った有害事象を付録表 2.7.4.7-47 に示す。

全体では、安全性解析対象集団 14 例中 8 例（57.1%）に治験薬の休薬又は減量に至った有害事象が認められた。2 例以上に認められた事象は、血小板数減少（4 例、28.6%）及び好中球数減少（2 例、14.3%）であった。休薬又は減量に至った有害事象が認められた 8 例中 7 例に Grade 3 以上の休薬又は減量に至った有害事象が認められ、それらの事象は好中球数減少（2 例、14.3%）、好中球減少症、血小板減少症、全身性皮疹、貧血、高トリグリセリド血症、結節性紅斑及び ALT 増加（各 1 例、7.1%）であった。本試験で認められた休薬又は減量に至った有害事象はいずれも治験薬と関連性があると判定された（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3）。本試験では、減量は 1 回までとしていたが、1 例が 2 回減量した（治験実施計画書からの逸脱として報告された）。被験者[redacted]は 2 回目の減量後、25 mg の用量で約 5 週間投与を継続し、有害事象（Grade 3 の多形紅斑）により治験薬の投与を中止した。当該被験者の総曝露期間は 98 日であった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.2, Listing 16.2.5.1, Listing 16.2.6.3）。

40 mg コホートでは、7 例中 4 例（57.1%）に治験薬の休薬又は減量に至った有害事象が認められた。2 例以上で認められた事象は血小板数減少（2 例、28.6%）であった。休薬又は減量に至った有害事象が認められた 4 例中 3 例に Grade 3 以上の休薬又は減量に至った有害事象が認められ、それらの事象は好中球減少症、血小板減少症、高トリグリセリド血症、結節性紅斑及び ALT 増加（各 1 例、14.3%）であった。本試験で認められた休薬又は減量に至った有害事象はいずれも治験薬と関連性があると判定された（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3）。2 回減量をした被験者は 40 mg コホートの被験者であった。

2.7.4.2.1.8.2.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

210 試験の治験薬の休薬又は減量に至った有害事象を付録表 2.7.4.7-49 に示す。

安全性解析対象集団 23 例中 16 例（69.6%）に治験薬の休薬又は減量に至った有害事象が認められた。いずれも Grade 3 以上で、治験薬と関連性のある事象であった。2 例以上に認められた事

象は、血小板減少症*及び好中球減少症*（各 10 例、43.5%）であった。

10 例が有害事象により治験薬を減量し、そのうち 3 例が 2 回減量した。1 例（被験者[redacted]）は、2 回目の減量後、途中休薬することなく、6 ヵ月以上投与を継続した。当該被験者は最終的に有害事象（Grade 3 の疲労）により治験薬の投与を中止しており、総曝露期間（休薬期間を含む、以降同様）は 388 日であった。1 例（被験者[redacted]）は 2 回目の減量後、約 3 週間投与を継続し、他の治療希望により治験薬の投与を中止した。当該被験者の総曝露期間は 83 日であった。1 例（被験者[redacted]）は 2 回目の減量後、1 回の休薬期間を含め約 4 ヵ月間投与を継続し、最終的に有害事象（Grade 4 の好中球数減少）により治験薬の投与を中止した。当該被験者の総曝露期間は 238 日であった（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.1, Listing 16.2.5.1, Listing 16.2.6.1）。

2.7.4.2.1.8.2.4 中国人第 2 相試験（902 試験）

902 試験の探索的試験及びピボタル試験における治験薬の用量調整に至った有害事象をそれぞれ 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.12.3 及び 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.12.3 に示す。

探索的試験では、19 例中 1 例（5.3%）に治験薬の用量調整に至った有害事象として Grade 3 の血小板数減少及び Grade 3 の白血球数減少が認められた。いずれも治験薬と関連性のある事象であった（5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.6.10）。

ピボタル試験では、83 例中 6 例（7.2%）に治験薬の用量調整に至った有害事象が認められ、いずれも治験薬と関連性のある事象であった。2 例以上で認められた用量調整に至った有害事象は、重症度別で、Grade 3 の血小板減少症（3 例、3.6%）及び Grade 3 の白血球減少症（2 例、2.4%）であった（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.6.10）。

2.7.4.2.1.9 器官別又は症候群別有害事象の解析

本項では、日本人患者を含む試験で認められた血液学的有害事象、注目すべき有害事象を含む臨床的に重要な有害事象を要約する。日本人患者を含む試験で用いた血液学的有害事象及び注目すべき有害事象の定義は表 2.7.4.1-2、表 2.7.4.1-3、及び付録表 2.7.4.7-1 に示す。日本人以外の患者を対象とした 902 試験で認められた血液学的有害事象及び注目すべき有害事象についても、同じ定義を適用して同定し、それらの事象の発現状況について簡潔に述べる。

2.7.4.2.1.9.1 血液学的有害事象

2.7.4.2.1.9.1.1 血小板減少症*

日本人患者を含む試験

日本人／韓国人第 2b 相試験（203 試験）

全体集団では、安全性解析対象集団 55 例中 46 例（83.6%）に血小板減少症*が認められた。重症度別では、Grade 3 及び Grade 4 の事象はそれぞれ 19 例（34.5%）及び 9 例（16.4%）に認められた（付録表 2.7.4.7-29）。血小板減少症*発現例のうち、9 例（16.4%）が輸血治療を受けた。9 例全例が Grade 3 以上の事象に対して輸血治療を受けており、それらの事象は 3 件を除きいずれも治験薬と関連性があると判定された。輸血治療を受けた 9 例中 7 例が回復した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.5）。発現した事象をコントロールするために 21 例（38.2%）が治験薬を休薬又は減量した（付録表 2.7.4.7-45）。また、4 例（7.3%）が血小板減少症*により治験薬の投

与を中止した（付録表 2.7.4.7-40）。血小板減少症*による出血の合併症のために死亡した被験者はなかった（付録表 2.7.4.7-34）。

血小板減少症*発現例のうち 9 例に、鼻出血、紫斑（各 2 例）、結膜出血、出血性関節症、血尿、尿中血陽性、肛門出血、口腔粘膜血腫、点状出血、及び痔出血（各 1 例）が認められた。そのうち治験薬と関連性のある事象は 5 例に認められ、その内訳は紫斑（2 例）、鼻出血、結膜出血及び点状出血（各 1 例）であった。いずれの事象も非重篤で、重症度は Grade 1 又は Grade 2 であった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.1）。

日本人集団では、39 例中 35 例（89.7%）に血小板減少症*が認められた。重症度別では、Grade 3 及び Grade 4 の事象はそれぞれ 14 例（35.9%）及び 8 例（20.5%）に認められた（付録表 2.7.4.7-29）。血小板減少症*発現例のうち、6 例（15.4%）が輸血治療を受けた。6 例全例が Grade 3 以上の事象に対して輸血治療を受けており、1 件の事象を除きいずれも治験薬と関連性があると判定された。輸血治療を受けた 6 例中 4 例が回復した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.1, Listing 16.2.6.5）。発現した事象をコントロールするために 18 例（46.2%）が治験薬を休薬又は減量した（付録表 2.7.4.7-45）。また、4 例（10.3%）が血小板減少症*により治験薬の投与を中止した（付録表 2.7.4.7-40）。全体集団で認められた出血関連有害事象発現例はいずれも日本人であった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.1, Listing 16.2.6.1）。

日本人第 1 相試験（201 試験）

全体では、安全性解析対象集団 14 例中 12 例（85.7%）に血小板減少症*が認められた。重症度別では、Grade 3 の事象が 2 例（14.3%）に認められ、Grade 4 の事象は認められなかった（付録表 2.7.4.7-51）。輸血治療を受けた被験者はなかった。発現した事象をコントロールするために 5 例（35.7%）が治験薬を休薬した。血小板減少症*により治験薬の投与を中止した被験者はなかった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3, Listing 16.2.6.4）。

40 mg コホートでは、7 例全例に血小板減少症*が認められた。重症度別では、Grade 3 の事象が 2 例（28.6%）に認められ、Grade 4 の事象は認められなかった（付録表 2.7.4.7-51）。3 例（42.9%）が血小板減少症*により治験薬を休薬した（5.3.3.2-1 /HBI-8000-201/CSR/Listing 16.2.6.3）。

日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

安全性解析対象集団 23 例中 18 例（78.3%）に血小板減少症*が認められた。重症度別では、Grade 3 及び Grade 4 の事象が各 6 例（26.1%）に認められた（付録表 2.7.4.7-31）。血小板減少症*発現例のうち、5 例（21.7%）が輸血治療を受けた。その 5 例中 4 例が Grade 3 以上の事象に対して輸血治療を受けており、それらの事象はいずれも治験薬と関連性があると判定された。輸血治療を受けた 5 例中 3 例が回復した（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.6.5）。発現した事象をコントロールするために 10 例(43.5%)が治験薬を休薬又は減量した(付録表 2.7.4.7-48)。また、4 例（17.4%）が血小板減少症*により治験薬の投与を中止した（付録表 2.7.4.7-43）。血小板減少症*による出血の合併症のために死亡した被験者はなかった（付録表 2.7.4.7-36）。

血小板数減少を発現した 1 例に Grade 1 の鼻出血が認められたが、本事象は、血小板数減少が認められる前に発現したものであった。鼻出血は治験薬と関連性があると判定された（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.6.1）。

日本人以外の患者を対象とした試験

中国人第 2 相試験（902 試験）

探索的試験では、19 例中 9 例（47.4%）に血小板数減少が認められた。重症度別では、Grade 3 及び Grade 4 の血小板数減少がそれぞれ 4 例（21.1%）及び 2 例（10.5%）に認められた（5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2）。

ピボタル試験では、83 例中 42 例（50.6%）に血小板減少症が認められた。重症度別では、Grade 3 及び Grade 4 の血小板減少症がそれぞれ 13 例（15.7%）及び 5 例（6.0%）に認められた（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2）。

2.7.4.2.1.9.1.2 好中球減少症*

日本人患者を含む試験

日本人／韓国人第 2b 相試験（203 試験）

全体集団では、安全性解析対象集団 55 例中 31 例（56.4%）に好中球減少症*が認められた。重症度別では、Grade 3 及び Grade 4 の事象はそれぞれ 15 例（27.3%）及び 5 例（9.1%）に認められた（付録表 2.7.4.7-29）。好中球減少症*発現例のうち、17 例（30.9%）が顆粒球コロニー形成刺激因子（G-CSF）による治療を受けた。その 17 例中 15 例が Grade 3 以上の事象に対して G-CSF による治療を受けており、それらの事象はいずれも治験薬と関連性があると判定された。G-CSF による治療を受けた 17 例全例が回復した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.5, Listing 16.2.6.5）。発現した事象をコントロールするために 19 例（34.5%）が治験薬を休薬又は減量した（付録表 2.7.4.7-45）。また、5 例（9.1%）が好中球減少症*のために治験薬の投与を中止した（付録表 2.7.4.7-40）。好中球減少症*により死亡した被験者はなかった（付録表 2.7.4.7-34）。

3 例（5.5%）に発熱性好中球減少症が認められた（付録表 2.7.4.7-23）。重症度はいずれも Grade 3 で、治験薬と関連性があると判定され、うち 2 例は重篤であった。いずれの事象も治験薬の休薬又は減量、及び支持療法によって回復した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.1）。

日本人集団では、39 例中 28 例（71.8%）に好中球減少症*が認められた。重症度別では、Grade 3 及び Grade 4 の事象はそれぞれ 13 例（33.3%）及び 4 例（10.3%）に認められた（付録表 2.7.4.7-29）。好中球減少症*発現例のうち、14 例（35.9%）が G-CSF による治療を受けた。その 14 例中 12 例が Grade 3 以上の事象に対して G-CSF による治療を受けており、それらの事象はいずれも治験薬と関連性があると判定された。G-CSF による治療を受けた 14 例全例が回復した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.1, Listing 16.2.4.5, Listing 16.2.6.5）。発現した事象をコントロールするために 16 例（41.0%）が治験薬を休薬又は減量した（付録表 2.7.4.7-45）。また、5 例（9.1%）が好中球減少症*のために治験薬の投与を中止した（付録表 2.7.4.7-40）。

2 例（5.1%）に発熱性好中球減少症が認められた（付録表 2.7.4.7-23）。重症度はいずれも Grade 3 で、治験薬と関連性があると判定され、うち 1 例は重篤であった。いずれの事象も治験薬の休薬又は減量、及び支持療法によって回復した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.1, Listing 16.2.6.1）。

日本人第 1 相試験（201 試験）

全体では、安全性解析対象集団 14 例中 5 例（35.7%）に好中球減少症*が認められた。重症度別では、Grade 3 及び Grade 4 の事象がそれぞれ 3 例（21.4%）及び 2 例（14.3%）に認められた（付録表 2.7.4.7-51）。好中球減少症*発現例のうち、2 例が G-CSF による治療を受けた。2 例ともが

Grade 3 以上の事象に対して G-CSF による治療を受けており、それらの事象はいずれも治験薬と関連性があると判定された。G-CSF による治療を受けた 2 例中 1 例が回復した。発現した事象をコントロールするために 3 例（21.4%）が治験薬の休薬又は減量を行い、1 例（7.1%）が好中球減少症*により治験薬の投与を中止した（5.3.3.2-1 /HBI-8000-201/CSR/Listing 16.2.4.6, Listing 16.2.6.3）。

40 mg コホートでは、7 例中 2 例（28.6%）に好中球減少症*が認められた。重症度は、いずれも Grade 4 であった（付録表 2.7.4.7-51）。好中球減少症*発現例のうち、2 例が G-CSF による治療を受けた。2 例ともが Grade 3 以上の事象に対して G-CSF による治療を受けており、それらの事象はいずれも治験薬と関連性があると判定された。G-CSF による治療を受けた 2 例中 1 例が回復した。発現した事象をコントロールするために 1 例（14.3%）が治験薬の休薬又は減量を行い、1 例（14.3%）が好中球減少症*により治験薬の投与を中止した（5.3.3.2-1 /HBI-8000-201/CSR/Listing 16.2.4.6, Listing 16.2.6.3）。

日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

安全性解析対象集団 23 例中 12 例（52.2%）に好中球減少症*が認められた。重症度別では、Grade 3 及び Grade 4 の事象がそれぞれ 7 例（30.4%）及び 3 例（13.0%）に認められた（付録表 2.7.4.7-31）。好中球減少症*発現例のうち、9 例（39.1%）が G-CSF による治療を受けた。9 例全例が Grade 3 以上の事象に対して G-CSF による治療を受けており、それらの事象はいずれも治験薬と関連性があると判定された。G-CSF による治療を受けた 9 例中 8 例が回復した（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.4.5, Listing 16.2.6.5）。発現した事象をコントロールするために 10 例（43.5%）が治験薬の休薬又は減量を行った（付録表 2.7.4.7-48）。また、3 例（13.0%）が好中球減少症*により治験薬の投与を中止した（付録表 2.7.4.7-43）。好中球減少症*により死亡した被験者はなかった（付録表 2.7.4.7-36）。

1 例（4.3%）に発熱性好中球減少症が認められた（付録表 2.7.4.7-25）。本事象は非重篤で、重症度は Grade 3 であり、治験薬と関連性があると判定された。本事象は、好中球減少症及び血小板数減少のため治験薬の投与を中止した後に発現しており、治験終了時点の転帰は未回復であった（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.6.1）。

日本人以外の患者を対象とした試験

中国人第 2 相試験（902 試験）

探索的試験では、19 例中 1 例（5.3%）に好中球数減少が認められた。当該事象の重症度は Grade 3 であった（5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2）。

ピボタル試験では、83 例中 18 例（21.7%）に好中球減少症が認められた。重症度別では、Grade 3 及び Grade 4 の事象はそれぞれ 7 例（8.4%）及び 2 例（2.4%）に認められた（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2）。

2.7.4.2.1.9.1.3 白血球減少症*

日本人患者を含む試験

日本人／韓国人第 2b 相試験（203 試験）

全体集団では、安全性解析対象集団 55 例中 24 例（43.6%）に白血球減少症*が認められた。重症度別では、Grade 3 及び Grade 4 の事象はそれぞれ 10 例（18.2%）及び 1 例（1.8%）に認められた（付録表 2.7.4.7-29）。白血球減少症*発現例のうち、2 例（3.6%）が併発した好中球減少症*に対

する治療として G-CSF の投与を受けた。2 例とも Grade 3 以上の白血球減少症*を発現しており、いずれも治験薬と関連性があると判定された。G-CSF を投与後、この 2 例の白血球減少症*はいずれも回復した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.5, Listing 16.2.6.5）。2 例（3.6%）が白血球減少症*により治験薬を休薬又は減量した（付録表 2.7.4.7-45）。また、1 例（1.8%）が白血球減少症*により治験薬の投与を中止した（付録表 2.7.4.7-40）。白血球減少症*により死亡した被験者はなかった（付録表 2.7.4.7-34）。

白血球減少症*を発現した被験者はいずれも日本人であった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.1, Listing 16.2.6.5）。

日本人第 1 相試験（201 試験）

全体では、安全性解析対象集団 14 例中 5 例（35.7%）に白血球減少症*が認められた。重症度別では、Grade 3 の事象が 2 例（14.3%）に認められ、Grade 4 の事象は認められなかった（付録表 2.7.4.7-51）。治療を必要とした事象はなく、治験終了時点で 1 例が未回復であった。白血球減少症*のために治験薬を休薬、減量又は中止した被験者はなかった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3）。

40 mg コホートでは、7 例中 1 例（14.3%）に白血球減少症*が認められた（付録表 2.7.4.7-51）。本事象の重症度は Grade 3 で、治療を行うことなく回復した（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3）。

日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

安全性解析対象集団 23 例中 10 例（43.5%）に白血球減少症*が認められた。重症度別では、Grade 3 の事象が 7 例（30.4%）に認められ、Grade 4 の事象は認められなかった（付録表 2.7.4.7-31）。本事象に対する治療は行われず、白血球減少症*発現例 10 例中 6 例が軽快又は回復し、Grade 1 の事象を発現した 1 例及び Grade 3 の事象を発現した 3 例は治験終了時点で未回復であった（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.6.5）。白血球減少症*のために治験薬を休薬、減量又は中止した被験者はなかった（付録表 2.7.4.7-48 及び付録表 2.7.4.7-43）。白血球減少症*により死亡した被験者もなかった（付録表 2.7.4.7-36）。

日本人以外の患者を対象とした試験

中国人第 2 相試験（902 試験）

探索的試験では、19 例中 5 例（26.3%）に白血球数減少が認められた。重症度別では、Grade 3 の事象が 2 例（10.5%）に認められ、Grade 4 の事象は認められなかった（5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2）。

ピボタル試験では、83 例中 33 例（39.8%）に白血球減少症が認められた。重症度別では、Grade 3 及び Grade 4 の事象はそれぞれ 10 例（12.0%）及び 1 例（1.2%）に認められた（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2）。

2.7.4.2.1.9.1.4 リンパ球減少症*

日本人患者を含む試験

日本人／韓国人第 2b 相試験（203 試験）

全体集団では、安全性解析対象集団 55 例中 16 例（29.1%）にリンパ球減少症*が認められた。

重症度別では、Grade 3 及び Grade 4 の事象がそれぞれ 10 例（18.2%）及び 2 例（3.6%）に認められた（付録表 2.7.4.7-29）。治療を必要とした事象はなく、リンパ球減少症*発現例 16 例中 12 例が回復し、Grade 4 の事象を発現した 1 例及び Grade 3 の事象を発現した 3 例はデータカットオフ時点で未回復であった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.5）。2 例（3.6%）がリンパ球減少症*により治験薬の投与を中止した（付録表 2.7.4.7-40）。リンパ球減少症*により死亡した被験者はなかった（付録表 2.7.4.7-34）。

リンパ球減少症*を発現した被験者はいずれも日本人であった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.1, Listing 16.2.6.1）。

日本人第 1 相試験（201 試験）

安全性解析対象集団 14 例中 1 例（7.1%）にリンパ球数減少が認められた（リンパ球減少症の報告はなかった）（付録表 2.7.4.7-24）。本事象の重症度は Grade 3 であった。本事象に対する治療は行われず、治験終了時点での転帰は未回復であった。当該被験者はリンパ球数減少のために治験薬を休薬、減量又は中止しなかった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3）。

リンパ球数減少発現例は 30 mg コホートの被験者であり、40 mg コホートでリンパ球減少症及びリンパ球数減少は認められなかった（付録表 2.7.4.7-24）。

日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

安全性解析対象集団 23 例中 2 例（8.7%）にリンパ球減少症*が認められた（付録表 2.7.4.7-31）。重症度別では、Grade 3 の事象が 1 例（4.3%）に認められたが、治療を行うことなく回復した（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.6.5）。リンパ球減少症*のために治験薬を休薬、減量又は中止した被験者はなかった（付録表 2.7.4.7-48 及び付録表 2.7.4.7-43）。リンパ球減少症*により死亡した被験者もなかった（付録表 2.7.4.7-36）。

日本人以外の患者を対象とした試験

中国人第 2 相試験（902 試験）

探索的試験では、リンパ球減少症及びリンパ球数減少は認められなかった（5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2）。

ピボタル試験では、83 例中 1 例（1.2%）にリンパ球百分率減少（reduced lymphocytes percentage）が認められた。本事象の重症度は Grade 3 であった（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2）。

2.7.4.2.1.9.1.5 貧血*

日本人患者を含む試験

日本人／韓国人第 2b 相試験（203 試験）

全体集団では、安全性解析対象集団 55 例中 18 例（32.7%）に貧血*が認められた。重症度別では、Grade 3 及び Grade 4 の事象がそれぞれ 8 例（14.5%）及び 1 例（1.8%）に認められた（付録表 2.7.4.7-29）。貧血*発現例のうち、8 例（14.5%）が輸血治療を受けた。8 例中 6 例が Grade 3 以上の事象に対して輸血治療を受けており、それらの事象は 1 件を除きいずれも治験薬と関連性があると判定された。輸血治療を受けた 8 例中 5 例が回復した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.5）。貧血*のために治験薬を休薬、減量又は中止した被験者はなかった（付録表 2.7.4.7-45 及

び付録表 2.7.4.7-40)。貧血*により死亡した被験者もなかった（付録表 2.7.4.7-34)。

日本人集団では、39 例中 14 例（35.9%）に貧血*が認められた。重症度別では、Grade 3 及び Grade 4 の事象がそれぞれ 6 例（15.4%）及び 1 例（2.6%）に認められた（付録表 2.7.4.7-29)。貧血*発現例のうち、4 例（10.3%）が輸血治療を受けた。4 例全例が Grade 3 以上の事象に対して輸血治療を受けており、それらの事象はいずれも治験薬と関連性があると判定された。輸血治療を受けた 4 例中 2 例が回復した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.1, Listing 16.2.6.5)。

日本人第 1 相試験（201 試験）

安全性解析対象集団 14 例中 5 例（35.7%）に貧血*が認められた。重症度別では、Grade 3 の事象が 1 例（7.1%）に認められ、Grade 4 の事象は認められなかった（付録表 2.7.4.7-51)。輸血治療を受けた被験者はなかった。発現した事象をコントロールするために 1 例が治験薬を休薬した。貧血*により治験薬の投与を中止した被験者はなかった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3)。

貧血*発現例は 30 mg コホートの被験者であり、40 mg コホートで貧血*は認められなかった（付録表 2.7.4.7-51)。

日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

安全性解析対象集団 23 例中 9 例（39.1%）に貧血*が認められた。重症度別では、Grade 3 の事象が 5 例（21.7%）に認められ、Grade 4 の事象は認められなかった（付録表 2.7.4.7-31)。貧血*発現例のうち、4 例（17.4%）が輸血治療を受けた。その 4 例中 3 例が Grade 3 以上の事象に対して輸血治療を受けており、それらの事象はいずれも治験薬と関連性があると判定された。輸血治療を受けた 4 例中 3 例が回復した（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.6.5)。貧血*のために治験薬を休薬、減量又は中止した被験者はなかった（付録表 2.7.4.7-48 及び付録表 2.7.4.7-43)。貧血*により死亡した被験者もなかった（付録表 2.7.4.7-36)。

日本人以外の患者を対象とした試験

中国人第 2 相試験（902 試験）

探索的試験では、19 例中 2 例（10.5%）にヘモグロビン減少が認められた。重症度別では、Grade 3 の事象が 1 例（5.3%）に認められ、Grade 4 の事象は認められなかった（5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2)。

ピボタル試験では、83 例中 7 例（8.4%）にヘモグロビン減少が認められた。重症度別では、Grade 3 及び Grade 4 の事象はそれぞれ 3 例（3.6%）及び 1 例（1.2%）に認められた（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2)。

2.7.4.2.1.9.2 注目すべき有害事象

203 試験及び 210 試験における注目すべき有害事象を、付録表 2.7.4.7-50 及び付録表 2.7.4.7-52 にそれぞれ示す。注目すべき有害事象の部分集団解析の結果は、203 試験は 5.3.5.2-1/HBI-8000-203/CSR/12.3.3.4.2 項、210 試験は初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/12.3.3.4.2 項を参照のこと。なお、これらの表では、2.7.4.1.1.2.1.2 項で示したグループ化した血液学的有害事象の定義は適用していない。その他の試験では、注目すべき有害事象の解析は行っておらず、注目すべき有害事象に該当する事象を特定する際に確認した表及び一覧の引用元を本文中に示している。

2.7.4.2.1.9.2.1 「血小板減少症」

注目すべき有害事象の「血小板減少症」に含まれる事象のうち、血液学的有害事象の血小板減少症*に該当する事象のみが発現したため、これらの集計結果は同じである。「血小板減少症」の発現状況は 2.7.4.2.1.9.1.1 項を参照のこと。

2.7.4.2.1.9.2.2 「好中球減少症」

注目すべき有害事象の「好中球減少症」には、血液学的有害事象の好中球減少症*に該当する事象に加え、他の事象も含まれる。以下に「好中球減少症」の発現状況を示す。

<u>日本人患者を含む試験</u>

<u>日本人／韓国人第 2b 相試験（203 試験）</u>

全体集団では、安全性解析対象集団 55 例中 35 例（63.6%）に「好中球減少症」が認められた。2 例以上に認められた事象は、好中球数減少（20 例、36.4%）、白血球数減少（18 例、32.7%）、好中球減少症（11 例、20.0%）、白血球減少症（6 例、10.9%）、及び発熱性好中球減少症（3 例、5.5%）であった。重症度別では、Grade 3 又は 4 の「好中球減少症」が 24 例（43.6%）に認められ、その内訳は Grade 3 が 19 例（34.5%）、Grade 4 が 5 例（9.1%）であった。21 例（38.2%）が「好中球減少症」により、治験薬を休薬又は減量した。5 例（9.1%）が「好中球減少症」により治験薬の投与を中止し、その重症度はいずれも Grade 3 であった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.5）。

日本人集団では、39 例中 32 例（82.1%）に「好中球減少症」が認められた。2 例以上に認められた事象は、好中球数減少、白血球数減少（各 18 例、46.2%）、好中球減少症（9 例、23.1%）、白血球減少症（6 例、15.4%）、及び発熱性好中球減少症（2 例、5.1%）であった。重症度別では、Grade 3 又は 4 の「好中球減少症」が 21 例（53.8%）に認められ、その内訳は Grade 3 が 17 例（43.6%）、Grade 4 が 4 例（10.3%）であった（付録表 2.7.4.7-53）。19 例（48.7%）が「好中球減少症」により、治験薬を休薬又は減量した。4 例（10.3%）が「好中球減少症」により治験薬の投与を中止し、その重症度はいずれも Grade 3 であった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.1, Listing 16.2.6.5）。

<u>日本人第 1 相試験（201 試験）</u>

全体では、安全性解析対象集団 14 例中 5 例（35.7%）に「好中球減少症」に該当する事象が認められた。その事象は、白血球数減少（4 例、28.6%）、好中球減少症（3 例、21.4%）、好中球数減少（2 例、14.3%）及び白血球減少症（1 例、7.1%）であった（付録表 2.7.4.7-24）。重症度別では、Grade 4 の好中球減少症、Grade 3 の好中球数減少、Grade 3 の白血球数減少が各 2 例（14.3%）、及び Grade 3 の好中球減少症が 1 例（7.1%）に認められた（付録表 2.7.4.7-30）。好中球減少症の 1 例及び好中球数減少の 2 例が、当該事象により治験薬を休薬した。Grade 4 の好中球減少症の 1 例が当該事象により治験薬の投与を中止した（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3）。

40 mg コホートでは、7 例中 2 例（28.6%）に「好中球減少症」に該当する事象が認められ、その事象は好中球減少症（2 例、28.6%）及び白血球数減少（1 例、14.3%）であった（付録表 2.7.4.7-24）。重症度別では、Grade 4 の好中球減少症が 2 例（28.6%）、Grade 3 の白血球数減少が 1 例（14.3%）に認められた（付録表 2.7.4.7-30）。好中球減少症の 1 例が当該事象により治験薬を休薬し、Grade 4 の好中球減少症の 1 例が当該事象により治験薬の投与を中止した（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3）。

日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

安全性解析対象集団 23 例中 13 例（56.5%）に「好中球減少症」が認められた。2 例以上に認められた事象は、好中球数減少（11 例、47.8%）及び白血球数減少（9 例、39.1%）であった。重症度別では、Grade 3 又は 4 の「好中球減少症」が 10 例（43.5%）に認められ、その内訳は Grade 3 が 7 例（30.4%）、Grade 4 が 3 例（13.0%）であった。10 例（43.5%）が「好中球減少症」により、治験薬を休薬又は減量した。3 例（13.0%）が「好中球減少症」により治験薬の投与を中止し、その重症度別の内訳は Grade 3 が 2 例（8.7%）及び Grade 2 が 1 例（4.3%）であった（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.6.5）。

日本人以外の患者を対象とした試験

902 試験では、注目すべき有害事象の「好中球減少症」に含まれる事象のうち、血液学的有害事象の好中球減少症*及び白血球減少症*に該当する事象のみが発現していることから、「好中球減少症」の集計結果と好中球減少症及び白血球減少症の集計結果は同じである。「好中球減少症」に該当する事象の発現状況は 2.7.4.2.1.9.1.2 項 好中球減少症*及び 2.7.4.2.1.9.1.3 項 白血球減少症*の各試験の項を参照のこと。

2.7.4.2.1.9.2.3 「リンパ球減少症」

注目すべき有害事象の「リンパ球減少症」に含まれる事象と、血液学的有害事象のリンパ球減少症*に該当する事象が同一のため、これらの集計結果は同じである。「リンパ球減少症」の発現状況は 2.7.4.2.1.9.1.4 項 リンパ球減少症*を参照のこと。

2.7.4.2.1.9.2.4 「貧血」

注目すべき有害事象の「貧血」に含まれる事象と、血液学的有害事象の貧血*に該当する事象が同一のため、これらの集計結果は同じである。「貧血」の発現状況は 2.7.4.2.1.9.1.5 項 貧血*を参照のこと。

2.7.4.2.1.9.2.5 「感染症」

日本人患者を含む試験

日本人／韓国人第 2b 相試験（203 試験）

安全性解析対象集団 55 例中 19 例（34.5%）に「感染症」が認められた。その事象は、上気道感染（（発現日：Day 27、Day 34、Day 64、Day 174）（4 例、7.3%）、咽頭炎（発現日：Day 13、Day 24、Day 289）（3 例、5.5%）、気管支炎（発現日：Day 44、Day 47）、結膜炎（発現日：Day 8、Day 60）、インフルエンザ（発現日：Day 15、Day 215）、及び上咽頭炎（発現日：Day 92、Day 134）（各 2 例、3.6%）、膀胱炎（発現日：Day 119）、サイトメガロウイルス感染（発現日：Day 15）、感染性小腸結腸炎（発現日：Day 70）、胃腸炎（発現日：Day 137）、帯状疱疹（発現日：Day 227）、膿痂疹（発現日：Day 106）、ニューモシスチス・イロベチイ肺炎（発現日：Day 29）、肺炎（発現日：Day 48）、鼻炎（発現日：Day 13）、及びブドウ球菌皮膚感染（発現日：Day 68）（各 1 例、1.8%）であった。重症度別では、Grade 3 の事象が 2 例（3.6%）に認められ、Grade 4 の事象は認められなかった。Grade 3 の事象は咽頭炎、感染性小腸結腸炎、ニューモシスチス・イロベチイ肺炎、及びブドウ球菌皮膚感染（各 1 例、1.8%）であった。16 例が抗生物質、抗真菌剤、及び抗ウイルス

剤の投与を受け、14 例が回復した。本事象をコントロールするために 2 例が治験薬を休薬した。また、2 例が「感染症」のために治験薬の投与を中止した。治験薬の投与を中止した 2 例中 1 例が「感染症」の肺炎により死亡した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.5, Listing 16.2.6.5）。

日本人集団では、39 例中 15 例（38.5%）に「感染症」が認められた。その事象は、咽頭炎（発現日：Day 13、Day 24、Day 289）（3 例、7.7%）、気管支炎（発現日：Day 44、Day 47）、結膜炎（発現日：Day 8、Day 60）、インフルエンザ（発現日：Day 15、Day 215）、上咽頭炎（発現日：Day 92、Day 134）、上気道感染（発現日：Day 34、Day 64）（各 2 例、5.1%）、膀胱炎（発現日：Day 119）、サイトメガロウイルス感染（発現日：Day 15）、帯状疱疹（発現日：Day 227）、膿痂疹（発現日：Day 106）、ニューモシスチス・イロベチイ肺炎（発現日：Day 29）、鼻炎（発現日：Day 13）（各 1 例、2.6%）であった。重症度別では、Grade 3 の事象が 1 例（2.6%）に認められ、Grade 4 の事象は認められなかった。Grade 3 の事象は咽頭炎、ニューモシスチス・イロベチイ肺炎であった。12 例が抗生物質、抗真菌剤、及び抗ウイルス剤の投与を受け、11 例が回復した。本事象をコントロールするために 2 例が治験薬を休薬した。また、1 例が「感染症」のために治験薬の投与を中止した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.4.1, Listing 16.2.4.5, Listing 16.2.6.5）。

日本人第 1 相試験（201 試験）

全体では、安全性解析対象集団 14 例中 5 例（35.7%）に「感染症」に該当する事象が認められた。その事象は、鼻咽頭炎（発現日：Day 2、Day 159）（2 例、14.3%）、結膜炎（発現日：Day 31）、膀胱炎（発現日：Day 25）、食道カンジダ症（発現日：Day 43）、咽頭炎（発現日：Day 38）、及び副鼻腔炎（発現日：Day 117）（各 1 例、7.1%）であった（付録表 2.7.4.7-24）。Grade 3 及び Grade 4 の事象は認められなかった（付録表 2.7.4.7-30）。「感染症」に該当する事象を発現した 5 例のうち、2 例が 3 件の事象（鼻咽頭炎、膀胱炎及び食道カンジダ症）に対して抗生物質及び抗真菌剤の投与を受け、うち 2 件（鼻咽頭炎及び膀胱炎）が回復した。発現した事象をコントロールするために 1 例が治験薬を休薬した。「感染症」に該当する事象により治験薬の投与を中止した被験者はなかった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.4.6, Listing 16.2.6.3）。

40 mg コホートでは、7 例中 3 例（42.9%）に「感染症」に該当する事象が認められた。その事象は、鼻咽頭炎（発現日：Day 2、Day 159）（2 例、28.6%）、膀胱炎（発現日：Day 25）及び食道カンジダ症（発現日：Day 43）（各 1 例、14.3%）であった（付録表 2.7.4.7-24）。2 例が 3 件の事象（鼻咽頭炎、膀胱炎及び食道カンジダ症）に対して抗生物質及び抗真菌剤の投与を受け、うち 2 件（鼻咽頭炎及び膀胱炎）が回復した。「感染症」に該当する事象により治験薬を休薬、減量又は中止した被験者はなかった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.4.6, Listing 16.2.6.3）。

日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

安全性解析対象集団 23 例中 7 例（30.4%）に「感染症」が認められた。その事象は、細菌感染（発現日：Day 19）、サイトメガロウイルス感染（発現日：Day 48）、医療機器関連感染（発現日：Day 46）、麦粒腫（発現日：Day 224）、口腔カンジダ症（発現日：Day 32）、ニューモシスチス・イロベチイ肺炎（発現日：Day 73）、皮膚感染（発現日：Day 22）、扁桃炎（発現日：Day 16）、上気道感染（発現日：Day 52）、及び尿路感染（発現日：Day 141）で、いずれも各 1 例での発現であった。重症度別では、Grade 3 の事象が 3 例（13.0%）に認められ、Grade 4 の事象は認められなかった。Grade 3 の事象は医療機器関連感染、ニューモシスチス・イロベチイ肺炎、及び尿路感染であった。7 例全例がスルファメトキサゾール・トリメトプリムやその他の抗生物質など治験実施

計画書で認められた抗生物質、抗真菌剤、及び抗ウイルス剤の投与を予防的に又は治療として受け、うち 5 例が回復した。「感染症」をコントロールするために 1 例が治験薬を休薬及び減量した。また、1 例が「感染症」のために治験薬の投与を中止した。「感染症」により死亡した被験者はなかった（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.4.5, Listing 16.2.6.5）。

日本人以外の患者を対象とした試験

中国人第 2 相試験（902 試験）

探索的試験では、「感染症」に該当する事象は認められなかった（5.3.5.4-1/TG0902CDM p2a /Statistical TFLs/Table 7.4.2）。

ピボタル試験では、83 例中 3 例（3.6%）に「感染症」に該当する事象が認められた。その事象は、鼻副鼻腔炎（nasosinusitis）、慢性鼻副鼻腔炎（chronic nasosinusitis）（各 2 例、2.4%）、壊疽、及び上気道ウイルス感染症（upper respiratory tract viral infection）（各 1 例、1.2%）であった。Grade 3 及び Grade 4 の事象は認められなかった（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2）。

2.7.4.2.1.9.2.6 「ウイルス再活性化」

日本人患者を含む試験

日本人／韓国人第 2b 相試験（203 試験）

安全性解析対象集団 55 例中 2 例（3.6%）に「ウイルス再活性化」が認められた。その事象は、Grade 2 の帯状疱疹（発現日：Day 227）及び Grade 1 のサイトメガロウイルス感染（発現日：Day 15）（各 1 例）であり、サイトメガロウイルス感染は治験薬と関連性があると判定された。両事象とも用量調整（治験薬の休薬又は減量）することなく、抗ウイルス剤の投与後に回復した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.5）。

「ウイルス再活性化」を発現した被験者はいずれも日本人であった。

日本人第 1 相試験（201 試験）

本試験では「ウイルス再活性化」に該当する事象は認められなかった（付録表 2.7.4.7-24）。

日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

安全性解析対象集団 23 例中 1 例（4.3%）に「ウイルス再活性化」が認められた。本事象は Grade 2 のサイトメガロウイルス感染（発現日：Day 48）であり、治験薬の投与を中止した後に発現した。本事象は治験薬と関連性があると判定され、転帰はデータカットオフ時点で未回復であった（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.6.5）。

日本人以外の患者を対象とした試験

中国人第 2 相試験（902 試験）

探索的試験では、「ウイルス再活性化」に該当する事象は認められなかった（5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2）。

ピボタル試験では、83 例中 1 例（1.2%）に「ウイルス再活性化」に該当する事象として、Grade 1 の上気道ウイルス感染症が認められた（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2）。

2.7.4.2.1.9.2.7 「ウイルス再活性化を除く肝障害」

日本人患者を含む試験

日本人／韓国人第 2b 相試験（203 試験）

全体集団では、安全性解析対象集団 55 例中 10 例（18.2%）に「ウイルス再活性化を除く肝障害」（以下、「肝障害」）が認められた。その事象は、GGT 増加（発現日：Day 8（2 例）、Day 3、Day 15、Day 22、Day 43、Day 99、Day 180）（8 例、14.5%）、アスパラギン酸アミノトランスフェラーゼ（AST）増加［発現日：Day 29（2 例）、Day 10、Day 21、Day 41、Day 90、Day 180］（7 例、12.7%）、ALT 増加（発現日： Day 8、Day 13、Day 21、Day 29、Day 180）（5 例、9.1%）であった。重症度別では、Grade 3 の事象が 3 例（5.5%）に認められ、Grade 4 の事象は認められなかった。Grade 3 の事象は GGT 増加（3 例、5.5%）であった。Grade 3 の GGT 増加が認められた 3 例のうち、2 例はデータカットオフ時点で未回復であった。2 例が「肝障害」（Grade 3 の GGT 増加）により治験薬の投与を中止した。「肝障害」により休薬又は減量した被験者はなく、死亡した被験者もなかった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.5）。

「肝障害」を発現した被験者はいずれも日本人であった。

日本人第 1 相試験（201 試験）

全体では、「肝障害」に該当する事象として ALT 増加（発現日：Day 8）、AST 増加（発現日：Day 8）、及びトランスアミナーゼ上昇（発現日：Day 39）（14 例中各 1 例、7.1%）が認められ、2 例以上に認められた事象はなかった（付録表 2.7.4.7-24）。重症度別では Grade 3 の ALT 増加が認められ、治験薬の休薬又は減量、及び支持療法後に回復した。これらの事象により治験薬の投与を中止した被験者はなかった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3）。

本試験で認められた「肝障害」に該当する事象はいずれも 40 mg コホートで認められた。

日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

安全性解析対象集団 23 例中 3 例（13.0%）に「肝障害」が認められた。その事象は AST 増加（発現日：Day 2、Day 23）、GGT 増加（発現日：Day 8、Day 23）（各 2 例、8.7%）、及び ALT 増加（発現日：Day 2）（1 例、4.3%）であった。重症度別では、Grade 3 の事象が 1 例（4.3%）に認められたが、Grade 4 の事象は認められなかった。Grade 3 の事象は GGT 増加であった。1 例（4.3%）が「肝障害」（Grade 3 の GGT 増加）のために治験薬の投与を中止し、投与中止及び支持療法後に回復した。「肝障害」により死亡した被験者はなかった（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.6.5）。

日本人以外の患者を対象とした試験

中国人第 2 相試験（902 試験）

探索的試験では、「肝障害」に該当する事象として Grade 2 の AST 増加が 19 例中 1 例（5.3%）に認められた（5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2）。

ピボタル試験では、「肝障害」に該当する事象として GGT 増加（elevated γ-GT）（83 例中 5 例、6.0%）、ALT 増加（elevated ALT）（3 例、3.6%）、AST 増加（elevated AST）、肝機能障害（各 2 例、2.4%）、血中ビリルビン増加（elevated haemobilirubin）、及びトランスアミナーゼ上昇（elevated transaminase）（各 1 例、1.2%）が認められた。重症度別では、Grade 3 の GGT 増加及び肝機能障

害（各 1 例、1.2%）が認められた。Grade 4 の事象は認められなかった（5.3.5.4-2/TG0902CDM p2b /Statistical Analysis Report/Table 7.4.2）。

2.7.4.2.1.9.2.8 「間質性肺疾患」

日本人患者を含む試験

日本人／韓国人第 2b 相試験（203 試験）

全体集団では、安全性解析対象集団 55 例中 5 例（9.1%）に「間質性肺疾患」が認められた。その事象は、肺臓炎（発現日：Day 57、Day 84、Day 124、Day 281）（4 例、7.3%）及び間質性肺疾患（発現日：Day 57）（1 例、1.8%）であった。重症度別では、Grade 3 の事象が 3 例（5.5%）に認められ、Grade 4 の事象は認められなかった。Grade 3 の事象は肺臓炎（2 例、3.6%）及び間質性肺疾患（1 例、1.8%）であった。「間質性肺疾患」が認められた 5 例のうち、1 例は用量調整（治験薬の休薬又は減量）又は治療を行うことなく回復した。3 例はステロイド等による治療を受け、うち 2 例は治験終了時点で未回復であった。1 例は治療を受けておらず治験終了時点で未回復であったが、本被験者は、治験薬の最終投与後に肺臓炎と診断されたものであった。また、3 例が「間質性肺疾患」により治験薬の投与を中止した。「間質性肺疾患」のため治験薬を休薬又は減量した被験者はなく、「間質性肺疾患」により死亡した被験者もなかった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.5）。

日本人集団では、39 例中 4 例（10.3%）に「間質性肺疾患」が認められた。その事象は、肺臓炎（発現日：Day 57、Day 84、Day 281）（3 例、7.7%）及び間質性肺疾患（発現日：Day 57）（1 例、2.6%）であった。重症度別では、Grade 3 の事象が 2 例（5.1%）に認められ、Grade 4 の事象は認められなかった。Grade 3 の事象は肺臓炎及び間質性肺疾患（各 1 例、2.6%）であった。「間質性肺疾患」が認められた 4 例のうち、1 例は用量調整（治験薬の休薬又は減量）又は治療を行うことなく回復した。2 例はステロイド等による治療を受け、1 例が治験終了時点で未回復であった。1 例は治療を受けておらず治験終了時点で未回復であったが、本被験者は、治験薬最終投与後に肺臓炎と診断されたものであった。2 例が「間質性肺疾患」により治験薬の投与を中止した。「間質性肺疾患」のため治験薬を休薬又は減量した被験者はなかった。また、「間質性肺疾患」により死亡した被験者もなかった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.5）。

日本人第 1 相試験（201 試験）

本試験では、「間質性肺疾患」に該当する事象は認められなかった（付録表 2.7.4.7-24）。

日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

安全性解析対象集団 23 例中 1 例（4.3%）に「間質性肺疾患」が認められた。認められた事象は重篤な Grade 4 の間質性肺疾患（発現日：Day 35）であり、本事象により被験者は治験薬の投与を中止した。当該被験者（被験者[redacted]）は、Grade 4 の好中球数減少の発現により治験薬を休薬していた。休薬 1 週間後に Grade 3 の間質性肺疾患が発現し、副腎皮質ステロイド等による治療開始後に Grade 4 に悪化した。被験者は集中治療室で追加の治療（ステロイドのパルス治療）を受け、発現 40 日後に回復した。本事象は治験薬と関連性があると判定された（初回申請資料 2.7.6.4.3 項参照）。

日本人以外の患者を対象とした試験

中国人第 2 相試験（902 試験）

探索的試験及びピボタル試験のいずれにおいても「間質性肺疾患」に該当する事象は認められなかった（5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2 及び 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2）。

2.7.4.2.1.9.2.9 「心臓障害」

日本人患者を含む試験

日本人／韓国人第 2b 相試験（203 試験）

全体集団では、安全性解析対象集団 55 例中 7 例（12.7%）に「心臓障害」が認められた。その事象は、動悸（発現日：Day 17、Day 33、Day 41）（3 例、5.5%）、心房細動（発現日：Day 3、Day 142）（2 例、3.6%）、不安定狭心症（発現日：Day 29）、不整脈（発現日：Day 20）及び心嚢液貯留（発現日：Day 7）（各 1 例、1.8%）であった。重症度別では、Grade 3 の事象が 1 例（1.8%）に認められた。その事象は不安定狭心症であり、重篤であったが本薬との関連性はないと判定された。Grade 4 の事象は認められなかった。1 例（1.8%）が「心臓障害」（Grade 3 の不安定狭心症）のために治験薬を休薬した。本事象は治験薬の休薬及び支持療法後に回復した。「心臓障害」により死亡した被験者はなかった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.5）。

日本人集団では、39 例中 6 例（15.4%）に「心臓障害」が認められた。その事象は、動悸（発現日：Day 17、Day 33、Day 41）（3 例、7.7%）、心房細動（発現日：Day 142）、不安定狭心症（発現日：Day 29）、不整脈（発現日：Day 20）及び心嚢液貯留（発現日：Day 7）（各 1 例、2.6%）であった。重症度別では、Grade 3 の不安定狭心症が 1 例（2.6%）に認められた。Grade 4 の事象は認められなかった。1 例（2.6%）が「心臓障害」（Grade 3 の不安定狭心症）のために治験薬を休薬した。本事象は治験薬の休薬及び支持療法後に回復した。「心臓障害」により死亡した被験者はなかった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.5）。

日本人第 1 相試験（201 試験）

本試験では「心臓障害」に該当する事象は認められなかった（付録表 2.7.4.7-24）。

日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

安全性解析対象集団 23 例中 2 例（8.7%）で「心臓障害」が認められた。その事象は、第一度房室ブロック（発現日：Day 1）及び動悸（発現日：Day 2）（各 1 例、4.3%）であった。重症度はいずれも Grade 1 であったが、動悸は重篤であり、データカットオフ時点で未回復であった。「心臓障害」のために治験薬を休薬、減量又は中止した被験者はなかった。「心臓障害」により死亡した被験者もなかった（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.6.5）。

日本人以外の患者を対象とした試験

中国人第 2 相試験（902 試験）

探索的試験では、19 例中 1 例（5.3%）に「心臓障害」に該当する事象が認められ、その事象は Grade 1 の心嚢液貯留であった（5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2）。

ピボタル試験では、83 例中 2 例（2.4%）に「心臓障害」に該当する事象が認められた。その事象は、心嚢液貯留（hydropericardium）及び心突然死（各 1 例、1.2%）であった。重症度別では、

Grade 5 の「心臓障害」として心突然死が 1 例（1.2%）に認められた（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2）。

2.7.4.2.1.9.2.10 「トルサード ド ポアント／QT 延長」

日本人患者を含む試験

日本人／韓国人第 2b 相試験（203 試験）

全体集団では、安全性解析対象集団 55 例中 5 例（9.1%）に「トルサード ド ポアント／QT 延長」として心電図 QT 延長（発現日：Day 1、Day 20、Day 108、Day 168、Day 171）が認められた。

重症度別では、Grade 3 及び Grade 4 の事象は認められなかった。Grade 2 の事象を発現した 1 例が、当該事象により治験薬を休薬し、その後回復した。「トルサード ド ポアント／QT 延長」により治験薬の投与を中止した被験者はなかった。また、「トルサード ド ポアント／QT 延長」により死亡した被験者もなかった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.5）。

「トルサード ド ポアント／QT 延長」を発現した被験者はいずれも日本人であった。

日本人第 1 相試験（201 試験）

本試験では「トルサード ド ポアント／QT 延長」に該当する事象は認められなかった（付録表 2.7.4.7-24）。

日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

本試験では「トルサード ド ポアント／QT 延長」は認められなかった。

日本人以外の患者を対象とした試験

中国人第 2 相試験（902 試験）

探索的試験及びピボタル試験のいずれにおいても「トルサード ド ポアント／QT 延長」に該当する事象は認められなかった（5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2 及び 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2）。

2.7.4.2.1.9.2.11 「過敏症」

日本人患者を含む試験

日本人／韓国人第 2b 相試験（203 試験）

全体集団では、安全性解析対象集団 55 例中 3 例（5.5%）に「過敏症」が認められた。それらの事象は、全身性剥脱性皮膚炎（発現日：Day 71）、薬物過敏症（発現日：Day 57）、及び多形紅斑（発現日：Day 14）（各 1 例、1.8%）であった。重症度別では、Grade 3 及び Grade 4 の事象は認められなかった。薬物過敏症を除き、いずれも治験薬と関連性があると判定された。Grade 1 の多形紅斑を発現した 1 例が、データカットオフ時点で未回復であった。「過敏症」に該当する事象により治験薬を休薬、減量又は中止した被験者はなかった。また、「過敏症」により死亡した被験者もなかった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.5）。

「過敏症」を発現した被験者はいずれも日本人であった。

日本人第 1 相試験（201 試験）

安全性解析対象集団 14 例中 1 例（7.1%）に「過敏症」に該当する事象として多形紅斑（発現

日：Day 96）が認められた（付録表 2.7.4.7-24）。重症度は Grade 3 で、治験薬と関連性があると判定された。当該被験者は、本事象により治験薬の休薬又は減量は行うことなく投与を中止した。多形紅斑は治験終了時点で未回復であった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3）。

「過敏症」に該当する事象を発現した被験者は 40 mg コホートの被験者であった。

日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

安全性解析対象集団 23 例中 1 例（4.3%）に「過敏症」として Grade 2 の多形紅斑（発現日：Day 40）が認められた。本事象は治験薬と関連性があると判定され、用量調整（治験薬の休薬又は減量）することなく支持療法後に回復した（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.6.5）。

日本人以外の患者を対象とした試験

中国人第 2 相試験（902 試験）

探索的試験では、19 例中 1 例（5.3%）に「過敏症」に該当する事象として Grade 1 の過敏症が認められた（5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2）。

ピボタル試験では「過敏症」に該当する事象は認められなかった（5.3.5.4-2/TG0902CDM p2b /Statistical Analysis Report/Table 7.4.2）。

2.7.4.2.1.9.3 その他の臨床的に重要な有害事象

2.7.4.2.1.9.3.1 二次性悪性腫瘍

二次性悪性腫瘍は 203 試験でのみ認められた。

日本人／韓国人第 2b 相試験（203 試験）

1 例の AITL を有する被験者に二次性悪性腫瘍として末梢性 T 細胞性リンパ腫 - 組織型不明（発現日：Day 102）が認められた。本事象は重篤で重症度は Grade 3 であり、被験者は本事象により治験薬の投与を中止した。当該被験者（被験者[redacted]）は 7[redacted] 歳の男性で、扁桃腫脹を伴う扁桃痛が認められた。CT 検査の結果から病勢進行が疑われたが、扁桃の感染症も否定できなかった。被験者は抗生物質及びロキソプロフェンの投与を受けたが、扁桃痛の悪化と血清乳酸脱水素酵素（LDH）上昇がみられ、これらの事象は病勢進行を強く示唆したことから、治験薬の投与を中止し、副腎皮質ステロイドの投与を開始した。その後、フローサイトメトリー法及び免疫組織学染色により末梢性 T 細胞性リンパ腫 - 組織型不明（サブタイプ：PTCL-NOS）であると治験担当医師により断定された。また、免疫組織学染色により EBER［エプスタイン・バーウイルス（EBV）小分子 RNA］陽性細胞が確認された。このリンパ腫細胞は本被験者の治験登録時に治験担当医師が AITL と診断した細胞とは異なる、EBV に感染した別の細胞で PTCL-NOS のリンパ腫を発現した可能性が考えられた。本事象は、被験者が別の抗がん剤治療を開始した時点で未回復であった。治験担当医師は治験薬が本事象の発現に関連した可能性を排除できなかった。しかし、中央病理評価委員会が本被験者から治験登録時に採取した生体サンプルを用いて実施した診断では、本被験者の原疾患のサブタイプは AITL ではなく、PTCL-NOS と判定された。他の日本人患者を含む試験及び日本人以外の患者を対象とした試験では二次性悪性腫瘍は報告されていないことから、申請者は、本被験者のデータは二次性悪性腫瘍のリスクを裏づけるものではないと考える（2.7.6.2.3 項参照）。

2.7.4.2.1.9.3.2 再生不良性貧血

再生不良性貧血は 203 試験でのみ認められた。

日本人／韓国人第 2b 相試験（203 試験）

1 例（被験者 [redacted]）に再生不良性貧血（発現日：Day 59）が認められた。本事象は重篤で重症度は Grade 4 であり、治験薬の投与中止後に認められた。被験者は本薬の投与を 3 回受けた後、Grade 4 の好中球減少症及び Grade 4 の血小板数減少により休薬し、投与再開することなく Grade 3 の血小板数減少のため治験薬の投与を中止した。被験者は Grade 4 の汎血球減少症と診断され、G-CSF の投与及び輸血治療を受けた。その後入院し、エルトロンボパグ オラミンの投与を受けた。他の抗がん剤治療開始後、臍帯血移植を受け、好中球の生着がみられたが、その後肝障害や腎障害、皮膚の移植片対宿主病を発現した。輸血依存となったが骨髄所見ではリンパ腫の浸潤はみられず、この汎血球減少症は追跡調査期間中に再生不良性貧血として報告された。被験者は Day 276 に死亡し、その時点で本事象の転帰は未回復であった。本事象は治験担当医師により治験薬と関連性があると判定された。なお、被験者は、骨髄性の血球減少症を発現することが報告されている複数の薬剤を併用していた。また、被験者は乳がん及び PTCL に対する前治療を受けており、その前治療により正常な骨髄機能を喪失した可能性がある。また確率は低いが、その前治療が二次性造血不全の発現に関与した可能性が考えられる（2.7.6.2.3 項参照）。

2.7.4.2.2 個別有害事象の文章による説明

日本人患者を含む試験である 203 試験及び 201 試験における、死亡に至った有害事象、重篤な有害事象及びその他の重要な有害事象の叙述は個々の試験のまとめ（2.7.6.2.3 項、2.7.6.1.3 項、及び初回申請資料 2.7.6.7.3 項）に示した。901 試験の叙述については、CSR（5.3.5.4-1/TG0902CDM p2a/CSR、5.3.5.4-2/TG0902CDM p2b/CSR）に含まれる。

2.7.4.3 臨床検査値の評価

2.7.4.3.1 血液学的検査

2.7.4.3.1.1 日本人／韓国人第 2b 相試験（203 試験）

血液学的検査値異常のベースライン後の Grade の概要を付録表 2.7.4.7-54 に、血液学的検査値異常のベースラインの Grade と投与後の Grade のシフトテーブルを付録表 2.7.4.7-55 に示す。

全体集団で、2 例以上で認められた Grade 3 又は 4 の血液学的検査値異常は、血小板数減少、リンパ球数減少（55 例中各 27 例、49.1%）、好中球数減少（23 例、41.8%）、白血球数減少（17 例、30.9%）、及び貧血（11 例、20.0%）であった。Grade 4 の血液学的検査値異常は、血小板数減少（9 例、16.4%）、リンパ球数減少（6 例、10.9%）、好中球数減少（5 例、9.1%）、及び白血球数減少（1 例、1.8%）であった。

ベースライン時の Grade 0 又は 1 から投与後 Grade 4 に推移した血液学的検査値異常は、血小板数減少（9 例、16.4%）、好中球数減少（5 例、9.1%）、及びリンパ球数減少（1 例、1.8%）であった。ベースライン時の Grade 0 又は 1 から投与後 Grade 3 に推移した血液学的検査値異常は、血小板数減少（18 例、32.7%）、好中球数減少（17 例、30.9%）、リンパ球数減少（12 例、21.8%）、白血球数減少（11 例、20.0%）、及び貧血（4 例、7.3%）であった。

日本人集団では、2 例以上で認められた Grade 3 又は 4 の血液学的検査値異常は、血小板数減少

（39 例中 22 例、56.4%）、リンパ球数減少（20 例、51.3%）、好中球数減少（19 例、48.7%）、白血球数減少（14 例、35.9%）、及び貧血（9 例、23.1%）であった。Grade 4 の血液学的検査値異常は、血小板数減少（9 例、23.1%）、リンパ球数減少（6 例、15.4%）、好中球数減少（4 例、10.3%）、及び白血球数減少（1 例、2.6%）であった。

ベースライン時の Grade 0 又は 1 から投与後 Grade 4 に推移した血液学的検査値異常は、血小板数減少（9 例、23.1%）、好中球数減少（4 例、10.3）、及びリンパ球数減少（1 例、2.6%）であった。ベースライン時の Grade 0 又は 1 から投与後 Grade 3 に推移した血液学的検査値異常は、好中球数減少（14 例、35.9%）、血小板数減少（13 例、33.3%）、白血球数減少（9 例、23.1%）、リンパ球数減少（7 例、17.9%）、及び貧血（3 例、7.7%）であった。

2.7.4.3.1.2 日本人第 1 相試験（201 試験）

血液学的検査値異常のベースライン後の Grade の概要を付録表 2.7.4.7-56、血液学的検査値異常のベースラインの Grade と投与後の Grade のシフトテーブルを付録表 2.7.4.7-57 に示す。

全体で、2 例以上で認められた Grade 3 又は 4 の血液学的検査値異常は、リンパ球数減少（14 例中 6 例、42.9%）、好中球数減少（5 例、35.7%）、血小板数減少（3 例、21.4%）、及び白血球数減少（2 例、14.3%）であった。Grade 4 の血液学的検査値異常は好中球数減少（2 例、14.3%）及びリンパ球数減少（1 例、7.1%）であった。

ベースライン時の Grade 0 又は 1 から投与後 Grade 4 に推移した血液学的検査値異常は、リンパ球数減少及び好中球数減少（各 1 例、7.1%）であった。ベースライン時の Grade 0 又は 1 から投与後 Grade 3 に推移した血液学的検査値異常は、好中球数減少、血小板数減少（各 3 例、21.4%）、リンパ球数減少（2 例、14.3%）、貧血、白血球数減少（各 1 例、7.1%）であった。

40 mg コホートでは、2 例以上で認められた Grade 3 又は 4 の血液学的検査値異常は、リンパ球数減少及び血小板数減少（7 例中各 3 例、42.9%）、及び好中球数減少（2 例、28.6%）であった。Grade 4 の血液学的検査値異常は、好中球数減少（2 例、28.6%）であった。

ベースライン時の Grade 0 又は 1 から投与後 Grade 4 に推移した血液学的検査値異常は、好中球数減少（1 例、14.3%）であった。ベースライン時の Grade 0 又は 1 から投与後 Grade 3 に推移した血液学的検査値異常は、血小板数減少（3 例、42.9%）、及びリンパ球数減少（1 例、14.3%）であった。

2.7.4.3.1.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

血液学的検査値異常のベースライン後の Grade の概要を付録表 2.7.4.7-58 に、血液学的検査値異常のベースラインの Grade と投与後の Grade のシフトテーブルを付録表 2.7.4.7-59 に示す。

2 例以上で認められた Grade 3 又は 4 の血液学的検査値異常は、血小板数減少（23 例中 12 例、52.2%）、リンパ球数減少（11 例、47.8%）、好中球数減少（9 例、39.1%）、白血球数減少（7 例、30.4%）及び貧血（5 例、21.7%）であった。Grade 4 の血液学的検査値異常は、血小板数減少（6 例、26.1%）、好中球数減少（3 例、13.0%）及びリンパ球数減少（2 例、8.7%）であった。

ベースライン時の Grade 0 又は 1 から投与後 Grade 4 に推移した血液学的検査値異常は、血小板数減少（6 例、26.1%）及び好中球数減少（3 例、13.0%）であった。ベースライン時の Grade 0 又は 1 から投与後 Grade 3 に推移した血液学的検査値異常は、血小板数減少及び好中球数減少（各 6 例、26.1%）、白血球数減少（5 例、21.7%）、リンパ球数減少（4 例、17.4%）、及び貧血（2 例、

8.7%）であった。

2.7.4.3.1.4 中国人第 2 相試験（902 試験）

探索的試験及びピボタル試験における血液学的検査の治験薬投与前後の正常値及び異常値の変化をそれぞれ 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.6.1 及び 5.3.5.4-2/TG0902CDM p2b /Statistical Analysis Report/Table 7.4.6.1 に、血液学的検査の臨床的に重大な異常をそれぞれ 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.6.2 及び 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.6.2 に示す。

探索的試験では、治験薬投与前後で正常値から異常値に変化した血液学的検査項目は、顆粒球百分率（投与前に正常値であった 16 例中 13 例が異常値、81.3%）、リンパ球百分率（11 例中 7 例、63.6%）、血小板数（16 例中 9 例、56.3%）、ヘモグロビン、赤血球数、及び総白血球数（それぞれ 14 例中 6 例、42.9%）であった。これらの異常値のうち、臨床的に重大な異常であると治験担当医師により判断された項目は、血小板数（正常値から異常値に変化した 9 例中 8 例、88.9%）、総白血球数（6 例中 4 例、66.7%）、赤血球数（6 例中 2 例、33.3%）、及びヘモグロビン（6 例中 1 例、16.7%）であった。

ピボタル試験では、治験薬投与前後で正常値から異常値に変化した血液学的検査項目は、顆粒球百分率（投与前に正常値であった 44 例中 37 例が異常値、84.1%）、血小板数（68 例中 50 例、73.5%）、リンパ球百分率（45 例中 32 例、71.1%）、総白血球数（60 例中 38 例、63.3%）、ヘモグロビン（50 例中 20 例、40.0%）、及び赤血球数（47 例中 18 例、38.3%）であった。これらの異常値のうち、臨床的に重大な異常であると治験担当医師により判断された項目は、血小板数（正常値から異常値に変化した 50 例中 39 例、78.0%）、総白血球数（38 例中 24 例、63.2%）、ヘモグロビン（20 例中 6 例、30.0%）、赤血球数（18 例中 5 例、27.8%）、顆粒球百分率（37 例中 8 例、21.6%）、及びリンパ球百分率（32 例中 1 例、3.1%）であった。

2.7.4.3.2 血液生化学検査

2.7.4.3.2.1 日本人／韓国人第 2b 相試験（203 試験）

血液生化学検査値異常のベースライン後の Grade の概要を付録表 2.7.4.7-60 に、血液生化学検査異常のベースラインの Grade と投与後の Grade のシフトテーブルを付録表 2.7.4.7-61 に示す。

全体集団で、2 例以上で認められた Grade 3 又は 4 の血液生化学検査値異常は、低ナトリウム血症（55 例中 5 例、9.1%）、リパーゼ増加、GGT 増加（各 4 例、7.3%）、低アルブミン血症、及び低カリウム血症（各 2 例、3.6%）であった。Grade 4 の血液生化学検査値異常は低カリウム血症（2 例、3.6%）であった。

ベースライン時の Grade 0 又は 1 から投与後 Grade 4 に推移した血液生化学検査異常は、低カリウム血症（2 例、3.6%）であった。ベースライン時の Grade 0 又は 1 から投与後 Grade 3 に推移した血液生化学検査異常は、低ナトリウム血症、GGT 増加（各 4 例、7.3%）、リパーゼ増加（3 例、5.5%）、低アルブミン血症、ALP 増加、及び AST 増加（各 1 例、1.8%）であった。

日本人集団では、2 例以上で認められた Grade 3 又は 4 の血液生化学検査値異常は、低ナトリウム血症、GGT 増加（39 例中各 4 例、10.3%）、リパーゼ増加、及び低アルブミン血症（各 2 例、5.1%）であった。

ベースライン時の Grade 0 又は 1 から投与後 Grade 4 に推移した血液生化学検査異常は、低カリウム血症（1 例、2.6%）であった。ベースライン時の Grade 0 又は 1 から投与後 Grade 3 に推移し

た血液生化学検査異常は、GGT 増加（4 例、10.3%）、低ナトリウム血症（3 例、7.7%）、リパーゼ増加（2 例、5.1%）、低アルブミン血症、ALP 増加、及び AST 増加（各 1 例、2.6%）であった。

2.7.4.3.2.2 日本人第 1 相試験（201 試験）

血液生化学検査値異常のベースライン後の Grade の概要を付録表 2.7.4.7-62 に、血液生化学検査異常のベースラインの Grade と投与後の Grade のシフトテーブルを付録表 2.7.4.7-63 に示す。

全体で、2 例以上で認められた Grade 3 の血液生化学検査値異常は、ALT 増加及び高血糖（14 例中各 2 例、14.3%）であった。Grade 4 の血液生化学検査値異常は認められなかった。

ベースライン時の Grade 0 又は 1 から投与後 Grade 3 に推移した血液生化学検査異常は、ALT 増加及び高血糖（各 2 例、14.3%）、低アルブミン血症、低ナトリウム血症、低リン酸血症及び高トリグリセリド血症（各 1 例、7.1%）であった。

血中ビリルビン増加及び低ナトリウム血症各 1 例を除く Grade 3 の血液生化学検査値異常はいずれも 40 mg コホートで認められた。

2.7.4.3.2.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

血液生化学検査値異常のベースライン後の Grade の概要を付録表 2.7.4.7-64 に、血液生化学検査値異常のベースラインの Grade と投与後の Grade のシフトテーブルを付録表 2.7.4.7-65 に示す。

2 例以上で認められた Grade 3 又は 4 の血液生化学検査値異常は、低ナトリウム血症（23 例中 3 例、13.0%）及びリパーゼ増加（2 例、8.7%）であった。Grade 4 の血液生化学検査値異常は低ナトリウム血症及びリパーゼ増加（各 1 例、4.3%）であった。

ベースライン時の Grade 0 又は 1 から投与後 Grade 4 に推移した血液生化学検査異常は、低ナトリウム血症（1 例、4.3%）であった。ベースライン時の Grade 0 又は 1 から投与後 Grade 3 に推移した血液生化学検査異常は、低ナトリウム血症（2 例、8.7%）、並びに ALP 増加、リパーゼ増加、高血糖及び GGT 増加（各 1 例、4.3%）であった。

2.7.4.3.2.4 中国人第 2 相試験（902 試験）

探索的試験及びピボタル試験における血液生化学検査の治験薬投与前後の正常値及び異常値の変化をそれぞれ 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.7.1 及び 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.7.1 に、血液生化学検査の臨床的に重大な異常をそれぞれ 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.7.2 及び 5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.7.2 に示す。

探索的試験では、治験薬投与前後で正常値から異常値に変化した主な血液生化学検査項目は、血清カルシウム（投与前に正常値であった 17 例中 9 例が異常値、52.9%）、血糖（13 例中 6 例、46.2%）、総蛋白（13 例中 4 例、30.8%）、血清カリウム（15 例中 4 例、26.7%）、及び血清リン（15 例中 3 例、20.0%）であった。異常値のうち、臨床的に重大な異常であると治験担当医師により判断された項目は、AST（正常値から異常値に変化した 2 例中 1 例、50.0%）、総ビリルビン（3 例中 1 例、33.3%）、及び血糖（6 例中 1 例、16.7%）であった。

ピボタル試験では、治験薬投与前後で正常値から異常値に変化した主な血液生化学検査項目は、血清カルシウム（投与前に正常値であった 65 例中 30 例が異常値、46.2%）、血清カリウム（67 例中 20 例、29.9%）、血清塩化物（68 例中 20 例、29.4%）、及び尿素窒素（65 例中 15 例、23.1%）

であった。異常値のうち、臨床的に重大な異常であると治験担当医師により判断された項目は、クレアチニン（正常値から異常値に変化した 1 例中 1 例、100.0%）、AST（9 例中 5 例、55.6%）、ALT（11 例中 3 例、27.3%）、GGT（5 例中 1 例、20.0%）、アルブミン（11 例中 2 例、18.2%）、血清カルシウム（30 例中 5 例 16.7%）、及び血清カリウム（20 例中 3 例、15.0%）であった。

2.7.4.4 バイタルサイン、身体的所見及び安全性に関連する他の観察項目

2.7.4.4.1 バイタルサイン

2.7.4.4.1.1 日本人／韓国人第 2b 相試験（203 試験）

臨床的に重大なバイタルサインの異常を付録表 2.7.4.7-66 に示す。

全体集団では、臨床的に重大な収縮期血圧の低下及び拡張期血圧の低下が 55 例中各 4 例（7.3%）に認められた。臨床的に重大な体重減少は 13 例（23.6%）に、体重増加は 5 例（9.1%）に認められた。

日本人集団では、臨床的に重大な収縮期血圧の低下が 39 例中 3 例（7.7%）、拡張期血圧の低下が 4 例（10.3%）に認められた。臨床的に重大な体重減少は 11 例（28.2%）に、体重増加は 4 例（10.3%）に認められた。

2.7.4.4.1.2 日本人第 1 相試験（201 試験）

臨床的に重大なバイタルサインの異常を付録表 2.7.4.7-67 に示す。

全体では、臨床的に重大な収縮期血圧の低下が 14 例中 4 例（28.6%）、拡張期血圧の低下が 3 例（21.4%）に認められた。臨床的に重大な体重減少はベースライン後の測定値が得られた 13 例中 2 例（15.4%）に、体重増加は 1 例（7.7%）に認められた。

40 mg コホートでは、臨床的に重大な収縮期血圧の低下及び拡張期血圧の低下が 7 例中各 1 例（14.3%）に認められた。臨床的に重大な体重減少が 1 例（14.3%）に認められ、体重増加は認められなかった。

2.7.4.4.1.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

臨床的に重大なバイタルサインの異常を付録表 2.7.4.7-68 に示す。

安全性解析対象集団のうち、ベースライン後の測定値が得られた 22 例において、臨床的に重大な収縮期血圧の低下が 3 例（13.6%）、拡張期血圧の低下が 5 例（22.7%）に認められた。臨床的に重大な体重減少は 8 例（36.4%）、体重増加は 1 例（4.5%）に認められた。

2.7.4.4.1.4 中国人第 2 相試験（902 試験）

探索的試験及びピボタル試験におけるバイタルサインの変化をそれぞれ 5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.5.1 及び 5.3.5.4-2/TG0902CDM p2/Statistical Analysis Report/Table 7.4.5.1 に示す。

探索的試験では、治験薬投与後に収縮期／拡張期血圧の異常は認められなかった。

ピボタル試験では、ベースライン時の収縮期／拡張期血圧が正常値であった 65 例のうち、治験薬投与後に異常値を示した被験者は 8 例（12.3%）であった。

2.7.4.4.2 心電図

2.7.4.4.2.1 日本人／韓国人第 2b 相試験（203 試験）

心電図パラメータの要約及び臨床的に重大な心電図の異常の結果をそれぞれ付録表 2.7.4.7-69 及び付録表 2.7.4.7-70 に要約した。

本試験では、すべての被験者の心電図を、Cycle 1 及び Cycle 2 では Day 1 の治験薬投与前及び投与後 3.5 時間に triplicate で、その後の Cycle では Day 1 に single で測定した。Cycle 1 及び Cycle

2 では、QTcF の平均値が 450 msec を超えた被験者はなかった。治験薬投与後 3.5 時間では、QTcF の平均値が投与前の値から 30 msec を超えて変化した被験者はなかった。その後の Cycle（Cycle 3 から Cycle 21 の Day 1）及び治療終了時来院では、QTcF の平均値が 450 msec を超えた被験者はなかった。

全体集団で、QTcF の絶対値が 450 msec を超えて延長した被験者は 55 例中 5 例（9.1%）、480 msec を超えて延長した被験者は 1 例（1.8%）であり、いずれの被験者でもこれらの延長がみられたのは 1 回のみであった。QTcF の絶対値が 500 msec を超えて延長した被験者はなかった。QTcF の変化量がベースライン時から 30 msec を超えて延長した被験者は 8 例（14.5%）であり、QTcF の変化量がベースライン時から 60 msec を超えて延長した被験者はなかった。

日本人集団で、QTcF の絶対値が 450 msec を超えて延長した被験者は 39 例中 5 例（12.8%）、480 msec を超えて延長した被験者は 1 例（2.6%）であり、いずれの被験者でもこれらの延長がみられたのは 1 回のみであった。QTcF の絶対値が 500 msec を超えて延長した被験者はなかった。QTcF の変化量がベースライン時から 30 msec を超えて延長した被験者は 5 例（12.8%）であり、QTcF の変化量がベースライン時から 60 msec を超えて延長した被験者はなかった。

2.7.4.4.2.2 日本人第 1 相試験（201 試験）

臨床的に重大な心電図の異常を付録表 2.7.4.7-71 に示す。

全体で、QTcF の絶対値が 450 msec を超えた被験者は 14 例中 5 例（35.7%）、480 msec を超えた被験者は 1 例（7.1%）であった。QTcF の絶対値が 500 msec を超えて延長した被験者はなかった。QTcF の変化量がベースライン時から 30 msec を超えて延長した被験者は 4 例（28.6%）であり、60 msec を超えて延長した被験者はなかった。

40 mg コホートでは、QTcF の絶対値が 450 msec を超えた被験者は 7 例中 2 例（28.6%）、480 msec を超えた被験者は 1 例（14.3%）であった。QTcF の絶対値が 500 msec を超えて延長した被験者はなかった。QTcF の変化量がベースライン時から 30 msec を超えて延長した被験者は 3 例（42.9%）であり、60 msec を超えて延長した被験者はなかった。

2.7.4.4.2.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

心電図パラメータの要約及び臨床的に重大な心電図の異常をそれぞれ付録表 2.7.4.7-72 及び付録表 2.7.4.7-73 に示す。

本試験では、すべての被験者の心電図を、Cycle 1 及び Cycle 2 では Day 1 の治験薬投与前及び投与後 3.5 時間に triplicate で、その後の Cycle では Day 1 に single で測定した。Cycle 1 及び Cycle 2 では、QTcF の平均値が 450 msec を超えた被験者はなかった。治験薬投与後 3.5 時間では、QTcF の平均値が投与前の値から 30 msec を超えて変化した被験者はなかった。その後の Cycle（Cycle 3 から Cycle 14 の Day 1）及び治療終了時来院では、QTcF の平均値が 450 msec を超えた被験者はなかった。

QTcF の絶対値が 450 msec を超えて延長した被験者は 23 例中 3 例（13.0%）、480 msec を超えて延長した被験者は 1 例（4.3%）であり、いずれも治験担当医師が臨床的に重大な異常と判定しておらず、有害事象として報告されなかった。QTcF の絶対値が 500 msec を超えて延長した被験者はなかった。QTcF の変化量がベースライン時から 30 msec を超えて延長した被験者は 2 例（8.7%）であり、60 msec を超えて延長した被験者はなかった。

2.7.4.4.2.4 中国人第 2 相試験（902 試験）

探索的試験及びピボタル試験における心電図の変化をそれぞれ 5.3.5.4-1/TG0902CDM p2a /Statistical TFLs/Table 7.4.10.1 及び 5.3.5.4-2TG0902CDM p2b/Statistical Analysis Report/Table 7.4.10.1 に示す。

探索的試験では、ベースライン時の心電図及び QTc が正常であった 12 例のうち、治験薬投与後に心電図の異常を示した被験者は 6 例（50.0%）、QTc の異常を示した被験者は 2 例（16.7%）であった。

ピボタル試験では、ベースライン時の心電図が正常であった 31 例のうち、治験薬投与後に異常を示した被験者は 10 例（32.3%）であり、ベースライン時の QTc が正常であった 44 例のうち、治験薬投与後に異常を示した被験者は 11 例（25.0%）であった。

2.7.4.4.3 ECOG PS

2.7.4.4.3.1 日本人／韓国人第 2b 相試験（203 試験）

ECOG PS の評価を付録表 2.7.4.7-74 に示す。

全体集団では、ECOG PS がベースライン時の 0 又は 1 から投与終了時に 4 へ推移した被験者は、両時点のデータがある 37 例のうち 1 例（2.7%）であった。ECOG PS が 3 に推移した被験者は 2 例（5.4%）であった。

日本人集団では、ECOG PS がベースライン時の 0 又は 1 から投与終了時に 3 又は 4 へ推移した被験者はなかった。

2.7.4.4.3.2 日本人第 1 相試験（201 試験）

ECOG PS の評価を付録表 2.7.4.7-75 に示す。

全体では、14 例全例のベースライン時の ECOG PS は 0 又は 1 であり、ECOG PS が 3 に推移した 1 例（7.1%）を除き、治験終了時の評価まで変化は認められなかった。

40 mg コホートでは、7 例全例のベースライン時の ECOG PS は 0 又は 1 であり、治験終了時の評価まで ECOG PS に変化は認められなかった。

2.7.4.4.3.3 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

ECOG PS の評価を付録表 2.7.4.7-76 に示す。

ECOG PS がベースライン時の 0 又は 1 から投与終了時に 4 へ推移した被験者は、両時点のデータがある 21 例のうち 2 例（9.5%）であった。ECOG PS が 3 に推移した被験者は 1 例（4.8%）であった。

2.7.4.5 特別な患者集団及び状況下における安全性

2.7.4.5.1 内因性要因

2.7.4.5.1.1 性別

2.7.4.5.1.1.1 日本人／韓国人第 2b 相試験（203 試験）

性別の有害事象の概要を表 2.7.4.5-1 に、性別の有害事象の発現割合を付録表 2.7.4.7-78 に示す。

安全性解析対象集団 55 例中、男性が 35 例、女性が 20 例であった。性別にかかわらず、すべての被験者で 1 件以上の有害事象が認められた。重篤な有害事象及び治験薬と関連性のある重篤な

有害事象の発現割合が、女性に比べて男性で 20%を超えて高かった。有害事象の発現割合が男性に比べて女性で 20%を超えて高かった項目はなかった。

PT 別では、発現割合が男性に比べて女性で 20%を超えて高かった有害事象は、貧血*［女性：50.0%（20 例中 10 例）、男性：22.9%（35 例中 8 例）］であった。発現割合が女性に比べて男性で 20%を超えて高かった有害事象はなかった。

表 2.7.4.5-1 性別の有害事象の概要（203 試験）（安全性解析対象集団）

Description	Male (N=35) n (%)	Female (N=20) n (%)
Number of subjects with		
At least one TEAE	35 (100.0%)	20 (100.0%)
At least one TEAE related to the study drug	33 (94.3%)	18 (90.0%)
At least one serious TEAE	12 (34.3%)	2 (10.0%)
At least one serious TEAE related to the study drug	9 (25.7%)	1 (5.0%)
At least one TEAE leading to dose reduction or interruption	27 (77.1%)	13 (65.0%)
At least one TEAE leading to study drug discontinuation	11 (31.4%)	7 (35.0%)
At least one TEAE leading to death	1 (2.9%)	0 (0.0%)
At least one TEAE with grade 3 or higher	28 (80.0%)	18 (90.0%)
At least one TEAE with grade 3 or higher and related to the study drug	26 (74.3%)	16 (80.0%)

Source: Appendix Table 2.7.4.7-77
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Data cut-off date: [redacted] 20[redacted]

2.7.4.5.1.1.2 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

性別の有害事象の概要を表 2.7.4.5-2 に、性別の有害事象の発現割合を付録表 2.7.4.7-80 に示す。

安全性解析対象集団 23 例中、男性が 15 例、女性が 8 例であった。性別にかかわらず、すべての被験者で 1 件以上の有害事象が認められた。重篤な有害事象、治験薬と関連性のある重篤な有害事象、休薬又は減量に至った有害事象、投与中止に至った有害事象、Grade 3 以上の有害事象、及び治験薬と関連性のある Grade 3 以上の有害事象の発現割合は、男性に比べて女性で 20%を超えて高かった。

PT 別では、発現割合が男性に比べて女性で 20%を超えて高かった有害事象は、食欲減退［女性：50.0%（8 例中 4 例）、男性：26.7%（15 例中 4 例）］及び背部痛［女性：37.5%（3 例）、男性：6.7%（1 例）］であった。発現割合が女性に比べて男性で 20%を超えて高かった有害事象はなかった。

表 2.7.4.5-2 性別の有害事象の概要（210 試験）（安全性解析対象集団）

Description	Male (N=15) n (%)	Female (N=8) n (%)
Number of subjects with		
At least one TEAE	15 (100.0%)	8 (100.0%)
At least one TEAE related to the study drug	15 (100.0%)	8 (100.0%)
At least one serious TEAE	1 (6.7%)	6 (75.0%)
At least one serious TEAE related to the study drug	1 (6.7%)	5 (62.5%)
At least one TEAE leading to dose reduction or interruption	9 (60.0%)	7 (87.5%)
At least one TEAE leading to study drug discontinuation	4 (26.7%)	5 (62.5%)
At least one TEAE leading to death	0 (0.0%)	0 (0.0%)
At least one TEAE with grade 3 or higher	10 (66.7%)	8 (100.0%)
At least one TEAE with grade 3 or higher and related to the study drug	10 (66.7%)	8 (100.0%)

Source: Appendix Table 2.7.4.7-79 (cited from the new drug application for relapsed or refractory ATL)
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Data cut-off date: [redacted] 20[redacted]

2.7.4.5.1.2 年齢

2.7.4.5.1.2.1 日本人／韓国人第 2b 相試験（203 試験）

年齢別の有害事象の概要を表 2.7.4.5-3 に、年齢別の有害事象の発現割合を付録表 2.7.4.7-82 に示す。

安全性解析対象集団 55 例中、65 歳未満が 15 例、65 歳以上 75 歳未満が 23 例、75 歳以上が 17 例であった。年齢にかかわらず、すべての被験者で 1 件以上の有害事象が認められた。重篤な有害事象及び治験薬と関連性のある重篤な有害事象の発現割合が、65 歳未満に比べて 65 歳以上 75 歳未満及び 75 歳以上で 20%を超えて高かった。休薬又は減量に至った有害事象、治験薬と関連性のある Grade 3 以上の有害事象の発現割合は、65 歳未満及び 65 歳以上 75 歳未満に比べて 75 歳以上で 20%を超えて高かった。

PT 別では、発現割合が 65 歳未満及び 65 歳以上 75 歳未満に比べて 75 歳以上で 20%を超えて高かった有害事象は、食欲減退［65 歳未満：13.3%（15 例中 2 例）、65 歳以上 75 歳未満：17.4%（23 例中 4 例）、75 歳以上：41.2%（17 例中 7 例）］であった。発現割合が 65 歳未満に比べて 65 歳以上 75 歳未満及び 75 歳以上で 20%を超えて高かった有害事象はなかった。発現割合が 75 歳以上に比べて 65 歳未満及び 65 歳以上 75 歳未満で 20%を超えて高かった有害事象は、リンパ球減少症*［65 歳未満：33.3%（5 例）、65 歳以上 75 歳未満：39.1%（9 例）、75 歳以上：11.8%（2 例）］であった。発現割合が 65 歳以上 75 歳未満及び 75 歳以上に比べて 65 歳未満で 20%を超えて高かった有害事象はなかった。

表 2.7.4.5-3 年齢別の有害事象の概要（203 試験）（安全性解析対象集団）

Description	<65 (N=15) n (%)	>=65 to <75 (N=23) n (%)	>=75 (N=17) n (%)
Number of subjects with			
At least one TEAE	15 (100.0%)	23 (100.0%)	17 (100.0%)
At least one TEAE related to the study drug	13 (86.7%)	21 (91.3%)	17 (100.0%)
At least one serious TEAE	1 (6.7%)	7 (30.4%)	6 (35.3%)
At least one serious TEAE related to the study drug	0 (0.0%)	6 (26.1%)	4 (23.5%)
At least one TEAE leading to dose reduction or interruption	10 (66.7%)	15 (65.2%)	15 (88.2%)
At least one TEAE leading to study drug discontinuation	6 (40.0%)	8 (34.8%)	4 (23.5%)
At least one TEAE leading to death	0 (0.0%)	0 (0.0%)	1 (5.9%)
At least one TEAE with grade 3 or higher	11 (73.3%)	19 (82.6%)	16 (94.1%)
At least one TEAE with grade 3 or higher and related to the study drug	10 (66.7%)	16 (69.6%)	16 (94.1%)

Source: Appendix Table 2.7.4.7-81
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Data cut-off date: [redacted] 20[redacted]

2.7.4.5.1.2.2 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

年齢別の有害事象の概要を表 2.7.4.5-4 に、年齢別の有害事象の発現割合を付録表 2.7.4.7-84 に示す。

安全性解析対象集団 23 例中、65 歳未満が 1 例、65 歳以上 75 歳未満が 13 例、75 歳以上が 9 例であった。年齢にかかわらず、すべての被験者で 1 件以上の有害事象が認められた。治験薬と関連性のある有害事象、重篤な有害事象を含むすべての項目において 65 歳以上 75 歳未満と 75 歳以上の有害事象発現割合に大きな違いはみられなかった。

PT 別では、発現割合が 75 歳以上に比べて 65 歳以上 75 歳未満で 20%を超えて高かった有害事象は、好中球減少症*［65 歳以上 75 歳未満：61.5%（8 例）、75 歳以上：33.3%（3 例）］、白血球減少症*［65 歳以上 75 歳未満：53.8%（13 例中 7 例）、75 歳以上：22.2%（9 例中 2 例）］、及び発熱［65 歳以上 75 歳未満：23.1%（3 例）、75 歳以上：0%（0 例）］であった。発現割合が 65 歳以上 75 歳未満に比べて 75 歳以上で 20%を超えて高かった有害事象は、倦怠感［65 歳以上 75 歳未満：23.1%（3 例）、75 歳以上：44.4%（4 例）］、疲労［65 歳以上 75 歳未満：0%（0 例）、75 歳以上：33.3%（3 例）］、及び頭痛［65 歳以上 75 歳未満：0%（0 例）、75 歳以上：22.2%（2 例）］であった。

表 2.7.4.5-4 年齢別の有害事象の概要（210 試験）（安全性解析対象集団）

Description	<65 (N=1) n (%)	>=65 to <75 (N=13) n (%)	>=75 (N=9) n (%)
Number of subjects with			
At least one TEAE	1 (100.0%)	13 (100.0%)	9 (100.0%)
At least one TEAE related to the study drug	1 (100.0%)	13 (100.0%)	9 (100.0%)
At least one serious TEAE	0 (0.0%)	5 (38.5%)	2 (22.2%)
At least one serious TEAE related to the study drug	0 (0.0%)	4 (30.8%)	2 (22.2%)
At least one TEAE leading to dose reduction or interruption	1 (100.0%)	9 (69.2%)	6 (66.7%)
At least one TEAE leading to study drug discontinuation	1 (100.0%)	5 (38.5%)	3 (33.3%)
At least one TEAE leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)
At least one TEAE with grade 3 or higher	1 (100.0%)	11 (84.6%)	6 (66.7%)
At least one TEAE with grade 3 or higher and related to the study drug	1 (100.0%)	11 (84.6%)	6 (66.7%)

Source: Appendix Table 2.7.4.7-83 (cited from the new drug application for relapsed or refractory ATL)
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Data cut-off date: [redacted] 20[redacted]

2.7.4.5.1.3 PTCL サブセット

本部分集団解析は 203 試験のみで実施した。

2.7.4.5.1.3.1 日本人／韓国人第 2b 相試験（203 試験）

PTCL サブセット（再発、難治性）別の有害事象の概要を表 2.7.4.5-5 に、PTCL サブセット別の有害事象の発現割合を付録表 2.7.4.7-86 に示す。

安全性解析対象集団 55 例中、再発が 32 例、難治性が 23 例であった。PTCL サブセットにかかわらず、すべての被験者で 1 件以上の有害事象が認められた。再発と難治性での有害事象の発現割合を比較すると、投与中止に至った有害事象の発現割合が再発で 20%を超えて高かった。有害事象の発現割合が、再発に比べて難治性で 20%を超えて高かった項目はなかった。

PT 別では、発現割合が再発に比べて難治性で 20%を超えて高かった有害事象は、悪心［再発：12.5%（4 例）、難治性：34.8%（8 例）］であった。発現割合が難治性に比べて再発で 20%を超えて高かった有害事象はなかった。

表 2.7.4.5-5 PTCL サブセット別の有害事象の概要（203 試験）（安全性解析対象集団）

Description	Relapsed (N=32) n (%)	Refractory (N=23) n (%)
Number of subjects with		
At least one TEAE	32 (100.0%)	23 (100.0%)
At least one TEAE related to the study drug	30 (93.8%)	21 (91.3%)
At least one serious TEAE	10 (31.3%)	4 (17.4%)
At least one serious TEAE related to the study drug	8 (25.0%)	2 (8.7%)
At least one TEAE leading to dose reduction or interruption	23 (71.9%)	17 (73.9%)
At least one TEAE leading to study drug discontinuation	14 (43.8%)	4 (17.4%)
At least one TEAE leading to death	1 (3.1%)	0 (0.0%)
At least one TEAE with grade 3 or higher	29 (90.6%)	17 (73.9%)
At least one TEAE with grade 3 or higher and related to the study drug	26 (81.3%)	16 (69.6%)

Source: Appendix Table 2.7.4.7-85
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by relapsed, recurrent or refractory ATL; n = number of subjects;
% = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Subjects with refractory and relapsed PTCL are confirmed by Medical Expert.
Data cut-off date: [redacted] 20[redacted]

2.7.4.5.1.4 人種

2.7.4.5.1.4.1 日本人／韓国人第 2b 相試験（203 試験）

安全性解析対象集団 55 例中、日本人が 39 例、韓国人が 16 例であった。人種にかかわらず、すべての被験者で 1 件以上の有害事象が認められた。治験薬と関連性のある有害事象、休薬又は減量に至った有害事象、及び治験薬と関連性のある Grade 3 以上の有害事象の発現割合が、韓国人に比べて日本人で 20%を超えて高かった。発現割合が日本人に比べて韓国人で 20%を超えて高かった項目はなかった（表 2.7.4.2-1）。

PT 別では、発現割合が韓国人に比べて日本人で 20%を超えて高かった有害事象は、血小板減少症*［日本人：89.7%（39 例中 35 例）、韓国人：68.8%（16 例中 11 例）］、好中球減少症*［日本人：71.8%（28 例）、韓国人：18.8%（3 例）］、白血球減少症*［日本人：61.5%（24 例）、韓国人：0%（0 例）］、リンパ球減少症*［日本人：41.0%（16 例）、韓国人：0%（0 例）］及び、倦怠感、血中 ALP 増加、GGT 増加［いずれも日本人：20.5%（8 例）、韓国人：0%（0 例）］であった。発現割合が日本人に比べて韓国人で 20%を超えて高かった有害事象は発熱［日本人：12.8%（5 例）、韓国人：37.5%（6 例）］であった（付録表 2.7.4.7-23）。

2.7.4.5.1.5 ECOG PS

2.7.4.5.1.5.1 日本人／韓国人第 2b 相試験（203 試験）

ベースライン時の ECOG PS 別の有害事象の概要を表 2.7.4.5-6 に、ECOG PS 別の有害事象の発現割合を付録表 2.7.4.7-88 に示す。

安全性解析対象集団 55 例中、ECOG PS 0 が 28 例、ECOG PS 1 が 25 例、ECOG PS 2 が 2 例であった。ECOG PS にかかわらず、すべての被験者で 1 件以上の有害事象が認められた。休薬又は

減量に至った有害事象の発現割合が、ECOG PS 1 に比べ ECOG PS 0 で 20%を超えて高かったことを除き、すべての項目で有害事象の発現割合に大きな違いはみられなかった。

PT 別では、発現割合が ECOG PS 1 に比べ ECOG PS 0 で 20%を超えて高かった有害事象は血小板減少症*［ECOG PS 0：96.4%（28 例中 27 例）、ECOG PS 1：72.0%（25 例中 18 例）］、好中球減少症*［ECOG PS 0：71.4%（20 例）、ECOG PS 1：40.0%（10 例）］、白血球減少症*［ECOG PS 0：60.7%（17 例）、ECOG PS 1：24.0%（6 例）］、及びリンパ球減少症*［ECOG PS 0：50.0%（14 例）、ECOG PS 1：8.0%（2 例）］であった。発現割合が ECOG PS 0 に比べ ECOG PS 1 で 20%を超えて高かった有害事象はなかった。

表 2.7.4.5-6 ECOG PS 別の有害事象の概要（203 試験）（安全性解析対象集団）

Description	ECOG PS: 0 (N=28) n (%)	ECOG PS: 1 (N=25) n (%)	ECOG PS: 2 (N=2) n (%)
Number of subjects with			
At least one TEAE	28 (100.0%)	25 (100.0%)	2 (100.0%)
At least one TEAE related to the study drug	27 (96.4%)	22 (88.0%)	2 (100.0%)
At least one serious TEAE	6 (21.4%)	7 (28.0%)	1 (50.0%)
At least one serious TEAE related to the study drug	4 (14.3%)	5 (20.0%)	1 (50.0%)
At least one TEAE leading to dose reduction or interruption	23 (82.1%)	15 (60.0%)	2 (100.0%)
At least one TEAE leading to study drug discontinuation	8 (28.6%)	10 (40.0%)	0 (0.0%)
At least one TEAE leading to death	0 (0.0%)	1 (4.0%)	0 (0.0%)
At least one TEAE with grade 3 or higher	25 (89.3%)	19 (76.0%)	2 (100.0%)
At least one TEAE with grade 3 or higher and related to the study drug	23 (82.1%)	17 (68.0%)	2 (100.0%)

Source: Appendix Table 2.7.4.7-87
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Data cut-off date: [redacted] 20[redacted]

2.7.4.5.1.5.2 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

ベースライン時の ECOG PS 別の有害事象の概要を表 2.7.4.5-7 に、ECOG PS 別の有害事象の発現割合を付録表 2.7.4.7-90 に示す。

安全性解析対象集団 23 例中、ECOG PS 0 が 12 例、ECOG PS 1 が 10 例、ECOG PS 2 が 1 例であった。ECOG PS にかかわらず、すべての被験者で 1 件以上の有害事象が認められた。すべての有害事象及び治験薬と関連性のある有害事象を除くすべての項目の有害事象の発現割合が、ECOG PS 1 に比べて ECOG PS 0 で 20%を超えて高かった。

PT 別では、発現割合が ECOG PS 1 に比べて ECOG PS 0 で 20%を超えて高かった有害事象は、好中球減少症*［ECOG PS 0：75.0%（12 例中 9 例）、ECOG PS 1：30.0%（10 例中 3 例）］及び白血球減少症*［ECOG PS 0：58.3%（7 例）、ECOG PS 1：20.0%（2 例）］であった。発現割合が ECOG PS 0 に比べて ECOG PS 1 で 20%を超えて高かった有害事象は味覚異常［ECOG PS 0：8.3%（1 例）、ECOG PS 1：30.0%（3 例）］であった。

表 2.7.4.5-7 ECOG PS 別の有害事象の概要（210 試験）（安全性解析対象集団）

Description	ECOG PS: 0 (N=12) n (%)	ECOG PS: 1 (N=10) n (%)	ECOG PS: 2 (N=1) n (%)
Number of subjects with			
At least one TEAE	12 (100.0%)	10 (100.0%)	1 (100.0%)
At least one TEAE related to the study drug	12 (100.0%)	10 (100.0%)	1 (100.0%)
At least one serious TEAE	5 (41.7%)	2 (20.0%)	0 (0.0%)
At least one serious TEAE related to the study drug	5 (41.7%)	1 (10.0%)	0 (0.0%)
At least one TEAE leading to dose reduction or interruption	11 (91.7%)	4 (40.0%)	1 (100.0%)
At least one TEAE leading to study drug discontinuation	7 (58.3%)	2 (20.0%)	0 (0.0%)
At least one TEAE leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)
At least one TEAE with grade 3 or higher	11 (91.7%)	6 (60.0%)	1 (100.0%)
At least one TEAE with grade 3 or higher and related to the study drug	11 (91.7%)	6 (60.0%)	1 (100.0%)

Source: Appendix Table 2.7.4.7-89 (cited from the new drug application for relapsed or refractory ATL)
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Data cut-off date: [redacted] 20[redacted]

2.7.4.5.1.6 腎機能障害

中等度又は重度の腎機能障害を有する患者を対象とした試験は実施していない。

203 試験では、SOC「腎および尿路障害」に分類される有害事象が 2 例に認められ、その事象は急性腎障害、血尿、及び蛋白尿（各 1 例）であった（付録表 2.7.4.7-29）。いずれの事象も重症度は Grade 1 又は 2 であった。急性腎障害は重篤、蛋白尿は治験薬と関連性があると判定されたが、これらの事象のために治験薬の投与を中止することはなく、休薬又は減量も行わなかった（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.6.1）。

201 試験では、SOC「腎および尿路障害」に分類される有害事象が 3 例に認められ、その事象は血尿、頻尿、蛋白尿及び尿管結石症（各 1 例）であった（付録表 2.7.4.7-24）。いずれの事象も重症度は Grade 1 又は 2 であり、尿管結石症を除いて、治験薬と関連性があると判定された。これらの事象のために治験薬の投与を中止もしくは休薬又は減量した被験者はなかった（5.3.3.2-1/HBI-8000-201/CSR/Listing 16.2.6.3）。

210 試験では、SOC「腎および尿路障害」に分類される Garde 2 の尿瘻が 1 例に認められた（付録表 2.7.4.7-31）。本事象は治験薬と関連性があると判定されたが、本事象のために治験薬の投与を中止することはなく、休薬又は減量も行わなかった（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.6.1）。

902 試験では、大分類「腎および尿路障害（kidneys and urinary system diseases）」に分類される事象が、探索的試験及びピボタル試験で各 1 例に認められ、その事象は、探索的試験では Grade 1 の血尿、ピボタル試験では Grade 2 の腎不全であった（5.3.5.4-1/TG0902CDM p2a/Statistical TFLs/Table 7.4.2、5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2）。いずれも治験薬と関連性はないと判定された。Grade 2 の腎不全を発現した

被験者は、当該事象により治験薬の投与を中止した（5.3.5.4-2/TG0902CDM p2b/Statistical Analysis Report/Table 7.6.10）。

2.7.4.5.1.7 肝機能障害

中等度又は重度の肝機能障害を有する患者を対象とした試験は実施していない。

注目すべき有害事象として検討した「ウイルス再活性化を除く肝障害」の発現状況は 2.7.4.2.1.9.2.7 項を参照のこと。

2.7.4.5.2 外因性要因

2.7.4.5.2.1 前治療のレジメン数

2.7.4.5.2.1.1 日本人／韓国人第 2b 相試験（203 試験）

前治療のレジメン数別の有害事象の概要を表 2.7.4.5-8 に、前治療のレジメン数別の有害事象の発現割合を付録表 2.7.4.7-92 に示す。

安全性解析対象集団 55 例中、前治療のレジメン数が 3 レジメン未満の被験者が 35 例、3 レジメン以上の被験者が 20 例であった。前治療のレジメン数にかかわらず、すべての被験者で 1 件以上の有害事象が認められた。3 レジメン未満に比べて 3 レジメン以上で治験薬の投与中止に至った有害事象の発現割合が 20%を超えて高かったことを除き、すべての項目で有害事象の発現割合に大きな違いはみられなかった。

PT 別では、3 レジメン未満と 3 レジメン以上で発現割合の差が 20%を超えた有害事象はなかった。

表 2.7.4.5-8 前治療のレジメン数別の有害事象の概要（203 試験）（安全性解析対象集団）

Description	Less than 3 regimens (N=35) n (%)	3 or more regimens (N=20) n (%)
Number of subjects with		
At least one TEAE	35 (100.0%)	20 (100.0%)
At least one TEAE related to the study drug	32 (91.4%)	19 (95.0%)
At least one serious TEAE	10 (28.6%)	4 (20.0%)
At least one serious TEAE related to the study drug	7 (20.0%)	3 (15.0%)
At least one TEAE leading to dose reduction or interruption	25 (71.4%)	15 (75.0%)
At least one TEAE leading to study drug discontinuation	8 (22.9%)	10 (50.0%)
At least one TEAE leading to death	0 (0.0%)	1 (5.0%)
At least one TEAE with grade 3 or higher	31 (88.6%)	15 (75.0%)
At least one TEAE with grade 3 or higher and related to the study drug	28 (80.0%)	14 (70.0%)

Source: Appendix Table 2.7.4.7-91
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Data cut-off date: [redacted] 20[redacted]

2.7.4.5.2.1.2 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

前治療のレジメン数別の有害事象の概要を表 2.7.4.5-9 に、前治療のレジメン数別の有害事象の発現割合を付録表 2.7.4.7-94 に示す。

安全性解析対象集団 23 例中、前治療のレジメン数が 3 レジメン未満の被験者が 11 例、3 レジメン以上の被験者が 12 例であった。前治療のレジメン数にかかわらず、すべての被験者で 1 件以上の有害事象が認められた。重篤な有害事象及び治験薬と関連性のある重篤な有害事象の発現割合は、3 レジメン以上に比べて 3 レジメン未満で 20%を超えて高かった。治験薬の投与中止に至った有害事象の発現割合は、3 レジメン未満に比べて 3 レジメン以上で 20%を超えて高かった。

PT 別では、3 レジメン以上に比べて 3 レジメン未満で発現割合が 20%を超えて高かった有害事象は、食欲減退［3 レジメン未満：45.5%（11 例中 5 例）、3 レジメン以上：25.0%（12 例中 3 例）］であった。3 レジメン未満に比べて 3 レジメン以上で発現割合が 20%を超えて高かった有害事象は、貧血*［3 レジメン未満：18.2%（2 例）、3 レジメン以上：58.3%（7 例）］、及び白血球減少症*［3 レジメン未満：27.3%（3 例）、3 レジメン以上：58.3%（7 例）］であった。

表 2.7.4.5-9 前治療のレジメン数別の有害事象の概要（210 試験）（安全性解析対象集団）

Description	Less than 3 regimens (N=11) n (%)	3 or more regimens (N=12) n (%)
Number of subjects with		
At least one TEAE	11 (100.0%)	12 (100.0%)
At least one TEAE related to the study drug	11 (100.0%)	12 (100.0%)
At least one serious TEAE	5 (45.5%)	2 (16.7%)
At least one serious TEAE related to the study drug	5 (45.5%)	1 (8.3%)
At least one TEAE leading to dose reduction or interruption	7 (63.6%)	9 (75.0%)
At least one TEAE leading to study drug discontinuation	3 (27.3%)	6 (50.0%)
At least one TEAE leading to death	0 (0.0%)	0 (0.0%)
At least one TEAE with grade 3 or higher	8 (72.7%)	10 (83.3%)
At least one TEAE with grade 3 or higher and related to the study drug	8 (72.7%)	10 (83.3%)

Source: Appendix Table 2.7.4.7-93 (cited from the new drug application for relapsed or refractory ATL)
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Data cut-off date: [redacted] 20[redacted]

2.7.4.5.2.2 直近のがん治療からの期間

2.7.4.5.2.2.1 日本人／韓国人第 2b 相試験（203 試験）

直近のがん治療からの期間別の有害事象の概要を表 2.7.4.5-10 に、有害事象の発現割合を付録表 2.7.4.7-96 に示す。

安全性解析対象集団 55 例中、直近のがん治療から 3 ヵ月未満の被験者が 27 例、3 ヵ月以上の被験者が 28 例であった。直近のがん治療からの期間にかかわらず、すべての被験者で 1 件以上の有害事象が認められた。治験薬と関連性のある有害事象、重篤な有害事象を含むすべての項目

において、直近のがん治療から 3 ヵ月未満と 3 ヵ月以上で有害事象の発現割合に大きな違いはみられなかった。

PT 別でも、直近のがん治療から 3 ヵ月未満と 3 ヵ月以上で発現割合の差が 20%を超えた有害事象はなかった。

表 2.7.4.5-10 直近のがん治療からの期間別の有害事象の概要（203 試験）
（安全性解析対象集団）

Description	<3 months (N=27) n (%)	>=3 months (N=28) n (%)
Number of subjects with		
At least one TEAE	27 (100.0%)	28 (100.0%)
At least one TEAE related to the study drug	25 (92.6%)	26 (92.9%)
At least one serious TEAE	5 (18.5%)	9 (32.1%)
At least one serious TEAE related to the study drug	4 (14.8%)	6 (21.4%)
At least one TEAE leading to dose reduction or interruption	18 (66.7%)	22 (78.6%)
At least one TEAE leading to study drug discontinuation	7 (25.9%)	11 (39.3%)
At least one TEAE leading to death	0 (0.0%)	1 (3.6%)
At least one TEAE with grade 3 or higher	20 (74.1%)	26 (92.9%)
At least one TEAE with grade 3 or higher and related to the study drug	19 (70.4%)	23 (82.1%)

Source: Appendix Table 2.7.4.7-95
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment; n = number of subjects;
% = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.
Data cut-off date: [redacted] 20[redacted]

2.7.4.5.2.2.2 日本人第 2b 相試験（210 試験）（再発又は難治性の ATL を対象とした申請資料より再掲）

直近のがん治療からの期間別の有害事象の概要を表 2.7.4.5-11 に、有害事象の発現割合を付録表 2.7.4.7-98 に示す。

安全性解析対象集団 23 例中、直近のがん治療から 3 ヵ月未満の被験者が 12 例、3 ヵ月以上の被験者が 11 例であった。直近のがん治療からの期間にかかわらず、すべての被験者で 1 件以上の有害事象が認められた。治験薬の休薬又は減量に至った有害事象の発現割合が、直近のがん治療から 3 ヵ月未満に比べて 3 ヵ月以上で 20%を超えて高かったことを除き、すべての項目で有害事象の発現割合に大きな違いはみられなかった。

PT 別では、直近のがん治療から 3 ヵ月未満に比べて 3 ヵ月以上で発現割合が 20%を超えて高かった有害事象は、好中球減少症*［3 ヵ月未満：41.7%（12 例中 5 例）、3 ヵ月以上：63.6%（11 例中 7 例）］、食欲減退［3 ヵ月未満：25.0%（3 例）、3 ヵ月以上：45.5%（5 例）］及び疲労［3 ヵ月未満：0%（0 例）、3 ヵ月以上：27.3%（3 例）］であった。直近のがん治療から 3 ヵ月以上に比べて 3 ヵ月未満で発現割合が 20%を超えて高かった有害事象は、悪心［3 ヵ月未満：25.0%（3 例）、3 ヵ月以上：0%（0 例）］であった。

表 2.7.4.5-11 直近のがん治療からの期間別の有害事象の概要（210 試験）
（安全性解析対象集団）

Description	<3 months (N=12) n (%)	>=3 months (N=11) n (%)
Number of subjects with		
At least one TEAE	12 (100.0%)	11 (100.0%)
At least one TEAE related to the study drug	12 (100.0%)	11 (100.0%)
At least one serious TEAE	3 (25.0%)	4 (36.4%)
At least one serious TEAE related to the study drug	2 (16.7%)	4 (36.4%)
At least one TEAE leading to dose reduction or interruption	7 (58.3%)	9 (81.8%)
At least one TEAE leading to study drug discontinuation	4 (33.3%)	5 (45.5%)
At least one TEAE leading to death	0 (0.0%)	0 (0.0%)
At least one TEAE with grade 3 or higher	9 (75.0%)	9 (81.8%)
At least one TEAE with grade 3 or higher and related to the study drug	9 (75.0%)	9 (81.8%)

Source: Appendix Table 2.7.4.7-97 (cited from the new drug application for relapsed or refractory ATL)
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment; n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Data cut-off date: [redacted] 20[redacted]

2.7.4.5.3 本薬曝露への食事の影響

本薬の臨床試験では、被験者は本薬を食後約 30 分後に服用することとしていた。最近完了した､健康被験者に対する本薬投与時の食事の影響を検討した米国第 1 相試験（HBI-8000-304 試験、以下 304 試験）（初回申請資料 5.3.1.1-1）では、絶食下投与時と比較して食後投与時に C_{max} 平均値が約 24%低下したが、総曝露量は食後投与時及び絶食下投与時で同様であった。本試験では、本薬の用量は臨床推奨用量の 40 mg ではなく 20 mg であった。これまでの PK 解析で 20 mg は PK の線形域内であったことから、食後投与時及び絶食下投与時の曝露量（PK）を、予期しない高用量曝露のリスクなしに健康被験者で安全に比較することが可能であった。また、本試験では、低用量であったことに加え投与間隔が 10 日間であったことから、投与量は 20 日間で 40 mg に過ぎなかった。本試験で C_{max} に関連付けられる安全性シグナルは認められなかった。

2.7.4.5.4 強い CYP3A4 阻害剤及び P-gp 阻害剤との薬物相互作用

非臨床試験の結果から、本薬はチトクロム P450（CYP）3A4 の基質であると考えられる。したがって、理論的には CYP3A4 阻害剤との併用で曝露量は増加する可能性があることから、イトラコナゾールとの薬物―薬物相互作用を検討した試験を実施した。

強い CYP3A4 阻害剤であるイトラコナゾールとの薬物動態相互作用を検討した 304 試験の結果、CYP3A4 阻害剤との相互作用は軽度であることが示唆された。イトラコナゾールとの併用では C_{max} で約 41%、$AUC_{0-\infty}$ で約 46%の血中曝露量の上昇がみられたため、強い CYP3A4 阻害剤との併用については注意が必要であると考えられる。なお、CYP3A4 阻害剤との併用に伴う明らか

な有害事象の発現増加は認められなかった。

304 試験の結果、イトラコナゾールの併用によるクリアランスの低下は軽度であった。また、CYP3A 誘導剤併用時のクリアランスの増加は臨床的に意義のあるものではないと考えられた。

なお、臨床試験では、CYP3A4 活性に影響を及ぼす可能性のある薬剤は、併用注意薬剤又は併用禁止薬剤として治験実施計画書で定義した。これらの薬剤を本薬と併用したときの安全性の検討は目的として設定していなかったが、試験中に併用注意薬剤を投与した被験者の安全性について評価した。臨床試験ではスルファメトキサゾール・トリメトプリムを含む抗生物質／抗真菌剤を予防的に投与可能としていたが、これらの薬剤の投与による有害事象の悪化は認められなかった。

2.7.4.5.5 妊娠及び授乳時の使用

妊娠中の女性に本薬を投与した試験は実施されていない。また、本薬がヒト乳汁に移行するかは明らかでない。

妊娠中の女性に本薬を投与してはならない。妊娠する可能性のある女性には本薬投与期間中及び投与終了後一定期間は適切な避妊を行うよう指導する。また、本薬投与期間中は授乳を中止する。

ICH S9 ガイドラインに従い、ラットにおける反復投与試験（試験番号 1515-002 及び試験番号 20092736）及びイヌにおける反復投与試験（試験番号 1515-001 及び試験番号 20092737）で生殖器官への影響を詳細に調べることにより、雌雄の生殖能に対する評価が可能であった。イヌでの 13 週間経口反復投与毒性試験（試験番号 20092737）で本薬の投与に関連する卵巣及び精巣所見（卵巣萎縮及び精巣管萎縮並びに精巣重量の減少）が認められた。また、ICH S9 ガイドラインに従い、出生前及び出生後の毒性試験は不要と判断された（初回申請資料 2.6.6.3.6 項及び 2.6.6.6 項）。そのことは 20[redacted] 年[redacted] 月[redacted] 日までに[redacted]、本薬販売後、本薬を投与する患者に適切な注意喚起が行われることを条件に許容可能と判断された（初回申請資料 1.13.2.5 項）。

2.7.4.5.6 過量投与

本薬の過量投与に関する試験は実施しておらず、過量投与時の治療に関する情報はない。

過量投与は、本薬投与のカウント方法（例えば、週 2 回の投与スケジュールで、患者が 3 回続けて 3 日間隔で本薬を服用すると、週 3 回投与とカウントされる）に従って報告された。

203 試験では、9 例に過量投与が認められた。その 9 例中 8 例は、本薬 40 mg を投与間隔 3 日で 3～4 回続けて服用した。そのため、予定用量は 80 mg／週（40 mg を週 2 回投与、投与間隔 3 日と 4 日を交互に繰り返す）であったが、投与間隔 3 日で投与した 3 回目、4 回目投与の直近の 7 日間（1 週）の投与量は 120 mg／週になっていた。残りの 1 例は、本薬 30 mg を投与間隔 3 日で 3 回続けて服用した。予定用量は 80 mg／週（40 mg を週 2 回投与）であったが、3 回目の投与時の投与量は 90 mg／週になっていた。なお、3 例でこのような過量投与が 2 回以上みられた（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.2）。1 サイクルあたりの投与量で考えた場合、28 日の投与サイクルで予定用量の 320 mg を超える投与を受けた被験者は 5 例（9.1%）であった（表 2.7.4.1-7）

また、203 試験の 1 例で過量投与に関連する有害事象が認められた。当該被験者（被験者[redacted]）は、本薬 40 mg を投与間隔 3 日で 4 回続けて服用しており、Grade 3 の血小板数減少を発現した。本事象は過量投与により発現したと判断された。本事象は治験薬の休薬及び減量により回復し、

当該被験者は治験薬の投与を再開した（5.3.5.2-1/HBI-8000-203/CSR/Listing 16.2.2, Listing 16.2.6.1）。

210 試験では、2 例に過量投与が認められた。1 例は、本薬 40 mg を週 2 回ではなく投与間隔 3 日で 4 回続けて服用し、投与間隔 3 日で投与した 3 回目、4 回目投与時の投与量が 120 mg／週になっていた。もう 1 例は、本薬 40 mg を週 2 回投与ではなく、30 mg を投与間隔 3 日で 3 回続けて服用し、3 回目の投与時の投与量は 90 mg／週になっていた（初回申請資料 5.3.5.2-1/HBI-8000-210/CSR/Listing 16.2.2）。1 サイクルあたりの投与量で考えた場合、28 日の投与サイクルで予定用量の 320 mg を超える投与を受けた被験者はなかった（表 2.7.4.1-9）。

2.7.4.5.7 薬物乱用

本薬に依存性又は乱用の可能性があるというエビデンスは得られていない。

2.7.4.5.8 離脱症状及び反跳現象

本薬の離脱症状及び反跳現象への影響に関する正式な試験は実施されていない。

2.7.4.5.9 自動車運転及び機械操作に対する影響又は精神機能の障害

運転又は機械操作もしくは精神機能に対する影響を検討するための試験は実施されていない。

頭痛、浮動性めまい、傾眠等の SOC「神経系障害」に分類される有害事象が 203 試験では 16.4%、201 試験では 28.6%、210 試験では 39.1%の被験者に認められた（付録表 2.7.4.7-23、付録表 2.7.4.7-24、及び付録表 2.7.4.7-25）。201 試験の Garde 3 の重篤なパーキンソニズムを除き、いずれも Garde 1 又は 2 の非重篤事象であった。203 試験の浮動性めまい及び 210 試験の傾眠の各 1 件の事象は治験薬と関連性があると判定された。SOC「神経系障害」に分類される有害事象により、治験薬の投与を中止もしくは休薬又は減量した被験者はなかった。902 試験では、ピボタル試験で SOC「神経系障害（Nervous system diseases）」に分類される有害事象が 7.2%の被験者に認められた（5.3.5.4-4/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.2）。Grade 3 以上の事象として Grade 3 の傾眠及び Grade 3 の頭痛が各 1 例に認められ、Grade 3 の傾眠を発現した被験者は当該事象により治験薬の投与を中止した（5.3.5.4-4/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.5）。Grade 1 のめまい感（dizzy）2 件及び Grade 1 の感覚鈍麻（hypoesthesia）1 件は治験薬と関連性があると判定された（5.3.5.4-4/TG0902CDM p2b/Statistical Analysis Report/Table 7.4.3）。

2.7.4.5.10 心臓に関する安全性評価

本薬の心臓に関する安全性の評価は、日本人患者を含む試験（203 試験、201 試験、及び 210 試験）で認められた QTc の変化、並びにこれらの試験で認められた注目すべき有害事象の「心臓障害」、「トルサード ド ポアント／QT 延長」に基づき、非臨床所見も含めて検討した。なお、QTc サブスタディを実施した米国第 1b/2 相試験（302 試験）の結果は、再発又は難治性の ATL を対象とした本薬の初回申請で既に提出している。

非臨床試験では、イヌでの 4 週間試験（試験番号 1515-001）で QTc の延長が認められたものの、投与量に関連して血清カリウム及び血清カルシウムが減少したことによる二次的変化と考えられた。また、イヌでの 13 週間試験（試験番号 20092737）では QTc の変化は認められなかった（初回申請資料 2.6.6.9 項）。

臨床試験では、203 試験、201 試験、及び 210 試験では QTc の変化に臨床的に意味のある異常は認められなかった（2.7.4.4.2.1 項、2.7.4.4.2.2 項、及び 2.7.4.4.2.3 項）。

これらの日本人患者を含む 3 試験で認められた心臓関連の有害事象については、注目すべき有害事象の「心臓障害」が 203 試験及び 210 試験それぞれで約 10%の被験者に認められたが、203 試験で認められた Grade 3 の不安定狭心症 1 件を除き、いずれも重症度は Grade 1 又は 2 であった。Grade 3 の不安定狭心症は重篤な事象であったが、本薬との関連性は否定され、治験薬の休薬及び支持療法後に回復した（2.7.4.2.1.9.2.9 項）。また、注目すべき有害事象の「トルサード ド ポアント／QT 延長」は 203 試験の約 10%の被験者に認められたが、いずれも Grade 1 又は 2 の心電図 QT 延長であった（2.7.4.2.1.9.2.10 項）。これらの「心臓障害」及び「トルサード ド ポアント／QT 延長」の事象のうち不整脈に関連する事象として、203 試験では心電図 QT 延長（55 例中 5 例、9.1%）、動悸（3 例、5.5%）、心房細動（2 例、3.6%）、及び不整脈（1 例、1.8%）が認められ、210 試験では動悸及び第一度房室ブロック（23 例中各 1 例、4.3%）が認められた。210 試験の動悸を除き、いずれの事象も非重篤であった。

非臨床毒性データ並びに幅広く固形がんやリンパ腫を有する患者を対象として日本及び米国で実施した 4 試験のいずれにおいても、本薬投与後に軽度から中等度の心臓関連事象が認められたものの発現割合は低く、その多くは治験薬の休薬又は投与中止には至らなかった。

2.7.4.5.11 他の患者集団を対象とした海外試験から得られた安全性データの要約

他の患者集団を対象とした海外試験から得られた安全性データは、本薬の初回申請時に既に提出している。

2.7.4.6 市販後データ

本邦では、2021 年 6 月 23 日に「再発又は難治性の成人 T 細胞白血病リンパ腫」を効能・効果とする医薬品製造販売承認を取得したが、本承認申請時点で本邦での市販後データは得られていない。

海外では、Chidamide 錠が、30 mg を週 2 回投与する用法・用量で、2014 年に PTCL、2019 年にアロマターゼ阻害剤との併用で乳がんを適応として中国で薬事承認されている。中国の Chipscreen 社により PTCL 患者を対象に chidamide 錠の市販後積極的サーベイランスが実施されており、定期的安全性最新報告（PSUR）2018 年版に記載されたそのサーベイランスの結果及び治験安全性最新報告（DSUR）2020 年版の概要を以下に示す。

2.7.4.6.1 海外市販後データ

2.7.4.6.1.1 市販後積極的サーベイランス（20[redacted] 年～20[redacted] 年実施）

中国での PTCL を適応とした薬事承認後、chidamide 錠の市販後積極的サーベイランスプログラム、すなわち「Chidamide Tablet Focused Monitoring（市販後積極的サーベイランス）」が、PTCL 患者を対象に 20[redacted] 年[redacted] 月から 20[redacted] 年[redacted] 月まで実施された。本プログラムに登録された患者は 20[redacted] 年[redacted] 月まで追跡された。その結果は、PSUR 2018 年版で報告された（5.3.6.1-1/2018 PSUR/7.1.2 項）。

本プログラムでは、合計 4,058 例の患者が追跡され、3,480 例の患者から薬剤投与情報が収集された。20[redacted] 年[redacted] 月までに「Patient Information Sheet」を提出した合計 3,382 例の患者が安全性解析対象集団に含まれた。

2.7.4.6.1.1.1 人口統計学的特性

安全性解析対象集団 3,382 例の患者の平均年齢は 51 歳で、男性患者は 62.8%であった。

病期分類は、多くの患者が III 期（33.4%）又は IV 期（50.5%）であった。3,382 例の患者のうち、1,787 例（52.8%）が chidamide 錠単剤投与による治療を受け、1,595 例（47.2%）が他の抗がん剤との併用投与を受けた。

曝露期間の中央値は 64 日、平均値は 150 日であった。3,382 例の患者のうち、1,286 例（38.02%）が chidamide 錠を 60 日以上投与され、991 例（29.30%）が 90 日以上、809 例（23.92%）が 120 日以上、675 例（19.96%）が 150 日以上、593 例（17.53%）が 180 日以上、297 例（8.78%）が 360 日以上投与された。

2.7.4.6.1.1.2 副作用

本プログラムでは、chidamide 錠を処方した医師が chidamide 錠に「関連あり」、「関連があるかもしれない」、又は「評価不能」と判断した有害事象を副作用と定義した。

全体（3,382 例）で発現割合の高かった副作用（発現割合 10%以上）は、好中球数減少（1,597 例、47.22%）、血小板数減少（1,546 例、45.71%）、無力症（1,337 例、39.53%）、ヘモグロビン減少（1,187 例、35.10%）、悪心及び嘔吐（各 766 例、22.65%）、下痢（360 例、10.64%）、並びに発熱（339 例、10.02%）であった。単剤投与の患者（1,787 例）で発現割合の高かった副作用は、好中球数減少（754 例、42.19%）、血小板数減少（749 例、41.91%）、無力症（642 例、35.93%）、ヘモグロビン減少（529 例、29.60%）、悪心及び嘔吐（各 354 例、19.81%）であった。他の抗がん剤との併用投与の患者（1,595 例）で発現割合の高かった副作用は、好中球数減少（843 例、52.85%）、血小板数減少（797 例、49.97%）、無力症（695 例、43.57%）、ヘモグロビン減少（658 例、41.26%）、悪心及び嘔吐（各 412 例、25.83%）、発熱（192 例、12.04%）、並びに下痢（189 例、11.85%）であった。

全体（3,382 例）で認められた Grade 3 又は 4 の副作用は、好中球数減少（606 例、17.92%）が最も多く、血小板数減少（559 例、16.53%）及びヘモグロビン減少（321 例、9.49%）がこれに次いで多かった。Chidamide 錠を単剤投与した患者と他の抗がん剤を併用投与した患者で認められた副作用の発現割合及び種類は類似していた。

最も発現割合の高かった副作用及び Grade 3 又は 4 の副作用はいずれも血液毒性に関する事象であり、Chidamide 錠を単剤投与した患者及び併用投与した患者で同様に認められた。

市販後積極的サーベイランスプログラムで報告された副作用の種類は、中国での承認取得前に臨床試験で認められた事象と同様であった。

本プログラムと日本人患者が含まれる試験の安全性プロファイルを比較するため、本プログラムで認められた副作用を本申請の安全性評価で設定した注目すべき有害事象の定義により分類した。本プログラムで認められた注目すべき有害事象に該当する副作用は、「血小板減少症」として血小板数減少（1,546 例、45.71%）、「好中球減少症」として好中球数減少（1,597 例、47.22%）及び白血球数減少（131 例、3.87%）、「貧血」としてヘモグロビン減少（1,187 例、35.10%）、「感染症」として肺感染（12 例、0.35%）、ヘルペスウイルス感染（2 例、0.06%）、腹部感染、尿路感染、及び真菌感染（各 1 例、0.03%）、「間質性肺疾患」として肺臓炎（9 例、0.27%）、間質性肺疾患（5 例、0.15%）、及び肺線維症（2 例、0.06%）、「肝障害」として ALT 増加（223 例、6.59%）、AST 増加（189 例、5.59%）、血中ビリルビン増加（6 例、0.18%）、肝機能異常（3 例、0.09%）、プロトロンビン時間延長、血中フィブリノゲン減少、及びトランスアミナーゼ上昇（各 1 例、0.03%）、「心

臓障害」として頻脈（107 例、3.16%）、心不全（14 例、0.41%）、徐脈（13 例、0.38%）、動悸（2 例、0.06%）、心嚢液貯留、及び心室性不整脈（各 1 例、0.03%）、「トルサード ド ポアント／QT 延長」として心電図 QT 延長（51 例、1.51%）が認められた。中国で実施した本プログラム及び日本人患者が含まれる試験のいずれにおいても多く認められた事象は血液学的有害事象であり、有害事象／副作用の発現傾向に大きな違いはなかった。市販後積極的サーベイランスプログラムと日本人患者が含まれる試験の安全性プロファイルに医学的に重要な違いは認められなかった。

2.7.4.6.1.1.3 死亡例

3,382 例のうち、123 例の死亡が報告された。本プログラムの死亡例 123 例のうち、病勢進行による死亡が 78 例、感染による死亡が 12 例、臓器不全、合併症、呼吸不全、同種異系移植、大量胃出血及び血球貪食症による死亡が各 1 例であり、その他の 27 例の患者の死因は不明であった。

死亡例の詳細情報は PSUR 2018 年版（5.3.6.1-1/2018 PSUR/付録 2）を参照のこと。

2.7.4.6.2 治験安全性最新報告（2020 年）

Chidamide 錠の安全性プロファイルの累積情報が記載された DSUR 2020 年版（報告対象期間：2019 年 12 月 23 日～2020 年 12 月 22 日）（5.3.6.1-2/2020 DSUR）を添付した。

Chidamide は 2014 年 12 月 22 日に承認され、以降の累積曝露数は、製造販売後の曝露数推定方法及び PSUR の推定値に基づくと、2020 年 12 月までに約 26,000 例である。

HUYABIO 社及び Chipscreen 社が実施した臨床試験において、HBI-8000/chidamide の累積曝露数は推計で約 832 例であった。当該報告対象期間中、中国にて約 449 例が Chipscreen による臨床試験に登録され、chidamide（二重盲検試験の場合は chidamide/プラセボ）の投与を 1 回以上受けた。

種々の臨床試験及び chidamide 錠の市販後積極的サーベイランスから得られた安全性情報に基づくと、よくみられる副作用は主に血液学的事象、消化器系事象、無力症、発熱及び食欲減退であり、このうち血液学的事象が Grade 3 又は 4 の副作用としてよくみられた事象であった。いずれの副作用も支持療法により管理可能であり、多くの場合、投与中止に至るものではなかった。

当該報告対象期間中、chidamide の安全性プロファイルは変わらず、chidamide 錠の現行の添付文書の内容と一致しており、安全性上の新たなシグナルは認められなかった。

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本付録に含めた表のうち、表 2.7.4.7-1 を除き、203 試験及び 201 試験についてはいずれの表も各試験の CSR の 16.2 項（5.3.5.2-1/HBI-8000-203/CSR/16.2 項及び 5.3.3.2-1/HBI-8000-201/CSR/16.2 項）に含まれる Listing から集計した。210 試験については本申請の臨床データパッケージには含まれないが、その他の参考として再発又は難治性の ATL を対象とした本薬の初回申請資料より再掲した。

表 2.7.4.7-1 注目すべき有害事象の定義（203 試験及び 210 試験）

AESI group	Term level	Term
血小板減少症	SMQ	造血障害による血小板減少症（SMQ）（狭域）
	PT	血小板減少症+血小板数減少 [a]
好中球減少症	PT	無顆粒球症
	PT	自己免疫性好中球減少症
	PT	周期性好中球減少症
	PT	発熱性好中球減少症
	PT	顆粒球数減少
	PT	顆粒球減少症
	PT	特発性好中球減少症
	PT	白血球減少症
	PT	骨髄球数減少
	PT	骨髄球百分率減少
	PT	好中球減少症
	PT	好中球数減少
	PT	好中球百分率減少
	PT	白血球検査異常
	PT	白血球数減少
	PT	好中球減少症+好中球数減少 [a]（210 試験）
		好中球減少症+好中球数減少+顆粒球減少症 [a]（203 試験）
	PT	白血球減少症+白血球数減少 [a]
感染症	SOC	感染症および寄生虫症
ウイルス再活性化	PT	後天性免疫不全症候群
	PT	急性Ｂ型肝炎
	PT	急性Ｃ型肝炎
	PT	急性ＨＩＶ感染
	PT	アデノウイルス性肝炎
	PT	エイズ胆管症
	PT	エイズ関連症候群
	PT	エイズ関連合併症
	PT	エイズ網膜症
	PT	無症候性ＨＩＶ感染
	PT	無症候性ウイルス性肝炎
	PT	ＢＫウイルス感染
	PT	血中ＨＣＶ－ＲＮＡ量測定限界以下
	PT	血中ＨＩＶ－ＲＮＡ量測定限界以下
	PT	血中ＨＩＶ－ＲＮＡ減少
	PT	血中ＨＩＶ－ＲＮＡ増加
	PT	慢性Ｂ型肝炎
	PT	慢性Ｃ型肝炎
	PT	先天性Ｂ型肝炎感染症
	PT	サイトメガロウイルス性脈絡網膜炎
	PT	サイトメガロウイルス性大腸炎
	PT	サイトメガロウイルス性十二指腸炎
	PT	サイトメガロウイルス性小腸炎
	PT	サイトメガロウイルス性腸炎
	PT	サイトメガロウイルス性胃炎

AESI group	Term level	Term
	PT	サイトメガロウイルス性胃腸炎
	PT	サイトメガロウイルス性消化管感染
	PT	サイトメガロウイルス性胃腸潰瘍
	PT	サイトメガロウイルス肝炎
	PT	サイトメガロウイルス感染
	PT	サイトメガロウイルス性単核症
	PT	サイトメガロウイルス性皮膚粘膜潰瘍
	PT	サイトメガロウイルス性脊髄髄膜神経根炎
	PT	サイトメガロウイルス性心筋炎
	PT	サイトメガロウイルス性食道炎
	PT	サイトメガロウイルス性膵炎
	PT	サイトメガロウイルス性心膜炎
	PT	サイトメガロウイルス症候群
	PT	サイトメガロウイルス検査陽性
	PT	サイトメガロウイルス性尿路感染
	PT	サイトメガロウイルス血症
	PT	播種性サイトメガロウイルス感染
	PT	播種性水痘帯状疱疹ワクチンウイルス感染
	PT	サイトメガロウイルス性脳炎
	PT	水痘後脳炎
	PT	末期エイズ
	PT	エイズ腸炎
	PT	エプスタイン・バーウイルス血症
	PT	エプスタイン・バーウイルス抗体
	PT	エプスタイン・バーウイルス抗体陽性
	PT	エプスタイン・バーウイルス抗原陽性
	PT	エプスタイン・バーウイルス感染
	PT	エプスタイン・バーウイルス検査陽性
	PT	ＨＢＶ－ＤＮＡポリメラーゼ増加
	PT	肝カンジダ症
	PT	肝ガス壊疽
	PT	Ａ型肝炎
	PT	Ａ型肝炎抗体
	PT	Ａ型肝炎抗体異常
	PT	Ａ型肝炎抗体正常
	PT	Ａ型肝炎抗体陽性
	PT	Ａ型肝炎抗原
	PT	Ａ型肝炎抗原陽性
	PT	Ａ型肝炎ウイルス検査陽性
	PT	Ｂ型肝炎
	PT	Ｂ型肝炎抗体
	PT	Ｂ型肝炎抗体異常
	PT	Ｂ型肝炎抗体正常
	PT	Ｂ型肝炎抗体陽性
	PT	Ｂ型肝炎抗原
	PT	Ｂ型肝炎抗原陽性
	PT	Ｂ型肝炎コア抗体
	PT	Ｂ型肝炎コア抗体陽性
	PT	Ｂ型肝炎コア抗原
	PT	Ｂ型肝炎コア抗原陽性
	PT	Ｂ型肝炎ＤＮＡ測定陽性
	PT	Ｂ型肝炎ＤＮＡ減少
	PT	Ｂ型肝炎ＤＮＡ増加
	PT	Ｂ型肝炎ｅ抗体
	PT	Ｂ型肝炎ｅ抗体陽性
	PT	Ｂ型肝炎ｅ抗原
	PT	Ｂ型肝炎ｅ抗原陽性
	PT	Ｂ型肝炎表面抗体

AESI group	Term level	Term
	PT	Ｂ型肝炎表面抗体陽性
	PT	Ｂ型肝炎表面抗原
	PT	Ｂ型肝炎表面抗原陽性
	PT	Ｂ型肝炎ウイルス検査陽性
	PT	Ｃ型肝炎
	PT	Ｃ型肝炎抗体
	PT	Ｃ型肝炎抗体陽性
	PT	Ｃ型肝炎コア抗体
	PT	Ｃ型肝炎コア抗体陽性
	PT	Ｃ型肝炎ＲＮＡ
	PT	Ｃ型肝炎ＲＮＡ減少
	PT	Ｃ型肝炎ＲＮＡ変動
	PT	Ｃ型肝炎ＲＮＡ増加
	PT	Ｃ型肝炎ＲＮＡ陽性
	PT	Ｃ型肝炎ウイルス検査陽性
	PT	Ｄ型肝炎
	PT	Ｄ型肝炎抗体
	PT	Ｄ型肝炎抗体陽性
	PT	Ｄ型肝炎抗原
	PT	Ｄ型肝炎抗原陽性
	PT	Ｄ型肝炎ＲＮＡ
	PT	Ｄ型肝炎ＲＮＡ陽性
	PT	Ｄ型肝炎ウイルス検査陽性
	PT	Ｅ型肝炎
	PT	Ｅ型肝炎抗体
	PT	Ｅ型肝炎抗体異常
	PT	Ｅ型肝炎抗体陽性
	PT	Ｅ型肝炎抗原
	PT	Ｅ型肝炎抗原陽性
	PT	Ｅ型肝炎ウイルス検査陽性
	PT	Ｆ型肝炎
	PT	Ｇ型肝炎
	PT	Ｈ型肝炎
	PT	伝染性単核症肝炎
	PT	ムンプス性肝炎
	PT	非Ａ非Ｂ型肝炎
	PT	非Ａ非Ｂ非Ｃ型肝炎
	PT	輸血後肝炎
	PT	トキソプラズマ性肝炎
	PT	ウイルス性肝炎
	PT	肝炎ウイルス検査陽性
	PT	肝炎ウイルス関連腎症
	PT	肝脾カンジダ症
	PT	単純ヘルペス脳炎
	PT	単純ヘルペス肝炎
	PT	帯状疱疹
	PT	皮膚播種性帯状疱疹
	PT	播種性帯状疱疹
	PT	神経合併症を伴う帯状疱疹感染
	PT	耳帯状疱疹
	PT	ＨＩＶ抗体
	PT	ＨＩＶ抗体陽性
	PT	ＨＩＶ抗原
	PT	ＨＩＶ抗原陽性
	PT	ＨＩＶ関連腎症
	PT	ＨＩＶ心筋症
	PT	ＨＩＶ腸症
	PT	ＨＩＶ感染

AESI group	Term level	Term
	PT	ＨＩＶ感染ＣＤＣ分類Ａ
	PT	ＨＩＶ感染ＣＤＣ分類Ｂ
	PT	ＨＩＶ感染ＣＤＣ分類Ｃ
	PT	ＣＤＣ分類第１群ＨＩＶ感染
	PT	ＣＤＣ分類第２群ＨＩＶ感染
	PT	ＣＤＣ分類第３群ＨＩＶ感染
	PT	ＣＤＣ分類第４群ＨＩＶ感染
	PT	ＣＤＣ分類第４群サブグループＡのＨＩＶ感染
	PT	ＣＤＣ分類第４群サブグループＢのＨＩＶ感染
	PT	ＣＤＣ分類第４群サブグループＣ１のＨＩＶ感染
	PT	ＣＤＣ分類第４群サブグループＣ２のＨＩＶ感染
	PT	ＣＤＣ分類第４群サブグループＤのＨＩＶ感染
	PT	ＣＤＣ分類第４群サブグループＥのＨＩＶ感染
	PT	ＨＩＶ感染ＷＨＯ分類臨床ステージ１
	PT	ＨＩＶ感染ＷＨＯ分類臨床ステージ２
	PT	ＨＩＶ感染ＷＨＯ分類臨床ステージ３
	PT	ＨＩＶ感染ＷＨＯ分類臨床ステージ４
	PT	ＨＩＶ末梢性ニューロパチー
	PT	ＨＩＶ検査陽性
	PT	ＨＩＶ消耗症候群
	PT	ヒトヘルペスウイルス６血清学的検査陽性
	PT	ヒトヘルペスウイルス８検査陽性
	PT	ヒトヘルペスウイルス８感染
	PT	ヒトポリオーマウイルス感染
	PT	伝染性単核症
	PT	ＣＳＦ中ＪＣウイルス検査陽性
	PT	ＪＣウイルス感染
	PT	エイズ関連カポジ肉腫
	PT	リンパ増殖性障害
	PT	リンパ増殖性障害、寛解期
	PT	ヘルペス性髄膜炎
	PT	複数病原体ＰＣＲ検査
	PT	眼部単純ヘルペス
	PT	眼帯状疱疹
	PT	口腔内毛様白斑症
	PT	周産期ＨＩＶ感染
	PT	持続性全身性リンパ節腫脹
	PT	サイトメガロウイルス性肺炎
	PT	ヘルペスウイルス肺炎
	PT	ポリオーマウイルス検査陽性
	PT	ポリオーマウイルス関連腎症
	PT	進行性多巣性白質脳症
	PT	レトロウイルス感染
	PT	レトロウイルスリバウンド症候群
	PT	持続的ウイルス反応
	PT	水痘
	PT	水痘ウイルス検査陽性
	PT	肝炎ウイルスキャリアー
	PT	ウイルス検査陽性
トルサード　ド　ポアント/QT 延長	SMQ	トルサード　ド　ポアント／QT 延長（SMQ）（狭域）
過敏症	SMQ	アナフィラキシー反応（SMQ）（狭域）
	SMQ	重症皮膚副作用（SMQ）（狭域）
	PT	薬物過敏症
	PT	過敏症
間質性肺疾患	SMQ	間質性肺疾患（SMQ）（狭域）
心臓障害	SOC	心臓障害
ウイルス再活性化を除く肝障害	SMQ	肝臓の先天性、家族性、新生児および遺伝性障害（SMQ）（狭域）

AESI group	Term level	Term
	SMQ	薬剤に関連する肝障害－包括的検索（SMQ）（狭域）
	SMQ	明確にアルコール関連と報告された肝障害（SMQ）（狭域）
	SMQ	妊娠関連の肝障害（SMQ）（狭域）
	PT	肝包虫症
	PT	梅毒性肝炎
	PT	肝膿瘍
	PT	門脈膿血症
	PT	肝住血吸虫症
	PT	ワイル病
	PT	肝嚢胞感染
	PT	ジアノッティ・クロスティ症候群
	PT	肝感染
	PT	肝胆道系感染
	PT	Ｂ型肝炎再活性化
	PT	肝アメーバ症
	PT	細菌性肝感染
	PT	蠕虫性肝感染
	PT	真菌性肝感染
	PT	投薬中断後肝炎
	PT	周産期ＨＢＶ感染
	PT	肝脾膿瘍
貧血	PT	貧血
	PT	ヘモグロビン減少
	PT	貧血+ヘモグロビン減少 [a]
リンパ球減少症	PT	リンパ球減少症
	PT	リンパ球数減少
	PT	リンパ球減少症+リンパ球数減少 [a]

PT = Preferred Term; SOC = System Organ Class; SMQ = Standard MedDRA Query
a: Grouped terms for haematological AEs.
MedDRA version 21.1

表 2.7.4.7-2　曝露状況の概要（203 試験）（安全性解析対象集団）

Variable (unit)	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Duration of exposure (days)	n	39	16	55
	Mean	125.2	111.7	121.3
	SD	132.3	133.0	131.4
	Median	80.0	54.0	80.0
	Minimum	10	22	10
	Maximum	580	486	580
Number of times study drug is administered	n	39	16	55
	Mean	31.4	29.2	30.7
	SD	36.3	37.8	36.4
	Median	16.0	14.0	16.0
	Minimum	3	6	3
	Maximum	164	139	164
Number of cycles	n	39	16	55
	Mean	4.473	3.989	4.332
	SD	4.724	4.749	4.692
	Median	2.857	1.929	2.857
	Minimum	0.36	0.79	0.36
	Maximum	20.71	17.36	20.71
Cumulative exposure (mg)	n	39	16	55
	Mean	1087.9	1112.5	1095.1
	SD	1256.6	1490.0	1314.5
	Median	640.0	540.0	600.0
	Minimum	110	220	110
	Maximum	6560	5560	6560

Source: Listing 16.2.5 1
Duration of exposure (days) = (Date of last study drug – Date of first study drug + 3), if date of last study drug minus date of first study drug is multiple of 7. Else, Duration of exposure (days) = (Date of last study drug – Date of first study drug + 4).
Number of times study drug is administered = the number of study drug administration where dose is greater than 0 mg.
Number of cycles = (Date of last study drug – Date of first study drug + 3) / 28, if date of last study drug minus date of first study drug is multiple of 7. Else, number of cycles = (Date of last study drug – Date of first study drug + 4) / 28.
Last study drug date is the date of last study drug administered as collected in case report form.

Variable (unit)	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Dose intensity (mg/cycle)	n	39	16	55
	Mean	247.7	271.4	254.6
	SD	65.4	58.3	63.8
	Median	237.0	291.6	273.2
	Minimum	133	166	133
	Maximum	336	332	336
Relative dose intensity	n	39	16	55
	Mean	0.774	0.848	0.796
	SD	0.204	0.182	0.199
	Median	0.741	0.911	0.854
	Minimum	0.42	0.52	0.42
	Maximum	1.05	1.04	1.05
Number of subjects who had dose reduction	n (%)	21 (53.8)	5 (31.3)	26 (47.3)
40mg to 30mg (only 1 dose reduction)	n (%)	15 (38.5)	5 (31.3)	20 (36.4)
40mg to 30mg to 20mg (2 dose reductions excluding 1 dose reduction)	n (%)	6 (15.4)	0 (0.0)	6 (10.9)
Number of subjects who had at least one dose interruptions	n (%)	27 (69.2)	10 (62.5)	37 (67.3)
Cycles with dose interruptions				
Number of subjects where dose interruption occurred only at 1 cycle	n (%)	7 (17.9)	6 (37.5)	13 (23.6)
Number of subjects where dose interruption occurred at a maximum 2 cycles	n (%)	9 (23.1)	2 (12.5)	11 (20.0)
Number of subjects where dose interruption occurred at a maximum 3 cycles	n (%)	7 (17.9)	1 (6.3)	8 (14.5)
Number of subjects where dose interruption occurred at a maximum 4 cycles	n (%)	1 (2.6)	0 (0.0)	1 (1.8)
Number of subjects where dose interruption occurred more than 5 cycles	n (%)	3 (7.7)	1 (6.3)	4 (7.3)

Source: Listing 16.2.5 1
% = percentages of subjects are calculated relative to the number of subjects in the respective country within the analysis set.
Dose intensity (mg/cycle) = Cumulative Exposure (mg) / Number of cycles.
Relative dose intensity = dose intensity (mg/cycle) / plan dose intensity. Where plan dose intensity is 320 mg/cycle.
Dose interruption is defined as the subject who did not have dose administered at a scheduled timepoint, and this is captured up to the last dose administered as collected in case report form.
Dose intensity and relative dose intensity are calculated based on the last dose administered as collected in case report form.

Variable (unit)	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Time to first dose interruption (days)	n	27	10	37
	Mean	39.1	43.9	40.4
	SD	70.3	65.6	68.2
	Median	15.0	21.5	15.0
	Minimum	4	7	4
	Maximum	366	224	366
Time to first dose reduction (days)	n	21	5	26
	Mean	50.7	34.6	47.6
	SD	35.5	20.9	33.5
	Median	36.0	31.0	32.5
	Minimum	11	15	11
	Maximum	127	70	127
Time of administration from last meal (minutes)	n*	1216	467	1683
	Mean	32.8	33.2	32.9
	SD	9.8	14.9	11.4
	Median	30.0	30.0	30.0
	Minimum	5	20	5
	Maximum	180	150	180
Number of subjects who had at least one overdose	n (%)	1 (2.6)	4 (25.0)	5 (9.1)

Source: Listing 16.2.5 1
% = percentages of subjects are calculated relative to the number of subjects in the respective country within the analysis set.
* denoted the total number of regular meals consumed prior to study drug administration by subjects in the analysis set.
Time to first dose interruption (days) = date of the last dose administered prior to dose interruption + 3 – date of first dose + 1.
Time to first dose reduction (days) = date of the 1st dose administered that is less than 40 mg – date of first dose + 1.
Time of administration from last meal (minutes) = Datetime of study drug – Datetime of most recent ingestion of food before study drug. Meal time is calculated for any regular meal consumed prior to study drug administration.
Overdose is defined as subjects who took more than 320 mg in a 28 days cycle. Particularly for this overdose calculation, 28 days cycle is calculated from C1D1.

表 2.7.4.7-3　曝露状況の概要（201 試験）（安全性解析対象集団）

Variable (unit)	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
Duration of exposure (day)	n	7	7	14
	Mean	58.4	103.0	80.7
	SD	42.04	89.90	71.28
	Median	62.0	56.0	59.0
	Minimum	4	24	4
	Maximum	119	239	239
Number of times study drug administered	n	7	7	14
	Mean	15.0	23.3	19.1
	SD	11.09	18.63	15.35
	Median	14.0	16.0	15.0
	Minimum	1	6	1
	Maximum	34	52	52

SOURCE: Listing 16.2.5.1
Duration of exposure = (Date of last study drug - Date of first study drug + 3), if date of last study drug minus date of first study drug is multiple of 7. Else, duration of exposure = (Date of last study drug - Date of first study drug + 4).
Number of times study drug administered = the number of study drug administration where dose is greater than 0mg.
Number of cycles = (Date of last study drug - Date of first study drug + 3) / 28, if date of last study drug minus date of first study drug is multiple of 7. Else, number of cycles = (Date of last study drug - Date of first study drug + 4) / 28.
% = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Percentages of planned dose received = [(Number of times study drug administered)/(Number of times planned dose administered)] * 100.
Number of times planned dose administered : Number of Cycles *8
Dose intensity (mg/body/week) = Cumulative Exposure / (Number of cycles *4)

Variable (unit)	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
Number of cycles	n	7	7	14
	Mean	2.087	3.679	2.883
	SD	1.5014	3.2108	2.5457
	Median	2.214	2.000	2.107
	Minimum	0.14	0.86	0.14
	Maximum	4.25	8.54	8.54
Cumulative exposure (mg)	n	7	7	14
	Mean	434.3	762.9	598.6
	SD	302.54	565.79	468.04
	Median	420.0	610.0	455.0
	Minimum	30	220	30
	Maximum	910	1630	1630
Number of patients who had dose reduction	n (%)	1 (14.3%)	5 (71.4%)	6 (42.9%)

SOURCE: Listing 16.2.5.1
Duration of exposure = (Date of last study drug - Date of first study drug + 3), if date of last study drug minus date of first study drug is multiple of 7. Else, duration of exposure = (Date of last study drug - Date of first study drug + 4).
Number of times study drug administered = the number of study drug administration where dose is greater than 0mg.
Number of cycles = (Date of last study drug - Date of first study drug + 3) / 28, if date of last study drug minus date of first study drug is multiple of 7. Else, number of cycles = (Date of last study drug - Date of first study drug + 4) / 28.
% = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Percentages of planned dose received = [(Number of times study drug administered)/(Number of times planned dose administered)] * 100.
Number of times planned dose administered : Number of Cycles *8
Dose intensity (mg/body/week) = Cumulative Exposure / (Number of cycles *4)

Variable (unit)	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
Percentages of planned dose received	n	7	7	14
	Mean	90.74	84.95	87.84
	SD	9.733	11.204	10.520
	Median	90.32	81.25	87.50
	Minimum	76.6	74.8	74.8
	Maximum	100.0	100.0	100.0
Dose intensity (mg/body/week)	n	7	7	14
	Mean	53.52	59.52	56.52
	SD	5.300	15.457	11.530
	Median	53.53	53.75	53.64
	Minimum	45.9	43.6	43.6
	Maximum	60.0	80.0	80.0

SOURCE: Listing 16.2.5 1
Duration of exposure = (Date of last study drug - Date of first study drug + 3), if date of last study drug minus date of first study drug is multiple of 7. Else, duration of exposure = (Date of last study drug - Date of first study drug + 4).
Number of times study drug administered = the number of study drug administration where dose is greater than 0mg.
Number of cycles = (Date of last study drug - Date of first study drug + 3) / 28, if date of last study drug minus date of first study drug is multiple of 7. Else, number of cycles = (Date of last study drug - Date of first study drug + 4) / 28.
% = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Percentages of planned dose received = [(Number of times study drug administered)/(Number of times planned dose administered)] * 100.
Number of times planned dose administered : Number of Cycles *8
Dose intensity (mg/body/week) = Cumulative Exposure / (Number of cycles *4)

表 2.7.4.7-4　曝露状況の概要（210 試験）（安全性解析対象集団）

Variable (unit)	Statistic	40 mg (N=23)
Duration of exposure (days)	n	23
	Mean	65.9
	SD	95.3
	Median	35.0
	Minimum	7
	Maximum	388
Number of times study drug is administered	n	23
	Mean	15.6
	SD	23.4
	Median	8.0
	Minimum	2
	Maximum	96
Number of cycles	n	23
	Mean	2.355
	SD	3.402
	Median	1.250
	Minimum	0.25
	Maximum	13.86
Cumulative exposure (mg)	n	23
	Mean	480.4
	SD	592.4
	Median	310.0
	Minimum	80
	Maximum	2260

Source: Listing 16.2.5 1

Duration of exposure (days) = (Date of last study drug – Date of first study drug + 3), if date of last study drug minus date of first study drug is multiple of 7. Else, Duration of exposure (days) = (Date of last study drug – Date of first study drug + 4).

Number of times study drug is administered = the number of study drug administration where dose is greater than 0 mg.

Number of cycles = (Date of last study drug – Date of first study drug + 3) / 28, if date of last study drug minus date of first study drug is multiple of 7. Else, number of cycles = (Date of last study drug – Date of first study drug + 4) / 28.

Last study drug date is the date of last study drug administered as collected in case report form.

Variable (unit)	Statistic	40 mg (N=23)
Dose intensity (mg/cycle)	n	23
	Mean	254.591
	SD	61.446
	Median	260.000
	Minimum	138.51
	Maximum	333.33
Relative dose intensity	n	23
	Mean	0.796
	SD	0.192
	Median	0.810
	Minimum	0.43
	Maximum	1.04
Number of subjects who had dose reduction	n (%)	10 (43.5%)
40mg to 30mg (only 1 dose reduction)	n (%)	7 (30.4%)
40mg to 30mg to 20mg (2 dose reductions excluding 1 dose reduction)	n (%)	3 (13.0%)
Number of subjects who had at least one dose interruptions	n (%)	13 (56.5%)
Cycles with dose interruptions		
Number of subjects where dose interruption occurred only at 1 cycle	n (%)	6 (26.1%)
Number of subjects where dose interruption occurred at a maximum 2 cycles	n (%)	3 (13.0%)
Number of subjects where dose interruption occurred at a maximum 3 cycles	n (%)	2 (8.7%)
Number of subjects where dose interruption occurred at a maximum 4 cycles	n (%)	0 (0.0%)
Number of subjects where dose interruption occurred more than 5 cycles	n (%)	2 (8.7%)

Source: Listing 16.2.5 1

% = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Dose intensity (mg/cycle) = Cumulative Exposure (mg) / Number of cycles.
Relative dose intensity = dose intensity (mg/cycle) / plan dose intensity. Where plan dose intensity is 320 mg/cycle.
Dose interruption is defined as the subject who did not have dose administered at a scheduled timepoint, and this is captured up to the last dose administered as collected in case report form.
Dose intensity and relative dose intensity are calculated based on the last dose administered as collected in case report form.

Variable (unit)	Statistic	40 mg (N=23)
Time to first dose interruption (days)	n	13
	Mean	19.2
	SD	8.3
	Median	18.0
	Minimum	7
	Maximum	40
Time to first dose reduction (days)	n	10
	Mean	42.0
	SD	16.2
	Median	38.0
	Minimum	25
	Maximum	78
Time of administration from last meal (minutes)	n *	354
	Mean	40.9
	SD	28.5
	Median	30.0
	Minimum	5
	Maximum	250
Number of subjects who had at least one overdose	n (%)	0 (0.0%)

Source: Listing 16.2.5 1

% = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

* denoted the total number of regular meals consumed prior to study drug administration by subjects in the analysis set.

Time to first dose interruption (days) = date of the last dose administered prior to dose interruption + 3 – date of first dose + 1.

Time to first dose reduction (days) = date of the 1st dose administered that is less than 40 mg – date of first dose + 1.

Time of administration from last meal (minutes) = Datetime of study drug – Datetime of most recent ingestion of food before study drug. Meal time is calculated for any regular meal consumed prior to study drug administration.

Overdose is defined as subjects who took more than 320 mg in a 28 days cycle. Particularly for this overdose calculation, 28 days cycle is calculated from C1D1.

表 2.7.4.7-5　被験者の内訳（203 試験）（全同意取得例）

Description	Japan (N=52) n (%)	Korea (N=22) n (%)	Total (N=74) n (%)
Consented	52	22	74
Screening failure	13	6	19
Treated with at least one dose of HBI-8000 (Safety Analysis Set)	39 (100.0)	16 (100.0)	55 (100.0)
Full Analysis Set (FAS)	37 (94.9)	12 (75.0)	49 (89.1)
Per Protocol Set	34 (87.2)	12 (75.0)	46 (83.6)
Subjects who are on study drug treatment	7 (17.9)	1 (6.3)	8 (14.5)
Subjects who had study drug treatment discontinuation	32 (82.1)	15 (93.8)	47 (85.5)
Primary reason for study drug treatment discontinuation			
Unacceptable toxicity (adverse event)	15 (46.9)	2 (13.3)	17 (36.2)
Progression disease	15 (46.9)	9 (60.0)	24 (51.1)
Decision by the Investigator to permanently discontinue study drug administration	0 (0.0)	0 (0.0)	0 (0.0)
Inter-current illness that would, in the judgment of the Investigator, affect clinical assessments, subject safety, or follow-up significantly	0 (0.0)	0 (0.0)	0 (0.0)
Significant protocol deviations that jeopardize the usefulness of the data	0 (0.0)	0 (0.0)	0 (0.0)
Repeated subject noncompliance	0 (0.0)	1 (6.7)	1 (2.1)
Withdrew consent	2 (6.3)	3 (20.0)	5 (10.6)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.1 and 16.2 5.1
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in the respective country within Safety Analysis set;
Percentages for study drug treatment discontinuation reasons are calculated based on the number of subjects in the respective country within Safety Analysis set who discontinued.
Progression disease in primary reason for study drug treatment discontinuation is defined as progression of the disease under study, which also included clinical progression disease, except for isolated progression in skin lesion.

Description	Japan (N=52) n (%)	Korea (N=22) n (%)	Total (N=74) n (%)
Subjects in FAS who completed 1 cycle of treatment (including subjects discontinued before C2D1 with >=75% protocol specified dose of 320mg)	31 (83.8)	12 (100.0)	43 (87.8)
Subjects in FAS who did not complete 1 cycle of treatment (where study medication taken within cycle 1 is <75% protocol specified dose of 320mg)	6 (16.2)	0 (0.0)	6 (12.2)
Subjects completed the study participation	14 (35.9)	13 (81.3)	27 (49.1)
Primary reason for completing the study participation			
Lost to follow-up	0 (0.0)	1 (7.7)	1 (3.7)
Death	14 (100.0)	4 (30.8)	18 (66.7)
Withdrew consent	0 (0.0)	8 (61.5)	8 (29.6)
Study reached pre-defined end	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.1 and 16.2 5.1
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in the respective country within Safety Analysis set.
Percentages for subjects who did or did not complete 1 cycle of treatment are calculated based on the number of subjects in the respective country within Full Analysis Set.
Percentages for primary reason for completing the study participation are calculated based on the number of subjects who completed study participation in the respective country within Safety Analysis set.

表 2.7.4.7-6　被験者の内訳（201 試験）（全同意取得例）

Description	30 mg (N=15) n (%)	40 mg (N=7) n (%)	Total (N=22) n (%)
Enrolled	15	7	22
Screening Failure	8	0	8
Treated with at least one dose of HBI-8000 (Safety Analysis Set)	7 (46.7%)	7 (100.0%)	14 (63.6%)
Treated with 2 or more dose of HBI-8000 and have valid efficacy assessment at screening and post-dose (Efficacy Analysis Set)	6 (40.0%)	7 (100.0%)	13 (59.1%)
Discontinued	7 (46.7%)	7 (100.0%)	14 (63.6%)
Primary reason for discontinuation			
Adverse event	2 (28.6%)	3 (42.9%)	5 (35.7%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tumor progression	3 (42.9%)	1 (14.3%)	4 (28.6%)
Unacceptable toxicity including: QTc prolongation >= Grade 3	0 (0.0%)	1 (14.3%)	1 (7.1%)
Become HBV positive during the study	0 (0.0%)	0 (0.0%)	0 (0.0%)
Significant protocol deviation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient non-compliance	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient request to withdraw informed consent	0 (0.0%)	1 (14.3%)	1 (7.1%)
Decision by the investigator to permanently discontinue HBI-8000	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pregnancy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Start of another anti-cancer treatment protocol	0 (0.0%)	0 (0.0%)	0 (0.0%)
In the event of sponsor or regulatory authorities obtain safety information which does not allow continuation the study	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.1
n = number of patients; % = percentage of patients calculated relative to the total number of enrolled patients in each cohort.
Percentage for discontinuation reasons is calculated based on the number of patients who had discontinuation in each cohort of the analysis set.

Description	30 mg (N=15) n (%)	40 mg (N=7) n (%)	Total (N=22) n (%)
Intercurrent, non-clear illness that would, in the judgment of the investigator, affect clinical assessments, patient safety, or follow-up to a significant degree	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sponsor decides to discontinue development of HBI-8000 or the study	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	2 (28.6%)	1 (14.3%)	3 (21.4%)

SOURCE: Listing 16.2.1
n = number of patients; % = percentage of patients calculated relative to the total number of enrolled patients in each cohort.
Percentage for discontinuation reasons is calculated based on the number of patients who had discontinuation in each cohort of the analysis set.

表 2.7.4.7-7　被験者の内訳（210 試験）（全同意取得例）

Description	40 mg (N=29) n (%)
Consented	29
Screening failure	6
Treated with at least one dose of HBI-8000 (Safety Analysis Set)	23 (100.0%)
Full Analysis Set (FAS)	23 (100.0%)
Per Protocol Set	23 (100.0%)
Subjects who are on study drug treatment	0 (0.0%)
Subjects who had study drug treatment discontinuation	23 (100.0%)
Primary reason for study drug treatment discontinuation	
Unacceptable toxicity (adverse event)	8 (34.8%)
Progression disease	12 (52.2%)
Decision by the Investigator to permanently discontinue study drug administration	0 (0.0%)
Inter-current illness that would, in the judgment of the Investigator, affect clinical assessments, subject safety, or follow-up significantly	0 (0.0%)
Significant protocol deviations that jeopardize the usefulness of the data	0 (0.0%)
Repeated subject noncompliance	0 (0.0%)
Withdrew consent	2 (8.7%)
Other	1 (4.3%)

Source: Listing 16.2.1 and 16.2.5.1

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the Safety Analysis set;
Percentages for study drug treatment discontinuation reasons are calculated based on the number of subjects in the Safety Analysis set who discontinued.
Progression disease in primary reason for study drug treatment discontinuation is defined as progression of the disease under study, which also included clinical progression disease, except for isolated progression in skin lesion.

Description	40 mg (N=29) n (%)
Subjects in FAS who completed 1 cycle of treatment (including subjects discontinued before C2D1 with >=75% protocol specified dose of 320mg)	16 (69.6%)
Subjects in FAS who did not complete 1 cycle of treatment (where study medication taken within cycle 1 is <75% protocol specified dose of 320mg)	7 (30.4%)
Subjects completed the study participation	13 (56.5%)
Primary reason for completing the study participation	
Lost to follow-up	0 (0.0%)
Death	12 (92.3%)
Withdrew consent	1 (7.7%)
Study reached pre-defined end	0 (0.0%)
Other	0 (0.0%)

Source: Listing 16.2.1 and 16.2 5.1

n = number of subjects; % = percentages of subjects calculated relative to the total number of subjects in the Safety Analysis set.
Percentages for subjects who did or did not complete 1 cycle of treatment are calculated based on the number of subjects in the Full Analysis Set.
Percentages for primary reason for completing the study participation are calculated based on the number of subjects who completed study participation in the Safety Analysis set.

表 2.7.4.7-8　人口統計学的特性及びその他のベースライン特性（203 試験）（安全性解析対象集団）

Characteristic (unit)	Category	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Age (years)		n	39	16	55
		Mean	68.9	64.7	67.7
		SD	12.1	10.7	11.7
		Median	73.0	67.0	71.0
		Minimum	38	44	38
		Maximum	87	79	87
	<65	n (%)	8 (20.5%)	7 (43.8%)	15 (27.3%)
	>=65 to <75	n (%)	17 (43.6%)	6 (37.5%)	23 (41.8%)
	>=75	n (%)	14 (35.9%)	3 (18.8%)	17 (30.9%)
Sex	Male	n (%)	28 (71.8%)	7 (43.8%)	35 (63.6%)
	Female	n (%)	11 (28.2%)	9 (56.3%)	20 (36.4%)
Race	Asian	n (%)	39 (100.0%)	16 (100.0%)	55 (100.0%)
	Other	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Reported	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity	Japanese	n (%)	39 (100.0%)	0 (0.0%)	39 (70.9%)
	Korean	n (%)	0 (0.0%)	16 (100.0%)	16 (29.1%)
	Other	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Reported	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ECOG Performance Status	0	n (%)	26 (66.7%)	2 (12.5%)	28 (50.9%)
	1	n (%)	12 (30.8%)	13 (81.3%)	25 (45.5%)
	2	n (%)	1 (2.6%)	1 (6.3%)	2 (3.6%)
	3	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.4.1, 16.2.5.3, 16.2.5.8, 16 2.5.9, 16.2.7.2, 16.2.7.5 and 16.2.11.1
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of normal.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
For maximum length of long dimension of target lesion, subjects who had multiple target lesions only have the biggest length of long dimension target lesion included in this analysis.

Characteristic (unit)	Category	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Height (cm)		n	39	16	55
		Mean	163.18	159.88	162.22
		SD	8.96	9.55	9.18
		Median	162.00	160.10	162.00
		Minimum	148.0	142.5	142.5
		Maximum	189.6	177.7	189.6
Weight (kg)		n	39	16	55
		Mean	58.52	56.93	58.05
		SD	11.59	9.79	11.03
		Median	57.10	58.50	57.40
		Minimum	36.4	41.3	36.4
		Maximum	88.2	69.3	88.2
BMI (kg/m^2)		n	39	16	55
		Mean	21.842	22.248	21.960
		SD	3.062	3.176	3.071
		Median	22.281	22.309	22.281
		Minimum	14.47	15.54	14.47
		Maximum	29.00	27.09	29.00
LDH (U/L)	<=ULN	n (%)	19 (48.7%)	7 (43.8%)	26 (47.3%)
	>ULN	n (%)	20 (51.3%)	9 (56.3%)	29 (52.7%)
LDH (U/L)	<=300 (U/L)	n (%)	31 (79.5%)	8 (50.0%)	39 (70.9%)
	>300 (U/L)	n (%)	8 (20.5%)	8 (50.0%)	16 (29.1%)

SOURCE: Listing 16.2.4.1, 16.2.5.3, 16 2.5.8, 16 2.5.9, 16.2.7.2, 16.2.7.5 and 16.2.11.1
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of normal.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
For maximum length of long dimension of target lesion, subjects who had multiple target lesions only have the biggest length of long dimension target lesion included in this analysis.

Characteristic (unit)	Category	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
HBsAg	Positive	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Negative	n (%)	39 (100.0%)	16 (100.0%)	55 (100.0%)
	Not Done	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anti-HBs	Positive	n (%)	6 (15.4%)	7 (43.8%)	13 (23.6%)
	Negative	n (%)	32 (82.1%)	9 (56.3%)	41 (74.5%)
	Not Done	n (%)	1 (2.6%)	0 (0.0%)	1 (1.8%)
Anti-HBc	Positive	n (%)	6 (15.4%)	7 (43.8%)	13 (23.6%)
	Negative	n (%)	32 (82.1%)	9 (56.3%)	41 (74.5%)
	Not Done	n (%)	1 (2.6%)	0 (0.0%)	1 (1.8%)
HBV-DNA	Positive	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Negative	n (%)	24 (61.5%)	11 (68.8%)	35 (63.6%)
	Not Done	n (%)	15 (38.5%)	5 (31.3%)	20 (36.4%)
HCV Antibody	Positive	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Negative	n (%)	39 (100.0%)	16 (100.0%)	55 (100.0%)
	Not Done	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatitis Assessment Result	Active	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Non Active	n (%)	39 (100.0%)	14 (87.5%)	53 (96.4%)

SOURCE: Listing 16.2.4.1, 16.2.5.3, 16 2.5.8, 16.2.5.9, 16.2.7.2, 16.2.7.5 and 16.2.11.1
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of normal.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
For maximum length of long dimension of target lesion, subjects who had multiple target lesions only have the biggest length of long dimension target lesion included in this analysis.

Characteristic (unit)	Category	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Maximum length of long dimension of target lesion (mm) based on Investigator Response Assessment		n	39	16	55
		Mean	32.0	30.9	31.7
		SD	13.5	15.2	13.9
		Median	28.0	23.5	28.0
		Minimum	17	16	16
		Maximum	70	70	70
Sum of 2-dimension products of target lesions (mm^2) based on Investigator Response Assessment		n	39	16	55
		Mean	1380.1	1660.6	1461.7
		SD	1051.8	1497.9	1190.9
		Median	1092.0	1107.0	1092.0
		Minimum	162	234	162
		Maximum	4487	5516	5516
Bone Marrow Infiltration	Positive	n (%)	12 (30.8%)	2 (12.5%)	14 (25.5%)
	Undetermined	n (%)	5 (12.8%)	0 (0.0%)	5 (9.1%)
	Negative	n (%)	22 (56.4%)	7 (43.8%)	29 (52.7%)
	Not Done	n (%)	0 (0.0%)	7 (43.8%)	7 (12.7%)

SOURCE: Listing 16.2.4.1, 16.2.5.3, 16.2.5.8, 16 2.5.9, 16 2.7.2, 16.2.7.5 and 16.2.11.1
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of normal.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
For maximum length of long dimension of target lesion, subjects who had multiple target lesions only have the biggest length of long dimension target lesion included in this analysis.

Characteristic (unit)	Category	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Hepatic enlargement and splenomegaly	Not Done	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatic enlargement result	Present	n (%)	0 (0.0%)	3 (18.8%)	3 (5.5%)
	Absent	n (%)	39 (100.0%)	13 (81.3%)	52 (94.5%)
Splenomegaly result	Present	n (%)	4 (10.3%)	1 (6.3%)	5 (9.1%)
	Absent	n (%)	35 (89.7%)	15 (93.8%)	50 (90.9%)
Hepatic enlargement result and splenomegaly result	Present	n (%)	0 (0.0%)	1 (6.3%)	1 (1.8%)

SOURCE: Listing 16.2.4.1, 16.2.5.3, 16.2.5.8, 16 2.5.9, 16 2.7.2, 16.2.7.5 and 16.2.11.1
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of normal.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
For maximum length of long dimension of target lesion, subjects who had multiple target lesions only have the biggest length of long dimension target lesion included in this analysis.

表 2.7.4.7-9　疾患特性（203 試験）（安全性解析対象集団）

Description	Subtype/Category	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Diagnosis at screening and confirmed by Central Pathology Review	Peripheral T-cell Lymphoma (PTCL):	38 (97.4%)	14 (87.5%)	52 (94.5%)
	Peripheral T-Cell Lymphoma Not Otherwise Specified (PTCL-NOS)	27 (69.2%)	10 (62.5%)	37 (67.3%)
	Angioimmunoblastic T-Cell Lymphoma (AITL)	8 (20.5%)	2 (12.5%)	10 (18.2%)
	Anaplastic Large-Cell Lymphoma (ALCL), ALK+	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Anaplastic Large-Cell Lymphoma (ALCL), ALK-	2 (5.1%)	1 (6.3%)	3 (5.5%)
	Enteropathy-Type T-Cell Lymphoma (EATL)	1 (2.6%)	1 (6.3%)	2 (3.6%)
	Hepatosplenic T-Cell Lymphoma (HSTCL)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Subcutaneous Panniculitis-Like T-Cell Lymphoma (SPTCL)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Non-PTCL	1 (2.6%)	1 (6.3%)	2 (3.6%)
Diagnosis at screening assessed by Investigator	Peripheral T-cell Lymphoma (PTCL):	39 (100.0%)	16 (100.0%)	55 (100.0%)
	Peripheral T-Cell Lymphoma Not Otherwise Specified (PTCL-NOS)	22 (56.4%)	6 (37.5%)	28 (50.9%)
	Angioimmunoblastic T-Cell Lymphoma (AITL)	14 (35.9%)	7 (43.8%)	21 (38.2%)
	Anaplastic Large-Cell Lymphoma (ALCL), ALK+	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Anaplastic Large-Cell Lymphoma (ALCL), ALK-	2 (5.1%)	2 (12.5%)	4 (7.3%)
	Enteropathy-Type T-Cell Lymphoma (EATL)	1 (2.6%)	1 (6.3%)	2 (3.6%)
	Hepatosplenic T-Cell Lymphoma (HSTCL)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Subcutaneous Panniculitis-Like T-Cell Lymphoma (SPTCL)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other PTCL	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.4.3

n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;
Duration since initial diagnosis (years)= (informed consent date - date of 1st diagnosis + 1)/365.25.
Duration from most recent progression (days) = (first study drug date - date of most recent progression + 1).
Duration from most recent progression (months) = (first study drug date - date of most recent progression + 1)/ 30.4375.
Central pathology reviewer could not confirm subject [redacted] disease subtype, due to the reason that subject's tumor slides were not submitted for central pathology review.

Description	Subtype/Category	Japan (N=39)	Korea (N=16)	Total (N=55)
		n (%)	n (%)	n (%)
Duration since initial diagnosis (years)	n	39	16	55
	Mean	3.133	2.576	2.971
	SD	3.190	3.262	3.191
	Median	1.202	1.392	1.339
	Minimum	0.06	0.35	0.06
	Maximum	10.95	12.88	12.88
Duration since initial diagnosis by category	> 5 years	10 (25.6%)	3 (18.8%)	13 (23.6%)
	<= 5 years	29 (74.4%)	13 (81.3%)	42 (76.4%)
Duration from most recent progression (days)	n	39	16	55
	Mean	53.0	50.3	52.2
	SD	99.7	54.8	88.5
	Median	27.0	26.0	27.0
	Minimum	9	7	7
	Maximum	605	205	605
Duration from most recent progression by category	> 1 months	17 (43.6%)	7 (43.8%)	24 (43.6%)
	<= 1 months	22 (56.4%)	9 (56.3%)	31 (56.4%)

SOURCE: Listing 16.2.4.3

n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;
Duration since initial diagnosis (years)= (informed consent date - date of 1st diagnosis + 1)/365.25.
Duration from most recent progression (days) = (first study drug date - date of most recent progression + 1).
Duration from most recent progression (months) = (first study drug date - date of most recent progression + 1)/ 30.4375.
Central pathology reviewer could not confirm subject [redacted] disease subtype, due to the reason that subject's tumor slides were not submitted for central pathology review.

表 2.7.4.7-10　人口統計学的特性及びその他のベースライン特性（201 試験）（安全性解析対象集団）

Characteristic (unit)	Category	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
Age (years)		n	7	7	14
		Mean	70.9	65.1	68.0
		SD	9.44	6.54	8.35
		Median	72.0	63.0	69.0
		Minimum	53	57	53
		Maximum	81	76	81
Sex	Male	n (%)	4 (57.1%)	3 (42.9%)	7 (50.0%)
	Female	n (%)	3 (42.9%)	4 (57.1%)	7 (50.0%)
Race	Asian	n (%)	7 (100.0%)	7 (100.0%)	14 (100.0%)
	Other	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not reported	n	0	0	0
Ethnicity	Japanese	n (%)	7 (100.0%)	7 (100.0%)	14 (100.0%)
	Other	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Unknown	n	0	0	0

SOURCE: Listing 16.2.4.1 and Listing 16.2.13.1
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set with data.
BMI = body mass index
ECOG = Eastern Cooperative Oncology Group

Characteristic (unit)	Category	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
ECOG Performance Status	0	n (%)	4 (57.1%)	5 (71.4%)	9 (64.3%)
	1	n (%)	3 (42.9%)	2 (28.6%)	5 (35.7%)
	2	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height (cm)		n	7	7	14
		Mean	160.30	156.04	158.17
		SD	11.657	7.703	9.746
		Median	161.10	158.80	159.90
		Minimum	138.3	146.6	138.3
		Maximum	171.1	167.4	171.1
Weight (kg)		n	7	7	14
		Mean	58.97	63.31	61.14
		SD	11.700	12.257	11.730
		Median	62.00	66.50	62.90
		Minimum	41.6	44.1	41.6
		Maximum	75.9	77.8	77.8

SOURCE: Listing 16.2.4.1 and Listing 16.2 13.1
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set with data.
BMI = body mass index
ECOG = Eastern Cooperative Oncology Group

Characteristic (unit)	Category	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
BMI (kg/m^2)		n	7	7	14
		Mean	22.83	25.84	24.33
		SD	3.108	3.579	3.578
		Median	22.20	25.68	24.21
		Minimum	17.7	19.7	17.7
		Maximum	27.3	29.8	29.8
Smoking history	Never	n (%)	4 (57.1%)	4 (57.1%)	8 (57.1%)
	Former	n (%)	3 (42.9%)	2 (28.6%)	5 (35.7%)
	Current	n (%)	0 (0.0%)	1 (14.3%)	1 (7.1%)
Duration of tobacco use:					
Former smokers (years)		n	3	2	5
		Mean	26.7	37.5	31.0
		SD	7.64	9.19	9.25
		Median	25.0	37.5	31.0
		Minimum	20	31	20
		Maximum	35	44	44

SOURCE: Listing 16.2.4.1 and Listing 16.2.13.1
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set with data.
BMI = body mass index
ECOG = Eastern Cooperative Oncology Group

Characteristic (unit)	Category	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
Current smokers (years)		n	0	1	1
		Mean	-	16.0	16.0
		SD	-	-	-
		Median	-	16.0	16.0
		Minimum	-	16	16
		Maximum	-	16	16
Alcohol history	Never	n (%)	1 (14.3%)	3 (42.9%)	4 (28.6%)
	Former	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Current	n (%)	6 (85.7%)	4 (57.1%)	10 (71.4%)
History of drug abuse	Yes	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	n (%)	7 (100.0%)	7 (100.0%)	14 (100.0%)

SOURCE: Listing 16.2.4.1 and Listing 16.2.13.1
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set with data.
BMI = body mass index
ECOG = Eastern Cooperative Oncology Group

表 2.7.4.7-11　疾患特性（201 試験）（安全性解析対象集団）

Description	Category	Type	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Initial diagnosis	Mature B-cell neoplasm	Follicular lymphoma	0 (0.0%)	2 (28.6%)	2 (14.3%)
		Extranodal marginal zone B-cell lymphoma of mucosa-associated	1 (14.3%)	0 (0.0%)	1 (7.1%)
		Diffuse large b-cell lymphoma NOS	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Mature T-cell and NK-cell neoplasm	N	3	4	7
		Adult T-cell leukemia/lymphoma	1 (33.3%)	4 (100.0%)	5 (71.4%)
		Peripheral T-cell lymphoma	2 (66.7%)	0 (0.0%)	2 (28.6%)
	Other		1 (14.3%)	0 (0.0%)	1 (7.1%)
HTLV-1 Result	Positive		1 (14.3%)	4 (57.1%)	5 (35.7%)
	Negative		2 (28.6%)	0 (0.0%)	2 (14.3%)
	Not done		0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.4.4
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Percentage of mature T-cell and NK-cell neoplasm results is calculated based on the number of patients with mature T-cell and NK-cell neoplasm in each cohort of the analysis set with data.
Subject [redacted] had initial diagnosis of ADULT T-CELL LEUKEMIA/LYMPHOMA, however there was no data available for relapse.

Description	Category	Type	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Most recent relapse	Mature B-cell neoplasm	Follicular lymphoma	0 (0.0%)	2 (28.6%)	2 (14.3%)
		Extranodal marginal zone B-cell lymphoma of mucosa-associated	1 (14.3%)	0 (0.0%)	1 (7.1%)
		Diffuse large B-cell lymphoma nos	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Mature T-cell and NK-cell neoplasm	N	3	3	6
		Adult T-cell leukemia/lymphoma	1 (33.3%)	3 (100.0%)	4 (66.7%)
		Peripheral T-cell lymphoma	2 (66.7%)	0 (0.0%)	2 (33.3%)
	Other		1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.4.4
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Percentage of mature T-cell and NK-cell neoplasm results is calculated based on the number of patients with mature T-cell and NK-cell neoplasm in each cohort of the analysis set with data.
Subject [redacted] had initial diagnosis of ADULT T-CELL LEUKEMIA/LYMPHOMA, however there was no data available for relapse.

Description	Category	Type	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Stage	Ann Arbor	I	1 (14.3%)	0 (0.0%)	1 (7.1%)
		II	1 (14.3%)	3 (42.9%)	4 (28.6%)
		IIa	1 (14.3%)	0 (0.0%)	1 (7.1%)
		III	0 (0.0%)	1 (14.3%)	1 (7.1%)
		IV	4 (57.1%)	1 (14.3%)	5 (35.7%)
		Not applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	I	0 (0.0%)	0 (0.0%)	0 (0.0%)
		II	0 (0.0%)	0 (0.0%)	0 (0.0%)
		IIa	0 (0.0%)	0 (0.0%)	0 (0.0%)
		III	0 (0.0%)	0 (0.0%)	0 (0.0%)
		IV	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Not applicable	0 (0.0%)	1 (14.3%)	1 (7.1%)

SOURCE: Listing 16.2.4.4
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Percentage of mature T-cell and NK-cell neoplasm results is calculated based on the number of patients with mature T-cell and NK-cell neoplasm in each cohort of the analysis set with data.
Subject [redacted] had initial diagnosis of ADULT T-CELL LEUKEMIA/LYMPHOMA however there was no data available for relapse.

表 2.7.4.7-12　人口統計学的特性及びその他のベースライン特性（210 試験）（安全性解析対象集団）

Characteristic (unit)	Category	Statistic	40 mg (N=23)
Age (years)		n	23
		Mean	73.4
		SD	7.1
		Median	72.0
		Minimum	60
		Maximum	89
	<65	n (%)	1 (4.3%)
	>=65 to <75	n (%)	13 (56.5%)
	>=75	n (%)	9 (39.1%)
Sex	Male	n (%)	15 (65.2%)
	Female	n (%)	8 (34.8%)
Race	Asian	n (%)	23 (100.0%)
	Other	n (%)	0 (0.0%)
	Not Reported	n (%)	0 (0.0%)
Ethnicity	Japanese	n (%)	23 (100.0%)
	Other	n (%)	0 (0.0%)
	Not Reported	n (%)	0 (0.0%)
ECOG Performance Status	0	n (%)	12 (52.2%)
	1	n (%)	10 (43.5%)
	2	n (%)	1 (4.3%)
	3	n (%)	0 (0.0%)
	4	n (%)	0 (0.0%)

Source: Listing 16.2.4 1, 16.2.5.3, 16.2.5.8, 16.2.5.9, 16.2.7 1, 16.2.7.2, 16 2.7.5 and 16.2.11.1
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set with data;
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of normal.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
For maximum length of long dimension of target lesion, subjects who had multiple target lesions only have the biggest length of long dimension target lesion included in this analysis.
Absolute lymphocyte count is not total absolute lymphocyte count, it is merely the normal absolute lymphocyte count.

Characteristic (unit)	Category	Statistic	40 mg (N=23)
Height (cm)		n	23
		Mean	158.47
		SD	8.68
		Median	158.00
		Minimum	143.0
		Maximum	176.0
Weight (kg)		n	23
		Mean	54.04
		SD	10.35
		Median	52.70
		Minimum	34.4
		Maximum	70.7
BMI (kg/m^2)		n	23
		Mean	21.440
		SD	3.348
		Median	21.290
		Minimum	15.88
		Maximum	29.60
Serum calcium (mmol/L)	<=ULN	n (%)	22 (95.7%)
	>ULN	n (%)	1 (4.3%)
LDH (U/L)	<=ULN	n (%)	8 (34.8%)
	>ULN	n (%)	15 (65.2%)

Source: Listing 16.2.4 1, 16.2.5.3, 16.2.5.8, 16.2.5.9, 16 2.7.1, 16 2.7.2, 16.2.7.5 and 16.2.11.1
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set with data;
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of normal.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
For maximum length of long dimension of target lesion, subjects who had multiple target lesions only have the biggest length of long dimension target lesion included in this analysis.
Absolute lymphocyte count is not total absolute lymphocyte count, it is merely the normal absolute lymphocyte count.

Characteristic (unit)	Category	Statistic	40 mg (N=23)
LDH (U/L)	<=300 (U/L)	n (%)	13 (56.5%)
	>300 (U/L)	n (%)	10 (43.5%)
Abnormal lymphocyte percent (Proportion of 1)		n	23
		Mean	0.1061
		SD	0.2088
		Median	0.0000
		Minimum	0.000
		Maximum	0.740
Absolute abnormal lymphocyte count (10^9/L)		n	23
		Mean	1.3385
		SD	3.1741
		Median	0.0000
		Minimum	0.000
		Maximum	13.401
Absolute lymphocyte count (10^9/L)		n	23
		Mean	0.9973
		SD	0.8866
		Median	0.8586
		Minimum	0.000
		Maximum	4.100
Corrected Calcium (mg/dL)	<=10.0 (mg/dL)	n (%)	19 (82.6%)
	>10.0 (mg/dL)	n (%)	4 (17.4%)

Source: Listing 16.2.4 1, 16.2.5.3, 16.2.5.8, 16.2.5.9, 16.2.7 1, 16.2.7.2, 16 2.7.5 and 16.2.11.1
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set with data;
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of normal.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
For maximum length of long dimension of target lesion, subjects who had multiple target lesions only have the biggest length of long dimension target lesion included in this analysis.
Absolute lymphocyte count is not total absolute lymphocyte count, it is merely the normal absolute lymphocyte count.

Characteristic (unit)	Category	Statistic	40 mg (N=23)
Corrected Calcium (mg/dL)		n	23
		Mean	9.579
		SD	0.670
		Median	9.460
		Minimum	8.76
		Maximum	11.54
HBsAg	Positive	n (%)	0 (0.0%)
	Negative	n (%)	23 (100.0%)
	Not Done	n (%)	0 (0.0%)
Anti-HBs	Positive	n (%)	7 (30.4%)
	Negative	n (%)	16 (69.6%)
	Not Done	n (%)	0 (0.0%)
Anti-HBc	Positive	n (%)	9 (39.1%)
	Negative	n (%)	14 (60.9%)
	Not Done	n (%)	0 (0.0%)
HBV-DNA	Positive	n (%)	0 (0.0%)
	Negative	n (%)	14 (60.9%)
	Not Done	n (%)	9 (39.1%)
HCV Antibody	Positive	n (%)	0 (0.0%)
	Negative	n (%)	23 (100.0%)
	Not Done	n (%)	0 (0.0%)

Source: Listing 16.2.4 1, 16.2.5.3, 16.2.5.8, 16.2.5.9, 16.2.7 1, 16.2.7.2, 16.2.7.5 and 16.2.11.1
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set with data;
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of normal.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
For maximum length of long dimension of target lesion, subjects who had multiple target lesions only have the biggest length of long dimension target lesion included in this analysis.
Absolute lymphocyte count is not total absolute lymphocyte count, it is merely the normal absolute lymphocyte count.

Characteristic (unit)	Category	Statistic	40 mg (N=23)
HTLV-I Antibody	Positive	n (%)	23 (100.0%)
	Negative	n (%)	0 (0.0%)
	Not Done	n (%)	0 (0.0%)
Hepatitis Assessment Result	Active	n (%)	0 (0.0%)
	Non Active	n (%)	23 (100.0%)
Maximum length of long dimension of target lesion (mm) based on Investigator Response Assessment		n	19
		Mean	34.3
		SD	20.4
		Median	26.0
		Minimum	18
		Maximum	93
Sum of 2-dimension products of target lesions (mm^2) based on Investigator Response Assessment		n	19
		Mean	2328.8
		SD	3940.3
		Median	1150.0
		Minimum	234
		Maximum	17591

Source: Listing 16.2.4 1, 16.2.5.3, 16.2.5.8, 16.2.5.9, 16.2.7 1, 16.2.7.2, 16 2.7.5 and 16.2.11.1
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set with data;
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of normal.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
For maximum length of long dimension of target lesion, subjects who had multiple target lesions only have the biggest length of long dimension target lesion included in this analysis.
Absolute lymphocyte count is not total absolute lymphocyte count, it is merely the normal absolute lymphocyte count.

Characteristic (unit)	Category	Statistic	40 mg (N=23)
Bone Marrow Infiltration	Positive	n (%)	6 (26.1%)
	Undetermined	n (%)	2 (8.7%)
	Negative	n (%)	15 (65.2%)
	Not Done	n (%)	0 (0.0%)
Hepatic enlargement and splenomegaly	Not Done	n (%)	0 (0.0%)
Hepatic enlargement result	Present	n (%)	2 (8.7%)
	Absent	n (%)	21 (91.3%)
Splenomegaly result	Present	n (%)	4 (17.4%)
	Absent	n (%)	19 (82.6%)
Hepatic enlargement result and splenomegaly result	Present	n (%)	1 (4.3%)

Source: Listing 16.2.4 1, 16.2.5.3, 16.2.5.8, 16.2.5.9, 16.2.7 1, 16.2.7.2, 16 2.7.5 and 16.2.11.1
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set with data;
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of normal.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
For maximum length of long dimension of target lesion, subjects who had multiple target lesions only have the biggest length of long dimension target lesion included in this analysis.
Absolute lymphocyte count is not total absolute lymphocyte count, it is merely the normal absolute lymphocyte count.

表 2.7.4.7-13　疾患特性（210 試験）（安全性解析対象集団）

Description	Subtype/Category	40 mg (N=23) n (%)
Diagnosis at screening	Adult T-cell Lymphoma:	23 (100.0%)
	Acute	13 (56.5%)
	Lymphoma	8 (34.8%)
	Unfavorable Chronic	2 (8.7%)
Duration since initial diagnosis (years)	n	23
	Mean	3.019
	SD	4.838
	Median	1.500
	Minimum	0.31
	Maximum	21.95
Duration since initial diagnosis by category	> 5 years	3 (13.0%)
	<= 5 years	20 (87.0%)
Duration from most recent progression (days)	n	23
	Mean	47.6
	SD	80.4
	Median	26.0
	Minimum	3
	Maximum	371
Duration from most recent progression by category	> 1 month	8 (34.8%)
	<= 1 month	15 (65.2%)

Source: Listing 16.2.4 3

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Duration since initial diagnosis (years)= (informed consent date - date of 1st diagnosis + 1)/365.25.
Duration from most recent progression (days) = (first study drug date - date of most recent progression + 1).
Duration from most recent progression (months) = (first study drug date - date of most recent progression + 1)/ 30.4375.

表 2.7.4.7-14　がんに対する前治療（203 試験）（安全性解析対象集団）

Description	Category	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Number of subjects with at least one treatment agent type		n	39	16	55
Type of previous cancer therapy	Chemotherapy	n (%)	39 (100.0%)	16 (100.0%)	55 (100.0%)
	Other anticancer therapy	n (%)	14 (35.9%)	2 (12.5%)	16 (29.1%)
	Brentuximab vedotin	n (%)	1 (2.6%)	1 (6.3%)	2 (3.6%)
	Darinaparsin	n (%)	7 (17.9%)	1 (6.3%)	8 (14.5%)
	E7777[a]	n (%)	2 (5.1%)	0 (0.0%)	2 (3.6%)
	Forodesine	n (%)	6 (15.4%)	0 (0.0%)	6 (10.9%)
	Mogamulizumab	n (%)	1 (2.6%)	0 (0.0%)	1 (1.8%)
	Rituximab	n (%)	2 (5.1%)	0 (0.0%)	2 (3.6%)
	Romidepsin	n (%)	4 (10.3%)	0 (0.0%)	4 (7.3%)
	Radiotherapy	n (%)	4 (10.3%)	2 (12.5%)	6 (10.9%)
	Hematopoietic stem cell transplantation	n (%)	2 (5.1%)	4 (25.0%)	6 (10.9%)
	Other prior therapy	n (%)	1 (2.6%)	1 (6.3%)	2 (3.6%)
Total number of previous cancer therapy regimens	1 regimen	n (%)	15 (38.5%)	2 (12.5%)	17 (30.9%)
	2 regimens	n (%)	10 (25.6%)	8 (50.0%)	18 (32.7%)
	3 regimens	n (%)	7 (17.9%)	1 (6.3%)	8 (14.5%)
	4 regimens	n (%)	2 (5.1%)	2 (12.5%)	4 (7.3%)
	5 or more regimens	n (%)	5 (12.8%)	3 (18.8%)	8 (14.5%)
	2 or more regimens	n (%)	24 (61.5%)	14 (87.5%)	38 (69.1%)
		Median	2.0	2.0	2.0
Refractory, relapsed and undetermined PTCL based on last previous treatment	Refractory	n (%)	15 (38.5%)	8 (50.0%)	23 (41.8%)
	Relapsed	n (%)	24 (61.5%)	8 (50.0%)	32 (58.2%)
	Undetermined	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.4.4

n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set.
a: development code for denileukin diftitox
Subjects may have more than one type of therapy.
Subjects with refractory, relapsed and undetermined PTCL are confirmed by Medical Expert.
Previous cancer therapy regimens included other prior therapy, radiotherapy and chemotherapy.

Description	Category	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Days from end of the last immediate previous treatment	< 3 months	n (%)	20 (51.3%)	7 (43.8%)	27 (49.1%)
	>=3 months	n (%)	19 (48.7%)	9 (56.3%)	28 (50.9%)
Number of days from end of the last immediate previous treatment (days)		n	39	16	55
		Mean	344.6	253.2	318.0
		SD	724.1	516.5	667.0
		Median	88.0	110.5	97.0
		Minimum	29	30	29
		Maximum	3861	2154	3861
Chemotherapy	Total number of regimens				
	1 regimen	n (%)	17 (43.6%)	3 (18.8%)	20 (36.4%)
	2 regimens	n (%)	10 (25.6%)	7 (43.8%)	17 (30.9%)
	3 regimens	n (%)	6 (15.4%)	2 (12.5%)	8 (14.5%)
	4 regimens	n (%)	3 (7.7%)	2 (12.5%)	5 (9.1%)
	5 or more regimens	n (%)	3 (7.7%)	2 (12.5%)	5 (9.1%)
	2 or more regimens	n (%)	22 (56.4%)	13 (81.3%)	35 (63.6%)
		Median	2.0	2.0	2.0
The last immediate previous chemotherapy best response	Complete response (CR)	n (%)	13 (33.3%)	4 (25.0%)	17 (30.9%)
	Unconfirmed complete response (CRu)	n (%)	1 (2.6%)	0 (0.0%)	1 (1.8%)
	Partial response (PR)	n (%)	10 (25.6%)	3 (18.8%)	13 (23.6%)
	Stable disease (SD)	n (%)	11 (28.2%)	1 (6.3%)	12 (21.8%)
	Relapsed disease or progressive disease (PD)	n (%)	4 (10.3%)	6 (37.5%)	10 (18.2%)
	Not assessable	n	0	1	1
	Unknown	n	0	1	1

SOURCE: Listing 16.2.4.4

n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set.
Number of days from end of the last immediate previous treatment (days) = date of first study drug – end date of last immediate previous treatment + 1
Days from end of the last immediate previous treatment (months) = (date of first study drug – end date of last immediate previous treatment + 1)/30.4375

Description	Category	Statistic	Japan (N=39)	Korea (N=16)	Total (N=55)
Type of transplantation	Autologous transplantation	n (%)	2 (5.1%)	4 (25.0%)	6 (10.9%)
	Allogeneic transplantation	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
The last immediate previous radiotherapy best response	Complete response (CR)	n (%)	2 (5.1%)	0 (0.0%)	2 (3.6%)
	Unconfirmed complete response (CRu)	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Partial response (PR)	n (%)	0 (0.0%)	1 (6.3%)	1 (1.8%)
	Stable disease (SD)	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Relapsed disease or progressive disease (PD)	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not assessable	n	0	0	0
	Unknown	n	2	1	3

SOURCE: Listing 16.2.4.4

n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set.

表 2.7.4.7-15　がんに対する前治療（201 試験）（安全性解析対象集団）

Description	Category	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
Number of patients with at least one treatment agent type		n	7	7	14
Previous Treatment agent type	Chemotherapy	n (%)	7 (100.0%)	7 (100.0%)	14 (100.0%)
	Radiation therapy	n (%)	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Biologic	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Myeloablative therapy	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Immuno therapy	n (%)	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Immuno-conjugated therapy	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	UV light therapy	n (%)	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Steroid therapy	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Previous Chemotherapy best response	Complete response	n (%)	4 (57.1%)	3 (42.9%)	7 (50.0%)
	Unconfirmed complete response	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Partial response	n (%)	0 (0.0%)	3 (42.9%)	3 (21.4%)
	Stable disease	n (%)	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Progressive disease	n (%)	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Not evaluable	n	0	0	0
	Unknown	n	1	0	1

SOURCE: Listing 16.2.4.5
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Patients may have more than one type of treatment agent.
Percentage of best responses, radiation source and type of UV light therapy is calculated based on the number of patients with chemotherapy, radiation therapy and UV light therapy in each cohort of the analysis set, respectively.
If patients had more than one chemotherapy regimen, best response to any prior therapy is presented. The number of cycle denotes the highest number of cycles given among all prior chemotherapy regimens.

Description	Category	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
Number of cycles	Chemotherapy	n	7	7	14
		Mean	6.4	5.9	6.1
		SD	1.62	2.48	2.03
		Median	6.0	6.0	6.0
		Minimum	5	2	2
		Maximum	10	8	10
Radiation source	X-ray	n (%)	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Gamma-ray	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Electron ray	n (%)	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Other	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Type of UV light therapy	PUVA	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	UVA	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	UVB	n (%)	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Other	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.4.5
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Patients may have more than one type of treatment agent.
Percentage of best responses, radiation source and type of UV light therapy is calculated based on the number of patients with chemotherapy, radiation therapy and UV light therapy in each cohort of the analysis set, respectively.
If patients had more than one chemotherapy regimen, best response to any prior therapy is presented. The number of cycle denotes the highest number of cycles given among all prior chemotherapy regimens.

Description	Category	Statistic	30 mg (N=7)	40 mg (N=7)	Total (N=14)
Total number of regimen		n	7	7	14
		Mean	3.0	3.1	3.1
		SD	2.89	2.27	2.50
		Median	2.0	3.0	2.5
		Minimum	1	1	1
		Maximum	9	8	9

SOURCE: Listing 16.2.4 5
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Patients may have more than one type of treatment agent.
Percentage of best responses, radiation source and type of UV light therapy is calculated based on the number of patients with chemotherapy, radiation therapy and UV light therapy in each cohort of the analysis set, respectively.
If patients had more than one chemotherapy regimen, best response to any prior therapy is presented. The number of cycle denotes the highest number of cycles given among all prior chemotherapy regimens.

表 2.7.4.7-16　がんに対する前治療（210 試験）（安全性解析対象集団）

Description	Category	Statistic	40 mg (N=23)
Number of subjects with at least one treatment agent type		n	23
Type of previous cancer therapy	Chemotherapy alone	n (%)	17 (73.9%)
	Chemotherapy plus Mogamulizumab Therapy	n (%)	11 (47.8%)
	Mogamulizumab Monotherapy	n (%)	12 (52.2%)
	Radiotherapy	n (%)	2 (8.7%)
	Hematopoietic stem cell transplantation	n (%)	0 (0.0%)
	Other prior therapy	n (%)	3 (13.0%)
Number of subjects with:	Mogamulizumab tolerance	n (%)	13 (56.5%)
	Mogamulizumab in-tolerance	n (%)	10 (43.5%)
Total number of previous cancer therapy regimens	1 regimen	n (%)	5 (21.7%)
	2 regimens	n (%)	6 (26.1%)
	3 regimens	n (%)	4 (17.4%)
	4 regimens	n (%)	4 (17.4%)
	5 or more regimens	n (%)	4 (17.4%)
	2 or more regimens	n (%)	18 (78.3%)
		Median	3.0
Refractory, recurrent, relapsed and undetermined ATL based on last previous treatment	Refractory	n (%)	5 (21.7%)
	Recurrent	n (%)	13 (56.5%)
	Relapsed	n (%)	5 (21.7%)
	Undetermined	n (%)	0 (0.0%)

Source: Listing 16.2.4.4

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects may have more than one type of cancer therapy. Data for mogamulizumab monotherapy and combination therapy are provided by Medical Reviewer.
Number of regimens are provided by Medical Reviewer. Previous cancer therapy regimens included other prior therapy, radiotherapy and chemotherapy.
Subjects with refractory, recurrent, relapsed and undetermined ATL are confirmed by Medical Expert.

Description	Category	Statistic	40 mg (N=23)
Days from end of the last immediate previous treatment	< 3 months	n (%)	12 (52.2%)
	>=3 months	n (%)	11 (47.8%)
Number of days from end of the last immediate previous treatment (days)		n	23
		Mean	131.0
		SD	138.6
		Median	89.0
		Minimum	30
		Maximum	496
Chemotherapy	Total number of regimens		
	1 regimen	n (%)	6 (26.1%)
	2 regimens	n (%)	6 (26.1%)
	3 regimens	n (%)	3 (13.0%)
	4 regimens	n (%)	5 (21.7%)
	5 or more regimens	n (%)	3 (13.0%)
	2 or more regimens	n (%)	17 (73.9%)
		Median	2.0

Source: Listing 16 2.4.4

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Days from end of the last immediate previous treatment (months) = (date of first study drug – end date of last immediate previous treatment + 1)/30.4375
Number of days from end of the last immediate previous treatment (days) = date of first study drug – end date of last immediate previous treatment + 1
Data for total number of regimens is provided by Medical Reviewer.
Total number of regimens for chemotherapy and the last immediate previous chemotherapy best response included mogamulizumab therapy.
Chemotherapy included molecular targeted therapy and others.

Description	Category	Statistic	40 mg (N=23)
The last immediate previous chemotherapy best response	Complete response (CR)	n (%)	4 (17.4%)
	Unconfirmed complete response (CRu)	n (%)	1 (4.3%)
	Partial response (PR)	n (%)	8 (34.8%)
	Stable disease (SD)	n (%)	3 (13.0%)
	Relapsed disease or progressive disease (PD)	n (%)	5 (21.7%)
	Not assessable	n	2
	Unknown	n	0
Type of transplantation	Autologous transplantation	n (%)	0 (0.0%)
	Allogeneic transplantation	n (%)	0 (0.0%)
The last immediate previous radiotherapy best response	Complete response (CR)	n (%)	1 (4.3%)
	Unconfirmed complete response (CRu)	n (%)	0 (0.0%)
	Partial response (PR)	n (%)	0 (0.0%)
	Stable disease (SD)	n (%)	0 (0.0%)
	Relapsed disease or progressive disease (PD)	n (%)	0 (0.0%)
	Not assessable	n	0
	Unknown	n	1
The last immediate previous mogamulizumab therapy best response	Complete response (CR)	n (%)	3 (13.0%)
	Unconfirmed complete response (CRu)	n (%)	0 (0.0%)
	Partial response (PR)	n (%)	6 (26.1%)
	Stable disease (SD)	n (%)	2 (8.7%)
	Relapsed disease or progressive disease (PD)	n (%)	1 (4.3%)
	Not assessable	n	2
	Unknown	n	0

Source: Listing 16.2.4.4

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Best response for last immediate previous mogamulizumab therapy included monotherapy and combination therapy. In the event when combination therapy was used, best response from the mogamulizumab treatment is presented.

Last immediate previous mogamulizumab therapy applies to subjects who had mogamulizumab therapy (either monotherapy or combination therapy) as last immediate therapy before the administration of tucidinostat.

Total number of regimens for chemotherapy and the last immediate previous chemotherapy best response included mogamulizumab therapy.

Description	Category	Statistic	40 mg (N=23)
Number of days from end of the last immediate previous Mogamulizumab therapy (days)		n	14
		Mean	210.1
		SD	159.1
		Median	134.0
		Minimum	30
		Maximum	534

Source: Listing 16.2.4.4

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Last immediate previous mogamulizumab therapy applies to subjects who had mogamulizumab therapy (either monotherapy or combination therapy) as last immediate therapy before the administration of tucidinostat.

表 2.7.4.7-17　併用薬（203 試験）（安全性解析対象集団）

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Number of subjects with at least one concomitant medication	39 (100.0)	16 (100.0)	55 (100.0)
ADRENERGICS FOR SYSTEMIC USE	1 (2.6)	1 (6.3)	2 (3.6)
HOKUNALIN /00654901/	1 (2.6)	0	1 (1.8)
METHYLEPHEDRINE HCL	0	1 (6.3)	1 (1.8)
ADRENERGICS, INHALANTS	6 (15.4)	0	6 (10.9)
SULTANOL	2 (5.1)	0	2 (3.6)
ADOAIR	1 (2.6)	0	1 (1.8)
PROCATEROL HYDROCHLORIDE	1 (2.6)	0	1 (1.8)
SALBUTAMOL SULFATE	1 (2.6)	0	1 (1.8)
VENETLIN	1 (2.6)	0	1 (1.8)
AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISEASES	2 (5.1)	0	2 (3.6)
ATOVAQUONE	2 (5.1)	0	2 (3.6)
AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMIASIS	5 (12.8)	1 (6.3)	6 (10.9)
BENAMBAX	3 (7.7)	0	3 (5.5)
PENTAMIDINE ISETIONATE	2 (5.1)	0	2 (3.6)
PENTAMIDINE	0	1 (6.3)	1 (1.8)
AGENTS FOR TREATMENT OF HEMORRHOIDS AND ANAL FISSURES FOR TOPICAL USE	1 (2.6)	0	1 (1.8)
POSTERISAN FORTE /01567801/	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

WHO-DDE Version 01SEP2018 was used to code medications.
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
ALL OTHER THERAPEUTIC PRODUCTS	1 (2.6)	1 (6.3)	2 (3.6)
ARGAMATE	1 (2.6)	0	1 (1.8)
FERBON	0	1 (6.3)	1 (1.8)
AMINOGLYCOSIDE ANTIBACTERIALS	1 (2.6)	1 (6.3)	2 (3.6)
GENTACIN	1 (2.6)	0	1 (1.8)
TOBRAMYCIN	0	1 (6.3)	1 (1.8)
ANESTHETICS, GENERAL	0	1 (6.3)	1 (1.8)
PROPOFOL	0	1 (6.3)	1 (1.8)
REMIFENTANIL	0	1 (6.3)	1 (1.8)
ANESTHETICS, LOCAL	7 (17.9)	2 (12.5)	9 (16.4)
XYLOCAINE /00033402/	3 (7.7)	0	3 (5.5)
LIDOCAINE	1 (2.6)	1 (6.3)	2 (3.6)
LIDOCAINE HYDROCHLORIDE MONOHYDRATE	2 (5.1)	0	2 (3.6)
XYLOCAINE WITH EPINEPHRINE	2 (5.1)	0	2 (3.6)
LIDOCAINE HCL	0	1 (6.3)	1 (1.8)
XYLOCAINE VISCOUS	1 (2.6)	0	1 (1.8)
ANGIOTENSIN II ANTAGONISTS, COMBINATIONS	1 (2.6)	0	1 (1.8)
CO DIO COMBINATION	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

WHO-DDE Version 01SEP2018 was used to code medications.

n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;

ATC class = Anatomical Therapeutic Chemical class.

Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
ANGIOTENSIN II ANTAGONISTS, PLAIN	8 (20.5)	1 (6.3)	9 (16.4)
OLMESARTAN MEDOXOMIL	2 (5.1)	0	2 (3.6)
TELMISARTAN	2 (5.1)	0	2 (3.6)
VALSARTAN	2 (5.1)	0	2 (3.6)
ATACAND	0	1 (6.3)	1 (1.8)
MICARDIS	1 (2.6)	0	1 (1.8)
OLMESARTAN OD	1 (2.6)	0	1 (1.8)
ANTACIDS	2 (5.1)	1 (6.3)	3 (5.5)
SODIUM BICARBONATE	2 (5.1)	0	2 (3.6)
ALMAGATE	0	1 (6.3)	1 (1.8)
ANTI-ACNE PREPARATIONS FOR TOPICAL USE	1 (2.6)	0	1 (1.8)
ACUATIM	1 (2.6)	0	1 (1.8)
ANTIARRHYTHMICS, CLASS I AND III	0	1 (6.3)	1 (1.8)
PROPAFENONE	0	1 (6.3)	1 (1.8)
ANTIBIOTICS FOR TOPICAL USE	3 (7.7)	1 (6.3)	4 (7.3)
GENTACIN	2 (5.1)	0	2 (3.6)
BEAROBAN	0	1 (6.3)	1 (1.8)
GENTAMICIN SULFATE	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

WHO-DDE Version 01SEP2018 was used to code medications.

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ATC class = Anatomical Therapeutic Chemical class.

Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
ANTIDEPRESSANTS	2 (5.1)	0	2 (3.6)
CYMBALTA	1 (2.6)	0	1 (1.8)
TRAZODONE HCL	1 (2.6)	0	1 (1.8)
ANTIDIARRHEAL MICROORGANISMS	5 (12.8)	1 (6.3)	6 (10.9)
BIO-THREE	2 (5.1)	0	2 (3.6)
BACILLUS SUBTILIS;ENTEROCOCCUS FAECIUM	0	1 (6.3)	1 (1.8)
BIOFERMIN /07746301/	1 (2.6)	0	1 (1.8)
BIOFERMIN /14521401/	1 (2.6)	0	1 (1.8)
LACTOBACILLUS ACIDOPHILUS	0	1 (6.3)	1 (1.8)
LACTOMIN	1 (2.6)	0	1 (1.8)
ANTIEMETICS AND ANTINAUSEANTS	0	2 (12.5)	2 (3.6)
EMEND /01627301/	0	1 (6.3)	1 (1.8)
RAMOSETRON HYDROCHLORIDE	0	1 (6.3)	1 (1.8)
ANTIFUNGALS FOR TOPICAL USE	1 (2.6)	0	1 (1.8)
LULICONAZOLE	1 (2.6)	0	1 (1.8)
TERBINAFINE HYDROCHLORIDE	1 (2.6)	0	1 (1.8)
ANTIGLAUCOMA PREPARATIONS AND MIOTICS	1 (2.6)	1 (6.3)	2 (3.6)
CARTEOLOL HYDROCHLORIDE	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

WHO-DDE Version 01SEP2018 was used to code medications.

n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;

ATC class = Anatomical Therapeutic Chemical class.

Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
COSOPT	0	1 (6.3)	1 (1.8)
ANTIGOUT PREPARATIONS	9 (23.1)	0	9 (16.4)
FEBURIC	5 (12.8)	0	5 (9.1)
FEBUXOSTAT	3 (7.7)	0	3 (5.5)
ALLOPURINOL	1 (2.6)	0	1 (1.8)
ANTIHISTAMINES FOR SYSTEMIC USE	11 (28.2)	9 (56.3)	20 (36.4)
OLOPATADINE HYDROCHLORIDE	5 (12.8)	0	5 (9.1)
FEXOFENADINE	1 (2.6)	2 (12.5)	3 (5.5)
BEPOTASTINE BESILATE	1 (2.6)	1 (6.3)	2 (3.6)
CHLORPHENIRAMINE MALEATE	0	2 (12.5)	2 (3.6)
FEXOFENADINE HYDROCHLORIDE	2 (5.1)	0	2 (3.6)
PENIRAMIN	0	2 (12.5)	2 (3.6)
ADIPAM /00058402/	0	1 (6.3)	1 (1.8)
BEPOTAN	0	1 (6.3)	1 (1.8)
CHLORPHENIRAMINE /00072501/	0	1 (6.3)	1 (1.8)
DEXCHLORPHENIRAMINE MALEATE	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

WHO-DDE Version 01SEP2018 was used to code medications.

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ATC class = Anatomical Therapeutic Chemical class.

Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
EBASTEL	0	1 (6.3)	1 (1.8)
EMEDASTINE DIFUMARATE	0	1 (6.3)	1 (1.8)
EPINASTINE HYDROCHLORIDE	1 (2.6)	0	1 (1.8)
LEVOCETIRIZINE HCL	0	1 (6.3)	1 (1.8)
LORATADINE	0	1 (6.3)	1 (1.8)
MEQUITAZINE	0	1 (6.3)	1 (1.8)
NEORESTAR	1 (2.6)	0	1 (1.8)
OLOPATADINE	0	1 (6.3)	1 (1.8)
PLAKON	0	1 (6.3)	1 (1.8)
POLARAMINE	1 (2.6)	0	1 (1.8)
TALION /01587402/	0	1 (6.3)	1 (1.8)
XYZAL	1 (2.6)	0	1 (1.8)
ANTIINFECTIVES	5 (12.8)	1 (6.3)	6 (10.9)
OFLOXACIN	2 (5.1)	0	2 (3.6)
COLISTIN SODIUM METHANESULFONATE	1 (2.6)	0	1 (1.8)
CRAVIT	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

WHO-DDE Version 01SEP2018 was used to code medications.

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ATC class = Anatomical Therapeutic Chemical class.

Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
LEVOFLOXACIN	1 (2.6)	0	1 (1.8)
LEVOFLOXACIN HYDRATE	1 (2.6)	0	1 (1.8)
TARIVID OTIC	0	1 (6.3)	1 (1.8)
VEGAMOX	1 (2.6)	0	1 (1.8)
ANTIINFLAMMATORY AGENTS	4 (10.3)	0	4 (7.3)
FLUOROMETHOLONE	2 (5.1)	0	2 (3.6)
DICLOD	1 (2.6)	0	1 (1.8)
FLUMETHOLON	1 (2.6)	0	1 (1.8)
NEVANAC	1 (2.6)	0	1 (1.8)
PRANOPROFEN	1 (2.6)	0	1 (1.8)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	15 (38.5)	8 (50.0)	23 (41.8)
LOXOPROFEN SODIUM HYDRATE	4 (10.3)	0	4 (7.3)
CELECOXIB	2 (5.1)	1 (6.3)	3 (5.5)
CAROL-F	0	2 (12.5)	2 (3.6)
LOBU	2 (5.1)	0	2 (3.6)
LOXOPROFEN	1 (2.6)	1 (6.3)	2 (3.6)

SOURCE: Listing 16.2.4.5

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ATC class = Anatomical Therapeutic Chemical class.

Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
NAPROXEN	2 (5.1)	0	2 (3.6)
AIRTAL	0	1 (6.3)	1 (1.8)
ARGININE W/IBUPROFEN	0	1 (6.3)	1 (1.8)
DICLOFENAC SODIUM	1 (2.6)	0	1 (1.8)
HYDROXYCHLOROQUINE	0	1 (6.3)	1 (1.8)
KETOPROFEN	1 (2.6)	0	1 (1.8)
KETOROLAC TROMETHAMINE	0	1 (6.3)	1 (1.8)
LOXONIN	1 (2.6)	0	1 (1.8)
LOXOPROFEN NA	1 (2.6)	0	1 (1.8)
LOXOPROFEN SODIUM	1 (2.6)	0	1 (1.8)
MELOXICAM	0	1 (6.3)	1 (1.8)
MOBIC	0	1 (6.3)	1 (1.8)
NAXEN S	0	1 (6.3)	1 (1.8)
SERACTIL	0	1 (6.3)	1 (1.8)
SOLANTAL	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

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ATC class = Anatomical Therapeutic Chemical class.

Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
VOLTAREN /00372301/	1 (2.6)	0	1 (1.8)
ZALTOPROFEN	0	1 (6.3)	1 (1.8)
ANTIMIGRAINE PREPARATIONS	1 (2.6)	0	1 (1.8)
AMERGE	1 (2.6)	0	1 (1.8)
IMIGRAN /01044801/	1 (2.6)	0	1 (1.8)
MIGSIS	1 (2.6)	0	1 (1.8)
ANTIMYCOTICS FOR SYSTEMIC USE	3 (7.7)	0	3 (5.5)
ITRIZOLE	2 (5.1)	0	2 (3.6)
ITRACONAZOLE	1 (2.6)	0	1 (1.8)
ANTIPROPULSIVES	2 (5.1)	2 (12.5)	4 (7.3)
LOPERAMIDE HYDROCHLORIDE	2 (5.1)	0	2 (3.6)
LOPMIN	0	2 (12.5)	2 (3.6)
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	4 (10.3)	0	4 (7.3)
RESTAMIN KOWA	2 (5.1)	0	2 (3.6)
DIPHENHYDRAMINE	1 (2.6)	0	1 (1.8)
LIDOCAINE	1 (2.6)	0	1 (1.8)
ANTIPSYCHOTICS	0	1 (6.3)	1 (1.8)
OLANZAPINE	0	1 (6.3)	1 (1.8)

SOURCE: Listing 16.2.4.5

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ATC class level 3 WHO-DDE drug name		Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
ANTISEPTICS AND DISINFECTANTS		2 (5.1)	0	2 (3.6)
CADEX	/00082201/	1 (2.6)	0	1 (1.8)
ISODINE	/00080001/	1 (2.6)	0	1 (1.8)
ANTITHROMBOTIC AGENTS		9 (23.1)	3 (18.8)	12 (21.8)
ASPIRIN	/00002701/	2 (5.1)	0	2 (3.6)
HEPARIN SODIUM		1 (2.6)	1 (6.3)	2 (3.6)
RIVAROXABAN		1 (2.6)	1 (6.3)	2 (3.6)
APIXABAN		1 (2.6)	0	1 (1.8)
BAYASPIRIN		1 (2.6)	0	1 (1.8)
GIGKYOTACIN		0	1 (6.3)	1 (1.8)
HEPAFLUSH		1 (2.6)	0	1 (1.8)
HEPARIN NA LOCK		1 (2.6)	0	1 (1.8)
LIXIANA		1 (2.6)	0	1 (1.8)
PRAZAXA		1 (2.6)	0	1 (1.8)
STREPTODORNASE W/STREPTOKINASE		0	1 (6.3)	1 (1.8)
WARFARIN POTASSIUM		1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
ANTIVARICOSE THERAPY	1 (2.6)	0	1 (1.8)
HEPARINOID	1 (2.6)	0	1 (1.8)
ANXIOLYTICS	4 (10.3)	2 (12.5)	6 (10.9)
CERCINE	2 (5.1)	0	2 (3.6)
CLOBAZAM	0	1 (6.3)	1 (1.8)
CLOTIAZEPAM	1 (2.6)	0	1 (1.8)
ETIZOLAM	1 (2.6)	0	1 (1.8)
LORAZEPAM	0	1 (6.3)	1 (1.8)
TOFISOPAM	0	1 (6.3)	1 (1.8)
ASCORBIC ACID (VITAMIN C), INCL. COMBINATIONS	1 (2.6)	0	1 (1.8)
CINAL	1 (2.6)	0	1 (1.8)
BACTERIAL AND VIRAL VACCINES, COMBINED	0	1 (6.3)	1 (1.8)
PENTAXIM	0	1 (6.3)	1 (1.8)
BACTERIAL VACCINES	0	1 (6.3)	1 (1.8)
PREVENAR	0	1 (6.3)	1 (1.8)
BELLADONNA AND DERIVATIVES, PLAIN	2 (5.1)	1 (6.3)	3 (5.5)
SCOPOLAMINE BUTYLBROMIDE	2 (5.1)	0	2 (3.6)
BUSCOPAN	0	1 (6.3)	1 (1.8)

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
BETA BLOCKING AGENTS	3 (7.7)	1 (6.3)	4 (7.3)
BISOPROLOL FUMARATE	2 (5.1)	0	2 (3.6)
AROTINOLOL HYDROCHLORIDE	1 (2.6)	0	1 (1.8)
CARVEDILOL	0	1 (6.3)	1 (1.8)
BETA-LACTAM ANTIBACTERIALS, PENICILLINS	3 (7.7)	3 (18.8)	6 (10.9)
AMOXICILLIN HYDRATE	2 (5.1)	0	2 (3.6)
NAFCILLIN	0	1 (6.3)	1 (1.8)
TAZOCIN	0	1 (6.3)	1 (1.8)
TAZOLACTAM	0	1 (6.3)	1 (1.8)
TAZOPERAN	0	1 (6.3)	1 (1.8)
TAZOPIPE	1 (2.6)	0	1 (1.8)
BILE THERAPY	3 (7.7)	3 (18.8)	6 (10.9)
URSODEOXYCHOLIC ACID	3 (7.7)	0	3 (5.5)
UDCA	0	2 (12.5)	2 (3.6)
URSA	0	1 (6.3)	1 (1.8)
BLOOD AND RELATED PRODUCTS	0	1 (6.3)	1 (1.8)
ALBUMIN	0	1 (6.3)	1 (1.8)

SOURCE: Listing 16.2.4.5

WHO-DDE Version 01SEP2018 was used to code medications.

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ATC class = Anatomical Therapeutic Chemical class.

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	9 (23.1)	2 (12.5)	11 (20.0)
SITAGLIPTIN PHOSPHATE MONOHYDRATE	5 (12.8)	0	5 (9.1)
GLACTIV	1 (2.6)	0	1 (1.8)
GLIMEPIRIDE	1 (2.6)	0	1 (1.8)
GLIMIN	0	1 (6.3)	1 (1.8)
LINAGLIPTIN	1 (2.6)	0	1 (1.8)
METFORMIN	0	1 (6.3)	1 (1.8)
METFORMIN HYDROCHLORIDE	1 (2.6)	0	1 (1.8)
METGLUCO	1 (2.6)	0	1 (1.8)
PIOGLITAZONE	1 (2.6)	0	1 (1.8)
SITAGLIPTIN	0	1 (6.3)	1 (1.8)
SUINY	1 (2.6)	0	1 (1.8)
TENELIGLIPTIN HYDROBROMIDE	1 (2.6)	0	1 (1.8)
TRAZENTA	1 (2.6)	0	1 (1.8)
CALCIUM	1 (2.6)	1 (6.3)	2 (3.6)
CALCIUM W/MAGNESIUM	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
DICAMAX-D	0	1 (6.3)	1 (1.8)
CAPILLARY STABILIZING AGENTS	0	1 (6.3)	1 (1.8)
VENITOL	0	1 (6.3)	1 (1.8)
CARDIOVASCULAR SYSTEM	1 (2.6)	0	1 (1.8)
MYOVIEW /02203201/	1 (2.6)	0	1 (1.8)
CORTICOSTEROIDS FOR SYSTEMIC USE, COMBINATIONS	2 (5.1)	0	2 (3.6)
BETAMETHASONE W/DEXCHLORPHENIRAMINE MALEATE	2 (5.1)	0	2 (3.6)
CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN	6 (15.4)	6 (37.5)	12 (21.8)
PREDNISOLONE	3 (7.7)	3 (18.8)	6 (10.9)
HYDROCORTISONE SODIUM SUCCINATE	2 (5.1)	1 (6.3)	3 (5.5)
CALCORT	0	1 (6.3)	1 (1.8)
HYDROCORTISONE	0	1 (6.3)	1 (1.8)
HYDROCORTISONE SODIUM	0	1 (6.3)	1 (1.8)
METHYLPREDNISOLONE SODIUM SUCCINATE	1 (2.6)	0	1 (1.8)
PREDNIN	1 (2.6)	0	1 (1.8)
TRIAMCINOLONE	0	1 (6.3)	1 (1.8)
CORTICOSTEROIDS, COMBINATIONS WITH ANTIBIOTICS	2 (5.1)	0	2 (3.6)
DERMOSOL G	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

WHO-DDE Version 01SEP2018 was used to code medications.

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ATC class = Anatomical Therapeutic Chemical class.

Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
STRONG RESTAMIN	1 (2.6)	0	1 (1.8)
CORTICOSTEROIDS, PLAIN	13 (33.3)	5 (31.3)	18 (32.7)
ANTEBATE	4 (10.3)	0	4 (7.3)
DERMOVATE	2 (5.1)	1 (6.3)	3 (5.5)
ALMETA	2 (5.1)	0	2 (3.6)
DESOWEN	0	2 (12.5)	2 (3.6)
LACTICARE HC /00028601/	0	2 (12.5)	2 (3.6)
LOCOID	2 (5.1)	0	2 (3.6)
ANFLAVATE	1 (2.6)	0	1 (1.8)
BETAMETHASONE BUTYRATE PROPIONATE	1 (2.6)	0	1 (1.8)
CLOBETASONE BUTYRATE	1 (2.6)	0	1 (1.8)
DESOXYMETHASONE	0	1 (6.3)	1 (1.8)
DIFLUPREDNATE	1 (2.6)	0	1 (1.8)
DRENISON /00182901/	1 (2.6)	0	1 (1.8)
ESPERSON	0	1 (6.3)	1 (1.8)
HYDROCORTISONE	0	1 (6.3)	1 (1.8)

SOURCE: Listing 16.2.4.5

WHO-DDE Version 01SEP2018 was used to code medications.
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
LIDOMEX	1 (2.6)	0	1 (1.8)
METHADERM	1 (2.6)	0	1 (1.8)
METHYLPREDNISOLONE ACEPONATE	0	1 (6.3)	1 (1.8)
MYSER /01249201/	1 (2.6)	0	1 (1.8)
PSOREX	0	1 (6.3)	1 (1.8)
RINDERON DP	1 (2.6)	0	1 (1.8)
RINDERON-V	1 (2.6)	0	1 (1.8)
SOLVEGA	1 (2.6)	0	1 (1.8)
COUGH SUPPRESSANTS AND EXPECTORANTS, COMBINATIONS	0	1 (6.3)	1 (1.8)
COUGH S	0	1 (6.3)	1 (1.8)
COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS	2 (5.1)	2 (12.5)	4 (7.3)
ASVERIN /00465502/	1 (2.6)	0	1 (1.8)
CODEINE	0	1 (6.3)	1 (1.8)
COUGH SYRUP /06155801/	0	1 (6.3)	1 (1.8)
MEDICON /00048102/	1 (2.6)	0	1 (1.8)
DECONGESTANTS AND ANTIALLERGICS	1 (2.6)	1 (6.3)	2 (3.6)
ALESION	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

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ATC class = Anatomical Therapeutic Chemical class.

Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
OLOPATADINE	0	1 (6.3)	1 (1.8)
DECONGESTANTS AND OTHER NASAL PREPARATIONS FOR TOPICAL USE	1 (2.6)	2 (12.5)	3 (5.5)
AVAMYS	0	1 (6.3)	1 (1.8)
AZELASTINE HCL	0	1 (6.3)	1 (1.8)
MOMETASONE FUROATE	0	1 (6.3)	1 (1.8)
NASONEX	1 (2.6)	0	1 (1.8)
DIGESTIVES, INCL. ENZYMES	0	3 (18.8)	3 (5.5)
PHAZYME COMPLEX	0	2 (12.5)	2 (3.6)
BESZYME	0	1 (6.3)	1 (1.8)
DIRECT ACTING ANTIVIRALS	13 (33.3)	1 (6.3)	14 (25.5)
ACICLOVIR	8 (20.5)	0	8 (14.5)
VICCLOX /00587301/	3 (7.7)	0	3 (5.5)
ACLOVA /00587301/	0	1 (6.3)	1 (1.8)
ENTECAVIR MONOHYDRATE	1 (2.6)	0	1 (1.8)
PERAMIVIR	1 (2.6)	0	1 (1.8)
VALGANCICLOVIR HYDROCHLORIDE	1 (2.6)	0	1 (1.8)
VALTREX	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

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Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
XOFLUZA	1 (2.6)	0	1 (1.8)
DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	2 (5.1)	0	2 (3.6)
ACTONEL	1 (2.6)	0	1 (1.8)
SODIUM RISEDRONATE HYDRATE	1 (2.6)	0	1 (1.8)
DRUGS FOR CONSTIPATION	18 (46.2)	2 (12.5)	20 (36.4)
MAGNESIUM OXIDE	10 (25.6)	0	10 (18.2)
MAGMITT	3 (7.7)	0	3 (5.5)
SENNOSIDE /00571901/	3 (7.7)	0	3 (5.5)
BISACODYL	1 (2.6)	0	1 (1.8)
DUPHALAC EASY	0	1 (6.3)	1 (1.8)
GLYCERIN /00200601/	1 (2.6)	0	1 (1.8)
LACTULOSE	0	1 (6.3)	1 (1.8)
LAXOBERON	1 (2.6)	0	1 (1.8)
LUBIPROSTONE	1 (2.6)	0	1 (1.8)
MACROGOL	1 (2.6)	0	1 (1.8)
MAGCOROL P	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
NIFLEC	1 (2.6)	0	1 (1.8)
PICOSULFATE NA	1 (2.6)	0	1 (1.8)
PURSENNID /00571902/	1 (2.6)	0	1 (1.8)
SENNARIDE	1 (2.6)	0	1 (1.8)
SENNOSIDE A+B CALCIUM	1 (2.6)	0	1 (1.8)
SODIUM PICOSULFATE	1 (2.6)	0	1 (1.8)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	4 (10.3)	2 (12.5)	6 (10.9)
DIMETHICONE	2 (5.1)	0	2 (3.6)
BALGIN ANTIFOAMING	1 (2.6)	0	1 (1.8)
BROMOCTYL	0	1 (6.3)	1 (1.8)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDE	0	1 (6.3)	1 (1.8)
GASCON	1 (2.6)	0	1 (1.8)
GLYCOPYRROLATE /00196201/	0	1 (6.3)	1 (1.8)
MENOCTYL	0	1 (6.3)	1 (1.8)
OCTYLONIUM BROMIDE	0	1 (6.3)	1 (1.8)
SPAROD	0	1 (6.3)	1 (1.8)

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Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
TIRAM /01183002/	0	1 (6.3)	1 (1.8)
TIROPRAMIDE HYDROCHLORIDE	0	1 (6.3)	1 (1.8)
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	26 (66.7)	11 (68.8)	37 (67.3)
LANSOPRAZOLE	7 (17.9)	2 (12.5)	9 (16.4)
REBAMIPIDE	5 (12.8)	1 (6.3)	6 (10.9)
NEXIUM /01479302/	3 (7.7)	2 (12.5)	5 (9.1)
RABEPRAZOLE SODIUM	5 (12.8)	0	5 (9.1)
ESOMEPRAZOLE MAGNESIUM	3 (7.7)	0	3 (5.5)
IRSOGLADINE MALEATE	2 (5.1)	1 (6.3)	3 (5.5)
ALBIS D	0	2 (12.5)	2 (3.6)
FAMOTIDINE	1 (2.6)	1 (6.3)	2 (3.6)
MUCOSTA	0	2 (12.5)	2 (3.6)
RABIET	0	2 (12.5)	2 (3.6)
RANITIDINE	0	2 (12.5)	2 (3.6)
AZUNOL /00317302/	1 (2.6)	0	1 (1.8)
CALCIUM CARBONATE W/SODIUM ALGINATE/SODIUM BI	0	1 (6.3)	1 (1.8)

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ATC class level 3 WHO-DDE drug name		Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
CURAN		0	1 (6.3)	1 (1.8)
EUPATILIN		0	1 (6.3)	1 (1.8)
GASTER	/00706001/	0	1 (6.3)	1 (1.8)
LANSOPRAZOLE TEVA		1 (2.6)	0	1 (1.8)
LANSOPRAZOLE TOWA		1 (2.6)	0	1 (1.8)
LANSTON		0	1 (6.3)	1 (1.8)
LANSTON LFDT		0	1 (6.3)	1 (1.8)
OMEPRAZOLE		1 (2.6)	0	1 (1.8)
POLAPREZINC		1 (2.6)	0	1 (1.8)
RABEPRAZOLE NA		1 (2.6)	0	1 (1.8)
STOGAR		0	1 (6.3)	1 (1.8)
TAKECAB		1 (2.6)	0	1 (1.8)
TEPRENONE		1 (2.6)	0	1 (1.8)
ULCERLMIN		0	1 (6.3)	1 (1.8)
ULCERMIN	/00434701/	0	1 (6.3)	1 (1.8)

SOURCE: Listing 16.2.4.5

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ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name		Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY		3 (7.7)	1 (6.3)	4 (7.3)
AVOLVE		1 (2.6)	0	1 (1.8)
FLIVAS		1 (2.6)	0	1 (1.8)
SILODOSIN		1 (2.6)	0	1 (1.8)
TAMSULOSIN		0	1 (6.3)	1 (1.8)
URIEF		1 (2.6)	0	1 (1.8)
EMOLLIENTS AND PROTECTIVES		13 (33.3)	0	13 (23.6)
HIRUDOID		6 (15.4)	0	6 (10.9)
HEPARINOID		5 (12.8)	0	5 (9.1)
WHITE PETROLATUM		2 (5.1)	0	2 (3.6)
BESOFTEN		1 (2.6)	0	1 (1.8)
JUVELA	/00110502/	1 (2.6)	0	1 (1.8)
PETROLATUM		1 (2.6)	0	1 (1.8)
SALICYLIC ACID		1 (2.6)	0	1 (1.8)
UREA		1 (2.6)	0	1 (1.8)
VASELINE	/01007601/	1 (2.6)	0	1 (1.8)

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ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
EXPECTORANTS, EXCL. COMBINATIONS WITH COUGH SUPPRESSANTS	6 (15.4)	4 (25.0)	10 (18.2)
CARBOCISTEINE	2 (5.1)	0	2 (3.6)
ERDOSTEINE	0	2 (12.5)	2 (3.6)
ACETYLCYSTEINE	0	1 (6.3)	1 (1.8)
AMBROXOL	0	1 (6.3)	1 (1.8)
AMBROXOL HYDROCHLORIDE	1 (2.6)	0	1 (1.8)
BISOLVON	1 (2.6)	0	1 (1.8)
MUCODYNE	1 (2.6)	0	1 (1.8)
MUCOMYST /00082801/	0	1 (6.3)	1 (1.8)
RESPLEN	1 (2.6)	0	1 (1.8)
HIGH-CEILING DIURETICS	1 (2.6)	2 (12.5)	3 (5.5)
FUROSEMIDE	0	2 (12.5)	2 (3.6)
AZOSEMIDE	1 (2.6)	0	1 (1.8)
HYPNOTICS AND SEDATIVES	10 (25.6)	3 (18.8)	13 (23.6)
ZOLPIDEM TARTRATE	3 (7.7)	1 (6.3)	4 (7.3)
BROTIZOLAM	2 (5.1)	0	2 (3.6)
ZOLPIDEM	1 (2.6)	1 (6.3)	2 (3.6)

SOURCE: Listing 16.2.4.5

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ATC class = Anatomical Therapeutic Chemical class.

Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
ARON	0	1 (6.3)	1 (1.8)
BELSOMRA	1 (2.6)	0	1 (1.8)
ESZOPICLONE	1 (2.6)	0	1 (1.8)
LUNESTA	1 (2.6)	0	1 (1.8)
MELATONIN	0	1 (6.3)	1 (1.8)
MYSLEE	1 (2.6)	0	1 (1.8)
RAMELTEON	1 (2.6)	0	1 (1.8)
ROZEREM	1 (2.6)	0	1 (1.8)
SUVOREXANT	1 (2.6)	0	1 (1.8)
I.V. SOLUTION ADDITIVES	3 (7.7)	5 (31.3)	8 (14.5)
MAGNESIUM SULFATE	0	3 (18.8)	3 (5.5)
NORMAL SALINE	2 (5.1)	0	2 (3.6)
CALCIUM CHLORIDE	0	1 (6.3)	1 (1.8)
CALCIUM GLUCONATE	0	1 (6.3)	1 (1.8)
KCL	0	1 (6.3)	1 (1.8)
PHOSTEN	0	1 (6.3)	1 (1.8)

SOURCE: Listing 16.2.4.5

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ATC class = Anatomical Therapeutic Chemical class.

Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
SODIUM BICARBONATE	0	1 (6.3)	1 (1.8)
SODIUM CHLORIDE	1 (2.6)	0	1 (1.8)
TAMIPOOL	0	1 (6.3)	1 (1.8)
I.V. SOLUTIONS	5 (12.8)	4 (25.0)	9 (16.4)
BFLUID	3 (7.7)	0	3 (5.5)
ELEJECT	1 (2.6)	0	1 (1.8)
FULCALIQ	1 (2.6)	0	1 (1.8)
KCL	0	1 (6.3)	1 (1.8)
LACTEC G	1 (2.6)	0	1 (1.8)
LIPIDS NOS	0	1 (6.3)	1 (1.8)
NORMAL SALINE	1 (2.6)	0	1 (1.8)
OLIMEL N9E	0	1 (6.3)	1 (1.8)
OMAPONE PERI	0	1 (6.3)	1 (1.8)
POTACOL R	1 (2.6)	0	1 (1.8)
POTASSIUM CHLORIDE	1 (2.6)	0	1 (1.8)
SODIUM CHLORIDE	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

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ATC class level 3 WHO-DDE drug name		Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
SOLDEM 1		1 (2.6)	0	1 (1.8)
IMMUNOGLOBULINS		1 (2.6)	0	1 (1.8)
VENOGLOBULIN IH		1 (2.6)	0	1 (1.8)
IMMUNOSTIMULANTS		15 (38.5)	4 (25.0)	19 (34.5)
FILGRASTIM		6 (15.4)	1 (6.3)	7 (12.7)
FILGRASTIM BS	/06441101/	3 (7.7)	0	3 (5.5)
FILGRASTIM RECOMBINANT		2 (5.1)	0	2 (3.6)
GRASIN		0	2 (12.5)	2 (3.6)
LENOGRASTIM		2 (5.1)	0	2 (3.6)
NEUTROGIN		2 (5.1)	0	2 (3.6)
G LASTA		1 (2.6)	0	1 (1.8)
G-CSF		0	1 (6.3)	1 (1.8)
GRAN		1 (2.6)	0	1 (1.8)
INSULINS AND ANALOGUES		3 (7.7)	3 (18.8)	6 (10.9)
INSULIN HUMAN		2 (5.1)	0	2 (3.6)
NOVORAPID		0	2 (12.5)	2 (3.6)
INSULIN		0	1 (6.3)	1 (1.8)

SOURCE: Listing 16.2.4.5

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ATC class level 3 WHO-DDE drug name		Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
INSULIN ASPART		1 (2.6)	0	1 (1.8)
INSULIN GLARGINE		0	1 (6.3)	1 (1.8)
LANTUS		0	1 (6.3)	1 (1.8)
TOUJEO		0	1 (6.3)	1 (1.8)
INTESTINAL ADSORBENTS		0	3 (18.8)	3 (5.5)
SMECTA	/07327601/	0	2 (12.5)	2 (3.6)
DIOSMECTITE		0	1 (6.3)	1 (1.8)
INTESTINAL ANTIINFECTIVES		0	1 (6.3)	1 (1.8)
NORMIX		0	1 (6.3)	1 (1.8)
IRON PREPARATIONS		2 (5.1)	0	2 (3.6)
FERROUS SODIUM CITRATE		2 (5.1)	0	2 (3.6)
IRRIGATING SOLUTIONS		1 (2.6)	0	1 (1.8)
NORMAL SALINE		1 (2.6)	0	1 (1.8)
LIPID MODIFYING AGENTS, PLAIN		9 (23.1)	1 (6.3)	10 (18.2)
ATORVASTATIN		2 (5.1)	0	2 (3.6)
ATORVASTATIN CALCIUM		1 (2.6)	0	1 (1.8)
BEZAFIBRATE		1 (2.6)	0	1 (1.8)
CRESTOR		1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

WHO-DDE Version 01SEP2018 was used to code medications.

n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
ETHYL ICOSAPENTATE	1 (2.6)	0	1 (1.8)
LIVALO	1 (2.6)	0	1 (1.8)
PRAVASTATIN	1 (2.6)	0	1 (1.8)
PRAVASTATIN SODIUM	1 (2.6)	0	1 (1.8)
SIMVASTATIN	0	1 (6.3)	1 (1.8)
ZETIA	1 (2.6)	0	1 (1.8)
LIVER THERAPY, LIPOTROPICS	1 (2.6)	1 (6.3)	2 (3.6)
HEPA-MERZ /01390204/	0	1 (6.3)	1 (1.8)
HISHIPHAGEN COMBINATION	1 (2.6)	0	1 (1.8)
LOW-CEILING DIURETICS, THIAZIDES	1 (2.6)	0	1 (1.8)
TRICHLORMETHIAZIDE	1 (2.6)	0	1 (1.8)
MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS	1 (2.6)	1 (6.3)	2 (3.6)
BACLOFEN	0	1 (6.3)	1 (1.8)
EPERISONE HYDROCHLORIDE	1 (2.6)	0	1 (1.8)
EXOPERINE	0	1 (6.3)	1 (1.8)
MUSCLE RELAXANTS, PERIPHERALLY ACTING AGENTS	0	1 (6.3)	1 (1.8)
ROCUMERON	0	1 (6.3)	1 (1.8)

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
MYDRIATICS AND CYCLOPLEGICS	1 (2.6)	0	1 (1.8)
MYDRIN-P	1 (2.6)	0	1 (1.8)
NASAL DECONGESTANTS FOR SYSTEMIC USE	1 (2.6)	2 (12.5)	3 (5.5)
ACTIFED /00005601/	0	1 (6.3)	1 (1.8)
ALLEGRA D	0	1 (6.3)	1 (1.8)
CONTAC 600 PLUS	1 (2.6)	0	1 (1.8)
PSEUDOEPHEDRINE	0	1 (6.3)	1 (1.8)
OPIOIDS	8 (20.5)	8 (50.0)	16 (29.1)
TRAMAL	3 (7.7)	0	3 (5.5)
TRAMCET	3 (7.7)	0	3 (5.5)
TARGIN	0	2 (12.5)	2 (3.6)
ULTRACET SEMI	0	2 (12.5)	2 (3.6)
DUROGESIC	0	1 (6.3)	1 (1.8)
FENTORA	0	1 (6.3)	1 (1.8)
IRCODON	0	1 (6.3)	1 (1.8)
MORPHINE	0	1 (6.3)	1 (1.8)
NUCYNTA ER	0	1 (6.3)	1 (1.8)

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
OXYCODONE	0	1 (6.3)	1 (1.8)
OXYCODONE HYDROCHLORIDE	1 (2.6)	0	1 (1.8)
PABRON S ALPHA	1 (2.6)	0	1 (1.8)
TACOPEN	0	1 (6.3)	1 (1.8)
TRIDOL	0	1 (6.3)	1 (1.8)
ULTRACET	0	1 (6.3)	1 (1.8)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	7 (17.9)	1 (6.3)	8 (14.5)
MIYA-BM	6 (15.4)	0	6 (10.9)
POLAPREZINC	1 (2.6)	1 (6.3)	2 (3.6)
OTHER ANALGESICS AND ANTIPYRETICS	22 (56.4)	4 (25.0)	26 (47.3)
ACETAMINOPHEN	8 (20.5)	4 (25.0)	12 (21.8)
CALONAL	8 (20.5)	0	8 (14.5)
LYRICA OD	3 (7.7)	0	3 (5.5)
CYMBALTA	1 (2.6)	1 (6.3)	2 (3.6)
BUFFERIN A /01754001/	1 (2.6)	0	1 (1.8)
DENOGAN	0	1 (6.3)	1 (1.8)

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ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
GABAPENTIN	0	1 (6.3)	1 (1.8)
PL	1 (2.6)	0	1 (1.8)
PREGABALIN	1 (2.6)	0	1 (1.8)
PROPACETAMOL HYDROCHLORIDE	0	1 (6.3)	1 (1.8)
OTHER ANTIANEMIC PREPARATIONS	0	3 (18.8)	3 (5.5)
NESP	0	3 (18.8)	3 (5.5)
OTHER ANTIBACTERIALS	0	3 (18.8)	3 (5.5)
METRONIDAZOLE	0	2 (12.5)	2 (3.6)
FLASINYL	0	1 (6.3)	1 (1.8)
TEICONIN	0	1 (6.3)	1 (1.8)
OTHER BETA-LACTAM ANTIBACTERIALS	6 (15.4)	5 (31.3)	11 (20.0)
CEFDINIR	2 (5.1)	1 (6.3)	3 (5.5)
CEFCAPENE PIVOXIL HYDROCHLORIDE	2 (5.1)	0	2 (3.6)
CEFPODOXIME	0	2 (12.5)	2 (3.6)
CEFACLOR	0	1 (6.3)	1 (1.8)
CEFDITOREN PIVOXIL	0	1 (6.3)	1 (1.8)
CEFEPIME DIHYDROCHLORIDE	1 (2.6)	0	1 (1.8)

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Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
CEFEPIME HCL	0	1 (6.3)	1 (1.8)
CEFTRIAXONE	0	1 (6.3)	1 (1.8)
CEPHRADINE MONOHYDRATE	0	1 (6.3)	1 (1.8)
FAROPENEM SODIUM	1 (2.6)	0	1 (1.8)
MAXIPIME	1 (2.6)	0	1 (1.8)
MEIACT MS	1 (2.6)	0	1 (1.8)
MEROPEN /01250501/	0	1 (6.3)	1 (1.8)
MEROPENEM	1 (2.6)	0	1 (1.8)
OTHER CARDIAC PREPARATIONS	1 (2.6)	0	1 (1.8)
ADENOSINE	1 (2.6)	0	1 (1.8)
OTHER COLD PREPARATIONS	1 (2.6)	0	1 (1.8)
OTHER COLD PREPARATIONS	1 (2.6)	0	1 (1.8)
OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS	0	1 (6.3)	1 (1.8)
ATROVENT UDV	0	1 (6.3)	1 (1.8)
OTHER HEMATOLOGICAL AGENTS	2 (5.1)	0	2 (3.6)
PRONASE	1 (2.6)	0	1 (1.8)
PRONASE MS	1 (2.6)	0	1 (1.8)

SOURCE: Listing 16.2.4.5

WHO-DDE Version 01SEP2018 was used to code medications.

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ATC class = Anatomical Therapeutic Chemical class.

Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
OTHER MINERAL SUPPLEMENTS	3 (7.7)	4 (25.0)	7 (12.7)
MAGNESIUM OXIDE	0	2 (12.5)	2 (3.6)
SODIUM CHLORIDE	2 (5.1)	0	2 (3.6)
JOULIE SOL	0	1 (6.3)	1 (1.8)
MAGMITT	1 (2.6)	0	1 (1.8)
MAGNESIUM LACTATE W/PYRIDOXINE HYDROCHLORIDE	0	1 (6.3)	1 (1.8)
MAGO /07349401/	0	1 (6.3)	1 (1.8)
ZINC SULFATE HEPTAHYDRATE	0	1 (6.3)	1 (1.8)
OTHER NUTRIENTS	0	4 (25.0)	4 (7.3)
ENCOVER	0	3 (18.8)	3 (5.5)
WINUF PERI	0	1 (6.3)	1 (1.8)
OTHER OPHTHALMOLOGICALS	5 (12.8)	1 (6.3)	6 (10.9)
KARY UNI /00528801/	2 (5.1)	0	2 (3.6)
SODIUM HYALURONATE	2 (5.1)	0	2 (3.6)
CYANOCOBALAMIN	1 (2.6)	0	1 (1.8)
DIQUAS	1 (2.6)	0	1 (1.8)
LANOLIN ANHYDROUS	0	1 (6.3)	1 (1.8)

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
OTHER OTOLOGICALS	1 (2.6)	0	1 (1.8)
GLYCERIN /00200601/	1 (2.6)	0	1 (1.8)
SODIUM BICARBONATE	1 (2.6)	0	1 (1.8)
OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0	1 (6.3)	1 (1.8)
LUKIO	0	1 (6.3)	1 (1.8)
OTHER VITAMIN PRODUCTS, COMBINATIONS	2 (5.1)	0	2 (3.6)
HERBAL NOS W/VITAMINS NOS	1 (2.6)	0	1 (1.8)
VITAMINS, OTHER COMBINATIONS	1 (2.6)	0	1 (1.8)
PARASYMPATHOMIMETICS	0	2 (12.5)	2 (3.6)
BETHANECHOL	0	1 (6.3)	1 (1.8)
PYRIDOSTIGMINE BROMIDE	0	1 (6.3)	1 (1.8)
PERIPHERAL VASODILATORS	2 (5.1)	0	2 (3.6)
PLETAAL	1 (2.6)	0	1 (1.8)
PRORENAL	1 (2.6)	0	1 (1.8)
POTASSIUM	4 (10.3)	1 (6.3)	5 (9.1)
POTASSIUM ASPARTATE	2 (5.1)	0	2 (3.6)
K-CONTIN	0	1 (6.3)	1 (1.8)
KCL	0	1 (6.3)	1 (1.8)

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ATC class level 3 WHO-DDE drug name		Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
POTASSIUM CHLORIDE		1 (2.6)	0	1 (1.8)
SLOW-K		1 (2.6)	0	1 (1.8)
POTASSIUM-SPARING AGENTS		1 (2.6)	0	1 (1.8)
SPIRONOLACTONE		1 (2.6)	0	1 (1.8)
PROGESTOGENS		0	1 (6.3)	1 (1.8)
MEGESTROL		0	1 (6.3)	1 (1.8)
PROPULSIVES		7 (17.9)	4 (25.0)	11 (20.0)
PRAMIEL	/00041901/	2 (5.1)	0	2 (3.6)
PRIMPERAN		2 (5.1)	0	2 (3.6)
TERPERAN		2 (5.1)	0	2 (3.6)
ACOTIAMIDE HYDROCHLORIDE		1 (2.6)	0	1 (1.8)
ITOPRIDE		0	1 (6.3)	1 (1.8)
ITOPRIDE HCL		0	1 (6.3)	1 (1.8)
MACPERAN		0	1 (6.3)	1 (1.8)
MECOOL		0	1 (6.3)	1 (1.8)
METOCLOPRAMIDE		1 (2.6)	0	1 (1.8)
METOCLOPRAMIDE HCL		0	1 (6.3)	1 (1.8)

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
QUINOLONE ANTIBACTERIALS	1 (2.6)	4 (25.0)	5 (9.1)
CRAVIT	0	2 (12.5)	2 (3.6)
LEVOPLUS /01278901/	0	1 (6.3)	1 (1.8)
MOXIFLOXACIN	0	1 (6.3)	1 (1.8)
TOSUFLOXACIN TOSILATE MONOHYDRATE	1 (2.6)	0	1 (1.8)
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS	0	1 (6.3)	1 (1.8)
DILTIAZEM	0	1 (6.3)	1 (1.8)
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS	9 (23.1)	1 (6.3)	10 (18.2)
AMLODIPINE	4 (10.3)	0	4 (7.3)
AMLODIPINE BESILATE	3 (7.7)	0	3 (5.5)
AMLODIN	1 (2.6)	0	1 (1.8)
AMODIPIN	0	1 (6.3)	1 (1.8)
NIFEDIPINE	1 (2.6)	0	1 (1.8)
STOMATOLOGICAL PREPARATIONS	9 (23.1)	1 (6.3)	10 (18.2)
AZUNOL GARGLE LIQUID	4 (10.3)	0	4 (7.3)
SODIUM GUALENATE HYDRATE	2 (5.1)	0	2 (3.6)
BENZYDAMINE HCL	0	1 (6.3)	1 (1.8)

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
ISOTONIC SODIUM CHLORIDE SOLUTION	1 (2.6)	0	1 (1.8)
LIDOCAINE HCL	0	1 (6.3)	1 (1.8)
NYSTATIN	0	1 (6.3)	1 (1.8)
POVIDONE-IODINE	1 (2.6)	0	1 (1.8)
SODIUM CHLORIDE	1 (2.6)	0	1 (1.8)
SULFONAMIDES AND TRIMETHOPRIM	19 (48.7)	2 (12.5)	21 (38.2)
DAIPHEN	11 (28.2)	0	11 (20.0)
BACTRAMIN	4 (10.3)	0	4 (7.3)
BAKTAR	4 (10.3)	0	4 (7.3)
SEPTRIN	0	1 (6.3)	1 (1.8)
SULFAMETHOXAZOLE W/TRIMETHOPRIM	0	1 (6.3)	1 (1.8)
THROAT PREPARATIONS	3 (7.7)	0	3 (5.5)
AZ COMBINATION	1 (2.6)	0	1 (1.8)
NEOSTELIN GREEN	1 (2.6)	0	1 (1.8)
SODIUM BICARBONATE W/SODIUM GUALENATE HYDRATE	1 (2.6)	0	1 (1.8)
THYROID PREPARATIONS	2 (5.1)	1 (6.3)	3 (5.5)
LEVOTHYROXINE	0	1 (6.3)	1 (1.8)

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
LEVOTHYROXINE SODIUM	1 (2.6)	0	1 (1.8)
THYRADIN	1 (2.6)	0	1 (1.8)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	8 (20.5)	2 (12.5)	10 (18.2)
KETOPROFEN	4 (10.3)	0	4 (7.3)
BENZYDAMINE HYDROCHLORIDE	0	1 (6.3)	1 (1.8)
FELBINAC PAP	1 (2.6)	0	1 (1.8)
LOXONIN	1 (2.6)	0	1 (1.8)
LOXOPROFEN SODIUM HYDRATE	1 (2.6)	0	1 (1.8)
MOHRUS	1 (2.6)	0	1 (1.8)
PIROXICAM	0	1 (6.3)	1 (1.8)
SUMILU STICK	1 (2.6)	0	1 (1.8)
ZEPOLAS	1 (2.6)	0	1 (1.8)
UROLOGICALS	2 (5.1)	0	2 (3.6)
SOLIFENACIN SUCCINATE	1 (2.6)	0	1 (1.8)
TOVIAZ	1 (2.6)	0	1 (1.8)
VASODILATORS USED IN CARDIAC DISEASES	2 (5.1)	0	2 (3.6)
ISOSORBIDE MONONITRATE	1 (2.6)	0	1 (1.8)

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
NITOROL	1 (2.6)	0	1 (1.8)
NITROGLYCERIN	1 (2.6)	0	1 (1.8)
VIRAL VACCINES	1 (2.6)	1 (6.3)	2 (3.6)
INFLUENZA HA VACCINE	1 (2.6)	0	1 (1.8)
INFLUENZA VACCINE INACT SAG 4V	0	1 (6.3)	1 (1.8)
VITAMIN A AND D, INCL. COMBINATIONS OF THE TWO	2 (5.1)	0	2 (3.6)
EDIROL	2 (5.1)	0	2 (3.6)
VITAMIN B-COMPLEX, INCL. COMBINATIONS	1 (2.6)	1 (6.3)	2 (3.6)
ASCORBIC ACID W/VITAMIN B NOS	0	1 (6.3)	1 (1.8)
EBIOS	1 (2.6)	0	1 (1.8)
VITAMIN B12 AND FOLIC ACID	7 (17.9)	1 (6.3)	8 (14.5)
MECOBALAMIN	5 (12.8)	0	5 (9.1)
METHYCOBAL	2 (5.1)	0	2 (3.6)
FOLIC ACID	0	1 (6.3)	1 (1.8)
VITAMIN K AND OTHER HEMOSTATICS	0	1 (6.3)	1 (1.8)
ROMIPLATE	0	1 (6.3)	1 (1.8)
VITAMIN K1	0	1 (6.3)	1 (1.8)

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ATC class level 3 WHO-DDE drug name	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
X-RAY CONTRAST MEDIA, IODINATED	21 (53.8)	0	21 (38.2)
OMNIPAQUE	8 (20.5)	0	8 (14.5)
IOPAMIDOL	6 (15.4)	0	6 (10.9)
IOPAMIRON	5 (12.8)	0	5 (9.1)
IOHEXOL	4 (10.3)	0	4 (7.3)
IOMEPROL	2 (5.1)	0	2 (3.6)
IOMERON	2 (5.1)	0	2 (3.6)
IOPAQUE	2 (5.1)	0	2 (3.6)
OPTIRAY	1 (2.6)	0	1 (1.8)
ATC Class Level 3 not Available	9 (23.1)	10 (62.5)	19 (34.5)
MEGESTROL	0	5 (31.3)	5 (9.1)
HERBAL PREPARATION	1 (2.6)	2 (12.5)	3 (5.5)
MEGACE F	0	3 (18.8)	3 (5.5)
DIAMOX /00016901/	2 (5.1)	0	2 (3.6)
SHAKUYAKUKANZOTO	2 (5.1)	0	2 (3.6)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	2 (5.1)	0	2 (3.6)

SOURCE: Listing 16.2.4.5

WHO-DDE Version 01SEP2018 was used to code medications.

n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;

ATC class = Anatomical Therapeutic Chemical class.

Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name		Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
ADJUST-A		1 (2.6)	0	1 (1.8)
ALOSENN	/00476901/	1 (2.6)	0	1 (1.8)
DAIKENCHUTO		1 (2.6)	0	1 (1.8)
HOCHUEKKITO	/07973001/	1 (2.6)	0	1 (1.8)
JUVELA	/00526901/	1 (2.6)	0	1 (1.8)
LEGALON		0	1 (6.3)	1 (1.8)
MEGACE		0	1 (6.3)	1 (1.8)
MEGESTROL ACETATE		0	1 (6.3)	1 (1.8)
SILYMARIN	/01131701/	0	1 (6.3)	1 (1.8)

SOURCE: Listing 16.2.4.5

WHO-DDE Version 01SEP2018 was used to code medications.
n = number of subjects; % = percentages are calculated based on the number of subjects in the respective country within the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

表 2.7.4.7-18　併用薬（201 試験）（安全性解析対象集団）

ATC class level 3 WHO-DDE drug name		30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Number of patients with at least one concomitant medication		7 (100.0%)	7 (100.0%)	14 (100.0%)
STOMATOLOGICAL PREPARATIONS		1 (14.3%)	1 (14.3%)	2 (14.3%)
XYLOCAINE	/00033401/	1 (14.3%)	0 (0.0%)	1 (7.1%)
GLYCERIN	/00200601/	1 (14.3%)	0 (0.0%)	1 (7.1%)
SODIUM GUALENATE HYDRATE		1 (14.3%)	1 (14.3%)	2 (14.3%)
TETRACYCLINE PRESTERON		1 (14.3%)	0 (0.0%)	1 (7.1%)
ANTACIDS		1 (14.3%)	2 (28.6%)	3 (21.4%)
MACMET	/00091001/	0 (0.0%)	1 (14.3%)	1 (7.1%)
MAGMITT		1 (14.3%)	1 (14.3%)	2 (14.3%)
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFL		3 (42.9%)	6 (85.7%)	9 (64.3%)
AZUNOL	/00317302/	1 (14.3%)	0 (0.0%)	1 (7.1%)
ISALON		0 (0.0%)	1 (14.3%)	1 (7.1%)
HACHIAZULE	/00523101/	1 (14.3%)	0 (0.0%)	1 (7.1%)
OMEPRAZOLE		1 (14.3%)	0 (0.0%)	1 (7.1%)
FAMOTIDINE		0 (0.0%)	2 (28.6%)	2 (14.3%)
TEPRENONE		1 (14.3%)	0 (0.0%)	1 (7.1%)
SELBEX		1 (14.3%)	0 (0.0%)	1 (7.1%)
REBAMIPIDE		1 (14.3%)	0 (0.0%)	1 (7.1%)
LANSOPRAZOLE		1 (14.3%)	1 (14.3%)	2 (14.3%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

ATC class level 3 WHO-DDE drug name		30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
LANSOPRAZOLE TOWA		0 (0.0%)	1 (14.3%)	1 (7.1%)
ESOMEPRAZOLE		1 (14.3%)	0 (0.0%)	1 (7.1%)
ESOMEPRAZOLE MAGNESIUM		0 (0.0%)	1 (14.3%)	1 (7.1%)
PROPULSIVES		1 (14.3%)	1 (14.3%)	2 (14.3%)
METOCLOPRAMIDE		0 (0.0%)	1 (14.3%)	1 (7.1%)
MOSAPRIDE CITRATE		1 (14.3%)	0 (0.0%)	1 (7.1%)
ANTIEMETICS AND ANTINAUSEANTS		1 (14.3%)	1 (14.3%)	2 (14.3%)
PROCHLORPERAZINE MALEATE		1 (14.3%)	0 (0.0%)	1 (7.1%)
GRANISETRON HYDROCHLORIDE		0 (0.0%)	1 (14.3%)	1 (7.1%)
BILE THERAPY		0 (0.0%)	1 (14.3%)	1 (7.1%)
URSODEOXYCHOLIC ACID		0 (0.0%)	1 (14.3%)	1 (7.1%)
LIVER THERAPY, LIPOTROPICS		0 (0.0%)	1 (14.3%)	1 (7.1%)
GLYCYRRHIZIC ACID		0 (0.0%)	1 (14.3%)	1 (7.1%)
DRUGS FOR CONSTIPATION		2 (28.6%)	4 (57.1%)	6 (42.9%)
POLYCARBOPHIL CALCIUM		0 (0.0%)	1 (14.3%)	1 (7.1%)
SENNOSIDE	/00571901/	0 (0.0%)	1 (14.3%)	1 (7.1%)
PURSENNIDE	/00571901/	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

ATC class level 3 WHO-DDE drug name	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
SENNOSIDE A+B CALCIUM	0 (0.0%)	2 (28.6%)	2 (14.3%)
MAGNESIUM OXIDE	1 (14.3%)	1 (14.3%)	2 (14.3%)
MAGLAX	0 (0.0%)	1 (14.3%)	1 (7.1%)
DAIKENCHUTO	0 (0.0%)	1 (14.3%)	1 (7.1%)
ANTIDIARRHEAL MICROORGANISMS	0 (0.0%)	3 (42.9%)	3 (21.4%)
ANTIBIOTICS-RESISTANT LACTIC ACID BACTERIAE	0 (0.0%)	1 (14.3%)	1 (7.1%)
BIO-THREE	0 (0.0%)	2 (28.6%)	2 (14.3%)
OTHER ANTIDIARRHEALS	0 (0.0%)	1 (14.3%)	1 (7.1%)
ALBUMIN TANNATE	0 (0.0%)	1 (14.3%)	1 (7.1%)
INSULINS AND ANALOGUES	0 (0.0%)	2 (28.6%)	2 (14.3%)
INSULIN HUMAN	0 (0.0%)	1 (14.3%)	1 (7.1%)
HUMULIN R	0 (0.0%)	1 (14.3%)	1 (7.1%)
TRESIBA	0 (0.0%)	1 (14.3%)	1 (7.1%)
BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	1 (14.3%)	2 (28.6%)	3 (21.4%)
METGLUCO	0 (0.0%)	1 (14.3%)	1 (7.1%)
GLIMEPIRIDE	0 (0.0%)	1 (14.3%)	1 (7.1%)
EQUA	0 (0.0%)	1 (14.3%)	1 (7.1%)
SITAGLIPTIN PHOSPHATE MONOHYDRATE	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

ATC class level 3 WHO-DDE drug name	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
GLACTIV	0 (0.0%)	1 (14.3%)	1 (7.1%)
VITAMIN B1, PLAIN AND IN COMBINATION WITH VITAMIN	1 (14.3%)	0 (0.0%)	1 (7.1%)
ALINAMIN F /00257801/	1 (14.3%)	0 (0.0%)	1 (7.1%)
OTHER PLAIN VITAMIN PREPARATIONS	1 (14.3%)	1 (14.3%)	2 (14.3%)
PANTETHINE	1 (14.3%)	1 (14.3%)	2 (14.3%)
OTHER VITAMIN PRODUCTS, COMBINATIONS	1 (14.3%)	0 (0.0%)	1 (7.1%)
VITAMEDIN /00274301/	1 (14.3%)	0 (0.0%)	1 (7.1%)
CALCIUM	0 (0.0%)	2 (28.6%)	2 (14.3%)
CALCIUM LACTATE	0 (0.0%)	1 (14.3%)	1 (7.1%)
CALCIUM L-ASPARTATE	0 (0.0%)	1 (14.3%)	1 (7.1%)
POTASSIUM	1 (14.3%)	0 (0.0%)	1 (7.1%)
POTASSIUM CHLORIDE	1 (14.3%)	0 (0.0%)	1 (7.1%)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	1 (14.3%)	2 (28.6%)	3 (21.4%)
CLOSTRIDIUM BUTYRICUM	1 (14.3%)	1 (14.3%)	2 (14.3%)
GLYCINE	0 (0.0%)	1 (14.3%)	1 (7.1%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

ATC class level 3 WHO-DDE drug name	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
ANTITHROMBOTIC AGENTS	2 (28.6%)	1 (14.3%)	3 (21.4%)
BAYASPIRIN	0 (0.0%)	1 (14.3%)	1 (7.1%)
HEPARIN SODIUM	1 (14.3%)	0 (0.0%)	1 (7.1%)
HEPAFLUSH	1 (14.3%)	0 (0.0%)	1 (7.1%)
VITAMIN B12 AND FOLIC ACID	1 (14.3%)	0 (0.0%)	1 (7.1%)
MECOBALAMIN	1 (14.3%)	0 (0.0%)	1 (7.1%)
I.V. SOLUTIONS	0 (0.0%)	1 (14.3%)	1 (7.1%)
HARTMAN G-3	0 (0.0%)	1 (14.3%)	1 (7.1%)
REPLAS	0 (0.0%)	1 (14.3%)	1 (7.1%)
LACTATE RINGER	0 (0.0%)	1 (14.3%)	1 (7.1%)
HIGH-CEILING DIURETICS	1 (14.3%)	0 (0.0%)	1 (7.1%)
FUROSEMIDE	1 (14.3%)	0 (0.0%)	1 (7.1%)
POTASSIUM-SPARING AGENTS	2 (28.6%)	0 (0.0%)	2 (14.3%)
SPIRONOLACTONE	1 (14.3%)	0 (0.0%)	1 (7.1%)
ALDACTONE A	1 (14.3%)	0 (0.0%)	1 (7.1%)
AGENTS FOR TREATMENT OF HEMORRHOIDS AND ANAL FISSU	1 (14.3%)	0 (0.0%)	1 (7.1%)
HYDROCORTISONE ACETATE	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

ATC class level 3 WHO-DDE drug name	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
ESCHERICHIA COLI	1 (14.3%)	0 (0.0%)	1 (7.1%)
NERIPROCT	1 (14.3%)	0 (0.0%)	1 (7.1%)
BORRAZA G	1 (14.3%)	0 (0.0%)	1 (7.1%)
POSTERISAN FORTE /01567801/	1 (14.3%)	0 (0.0%)	1 (7.1%)
ANTIVARICOSE THERAPY	0 (0.0%)	1 (14.3%)	1 (7.1%)
HEPARINOID	0 (0.0%)	1 (14.3%)	1 (7.1%)
BETA BLOCKING AGENTS	2 (28.6%)	0 (0.0%)	2 (14.3%)
TENORMIN	2 (28.6%)	0 (0.0%)	2 (14.3%)
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VAS	2 (28.6%)	2 (28.6%)	4 (28.6%)
AMLODIPINE BESILATE	1 (14.3%)	2 (28.6%)	3 (21.4%)
NORVASC	2 (28.6%)	0 (0.0%)	2 (14.3%)
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CAR	0 (0.0%)	1 (14.3%)	1 (7.1%)
DILTIAZEM HYDROCHLORIDE R	0 (0.0%)	1 (14.3%)	1 (7.1%)
ACE INHIBITORS, PLAIN	1 (14.3%)	0 (0.0%)	1 (7.1%)
LONGES	1 (14.3%)	0 (0.0%)	1 (7.1%)
ANGIOTENSIN II ANTAGONISTS, PLAIN	1 (14.3%)	1 (14.3%)	2 (14.3%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

ATC class level 3 WHO-DDE drug name	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
CANDESARTAN CILEXETIL	0 (0.0%)	1 (14.3%)	1 (7.1%)
BLOPRESS	1 (14.3%)	0 (0.0%)	1 (7.1%)
LIPID MODIFYING AGENTS, PLAIN	0 (0.0%)	2 (28.6%)	2 (14.3%)
BEZAFIBRATE	0 (0.0%)	1 (14.3%)	1 (7.1%)
CRESTOR	0 (0.0%)	1 (14.3%)	1 (7.1%)
EMOLLIENTS AND PROTECTIVES	2 (28.6%)	1 (14.3%)	3 (21.4%)
UREPEARL	1 (14.3%)	0 (0.0%)	1 (7.1%)
HEPARINOID	1 (14.3%)	1 (14.3%)	2 (14.3%)
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS,	1 (14.3%)	1 (14.3%)	2 (14.3%)
DIPHENHYDRAMINE	0 (0.0%)	1 (14.3%)	1 (7.1%)
RESTAMIN /00000401/	1 (14.3%)	0 (0.0%)	1 (7.1%)
ANTIBIOTICS FOR TOPICAL USE	0 (0.0%)	1 (14.3%)	1 (7.1%)
GENTAMICIN SULFATE	0 (0.0%)	1 (14.3%)	1 (7.1%)
CHEMOTHERAPEUTICS FOR TOPICAL USE	1 (14.3%)	0 (0.0%)	1 (7.1%)
METRONIDAZOLE	1 (14.3%)	0 (0.0%)	1 (7.1%)
SULFADIAZINE SILVER	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

ATC class level 3 WHO-DDE drug name	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
CORTICOSTEROIDS, PLAIN	3 (42.9%)	1 (14.3%)	4 (28.6%)
BETAMETHASONE	1 (14.3%)	0 (0.0%)	1 (7.1%)
BETAMETHASONE BUTYRATE PROPIONATE	1 (14.3%)	0 (0.0%)	1 (7.1%)
ANTEBATE	1 (14.3%)	0 (0.0%)	1 (7.1%)
DIFLUPREDNATE	0 (0.0%)	1 (14.3%)	1 (7.1%)
DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY	1 (14.3%)	0 (0.0%)	1 (7.1%)
TAMSULOSIN HCL	1 (14.3%)	0 (0.0%)	1 (7.1%)
CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN	1 (14.3%)	1 (14.3%)	2 (14.3%)
PREDNISOLONE	0 (0.0%)	1 (14.3%)	1 (7.1%)
KENALOG IN ORABASE	1 (14.3%)	0 (0.0%)	1 (7.1%)
THYROID PREPARATIONS	1 (14.3%)	0 (0.0%)	1 (7.1%)
LEVOTHYROXINE SODIUM	1 (14.3%)	0 (0.0%)	1 (7.1%)
OTHER BETA-LACTAM ANTIBACTERIALS	0 (0.0%)	3 (42.9%)	3 (21.4%)
CEFPODOXIME PROXETIL	0 (0.0%)	1 (14.3%)	1 (7.1%)
CEFDINIR	0 (0.0%)	1 (14.3%)	1 (7.1%)
MEROPENEM	0 (0.0%)	1 (14.3%)	1 (7.1%)
CEFCAPENE PIVOXIL HYDROCHLORIDE	0 (0.0%)	1 (14.3%)	1 (7.1%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

ATC class level 3 WHO-DDE drug name	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
SULFONAMIDES AND TRIMETHOPRIM	0 (0.0%)	1 (14.3%)	1 (7.1%)
SULFAMETHOXAZOLE	0 (0.0%)	1 (14.3%)	1 (7.1%)
BACTRAMIN	0 (0.0%)	1 (14.3%)	1 (7.1%)
TRIMETHOPRIM	0 (0.0%)	1 (14.3%)	1 (7.1%)
ANTIMYCOTICS FOR SYSTEMIC USE	0 (0.0%)	3 (42.9%)	3 (21.4%)
AMPHOTERICIN B	0 (0.0%)	1 (14.3%)	1 (7.1%)
MYCOSYST	0 (0.0%)	1 (14.3%)	1 (7.1%)
MICAFUNGIN SODIUM	0 (0.0%)	1 (14.3%)	1 (7.1%)
DIRECT ACTING ANTIVIRALS	1 (14.3%)	2 (28.6%)	3 (21.4%)
ACICLOVIR	1 (14.3%)	2 (28.6%)	3 (21.4%)
IMMUNOSTIMULANTS	0 (0.0%)	2 (28.6%)	2 (14.3%)
FILGRASTIM	0 (0.0%)	1 (14.3%)	1 (7.1%)
GRAN	0 (0.0%)	1 (14.3%)	1 (7.1%)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-S	0 (0.0%)	4 (57.1%)	4 (28.6%)
FLURBIPROFEN AXETIL	0 (0.0%)	1 (14.3%)	1 (7.1%)
LOBU	0 (0.0%)	1 (14.3%)	1 (7.1%)
LOXOPROFEN SODIUM HYDRATE	0 (0.0%)	2 (28.6%)	2 (14.3%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

ATC class level 3 WHO-DDE drug name	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	1 (14.3%)	0 (0.0%)	1 (7.1%)
MOHRUS	1 (14.3%)	0 (0.0%)	1 (7.1%)
ANTIGOUT PREPARATIONS	4 (57.1%)	1 (14.3%)	5 (35.7%)
ALLOPURINOL	1 (14.3%)	0 (0.0%)	1 (7.1%)
SALOBEL	0 (0.0%)	1 (14.3%)	1 (7.1%)
FEBUXOSTAT	1 (14.3%)	0 (0.0%)	1 (7.1%)
FEBURIC	2 (28.6%)	0 (0.0%)	2 (14.3%)
DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	0 (0.0%)	1 (14.3%)	1 (7.1%)
ALENDRONATE SODIUM HYDRATE	0 (0.0%)	1 (14.3%)	1 (7.1%)
ANESTHETICS, LOCAL	0 (0.0%)	1 (14.3%)	1 (7.1%)
LIDOCAINE HYDROCHLORIDE MONOHYDRATE	0 (0.0%)	1 (14.3%)	1 (7.1%)
OTHER ANALGESICS AND ANTIPYRETICS	3 (42.9%)	2 (28.6%)	5 (35.7%)
ACETAMINOPHEN	3 (42.9%)	0 (0.0%)	3 (21.4%)
CALONAL	0 (0.0%)	2 (28.6%)	2 (14.3%)
CAFFEINE W/PARACETAMOL/PROMETHAZINE/SALICYLAM	0 (0.0%)	1 (14.3%)	1 (7.1%)
ANXIOLYTICS	0 (0.0%)	1 (14.3%)	1 (7.1%)
ETIZOLAM	0 (0.0%)	1 (14.3%)	1 (7.1%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

ATC class level 3 WHO-DDE drug name	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
HYPNOTICS AND SEDATIVES	2 (28.6%)	2 (28.6%)	4 (28.6%)
NITRAZEPAM	1 (14.3%)	0 (0.0%)	1 (7.1%)
SILECE	0 (0.0%)	1 (14.3%)	1 (7.1%)
ESTAZOLAM	0 (0.0%)	1 (14.3%)	1 (7.1%)
ZOPICLONE	1 (14.3%)	0 (0.0%)	1 (7.1%)
ZOLPIDEM TARTRATE	1 (14.3%)	1 (14.3%)	2 (14.3%)
MYSLEE	1 (14.3%)	0 (0.0%)	1 (7.1%)
ANTI-DEMENTIA DRUGS	0 (0.0%)	1 (14.3%)	1 (7.1%)
ARICEPT	0 (0.0%)	1 (14.3%)	1 (7.1%)
AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISE	0 (0.0%)	3 (42.9%)	3 (21.4%)
ATOVAQUONE	0 (0.0%)	2 (28.6%)	2 (14.3%)
SAMTIREL	0 (0.0%)	1 (14.3%)	1 (7.1%)
AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMIASIS	2 (28.6%)	0 (0.0%)	2 (14.3%)
BENAMBAX	1 (14.3%)	0 (0.0%)	1 (7.1%)
PENTAMIDINE ISETIONATE	1 (14.3%)	0 (0.0%)	1 (7.1%)
THROAT PREPARATIONS	1 (14.3%)	0 (0.0%)	1 (7.1%)
SP TROCHES	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

ATC class level 3 WHO-DDE drug name	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHAL	1 (14.3%)	0 (0.0%)	1 (7.1%)
INTAL	1 (14.3%)	0 (0.0%)	1 (7.1%)
ADRENERGICS FOR SYSTEMIC USE	1 (14.3%)	0 (0.0%)	1 (7.1%)
SULTANOL	1 (14.3%)	0 (0.0%)	1 (7.1%)
EXPECTORANTS, EXCL. COMBINATIONS WITH COUGH SUPPRE	0 (0.0%)	2 (28.6%)	2 (14.3%)
CARBOCISTEINE	0 (0.0%)	1 (14.3%)	1 (7.1%)
AMBROXOL HYDROCHLORIDE	0 (0.0%)	1 (14.3%)	1 (7.1%)
MUCOSAL /00546002/	0 (0.0%)	1 (14.3%)	1 (7.1%)
COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECT	0 (0.0%)	2 (28.6%)	2 (14.3%)
DEXTROMETHORPHAN HYDROBROMIDE	0 (0.0%)	2 (28.6%)	2 (14.3%)
MEDICON /00048102/	0 (0.0%)	1 (14.3%)	1 (7.1%)
ASTOMIN /00426502/	0 (0.0%)	1 (14.3%)	1 (7.1%)
ANTIHISTAMINES FOR SYSTEMIC USE	1 (14.3%)	1 (14.3%)	2 (14.3%)
FEXOFENADINE	1 (14.3%)	0 (0.0%)	1 (7.1%)
OLOPATADINE HYDROCHLORIDE	0 (0.0%)	1 (14.3%)	1 (7.1%)
BEPOTASTINE BESILATE	0 (0.0%)	1 (14.3%)	1 (7.1%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

ATC class level 3 WHO-DDE drug name	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
ANTIINFECTIVES	1 (14.3%)	0 (0.0%)	1 (7.1%)
MOXIFLOXACIN HYDROCHLORIDE	1 (14.3%)	0 (0.0%)	1 (7.1%)
ANTIINFLAMMATORY AGENTS	1 (14.3%)	1 (14.3%)	2 (14.3%)
FLUOROMETHOLONE	0 (0.0%)	1 (14.3%)	1 (7.1%)
ODOMEL	1 (14.3%)	0 (0.0%)	1 (7.1%)
ANTIGLAUCOMA PREPARATIONS AND MIOTICS	1 (14.3%)	0 (0.0%)	1 (7.1%)
TIMOLOL MALEATE	1 (14.3%)	0 (0.0%)	1 (7.1%)
DECONGESTANTS AND ANTIALLERGICS	0 (0.0%)	1 (14.3%)	1 (7.1%)
TRANILAST	0 (0.0%)	1 (14.3%)	1 (7.1%)
OTHER OPHTHALMOLOGICALS	2 (28.6%)	0 (0.0%)	2 (14.3%)
PIRENOXINE	1 (14.3%)	0 (0.0%)	1 (7.1%)
SODIUM HYALURONATE	1 (14.3%)	0 (0.0%)	1 (7.1%)
ALL OTHER THERAPEUTIC PRODUCTS	0 (0.0%)	1 (14.3%)	1 (7.1%)
DL-METHIONINE	0 (0.0%)	1 (14.3%)	1 (7.1%)
MAGNETIC RESONANCE IMAGING CONTRAST MEDIA	1 (14.3%)	0 (0.0%)	1 (7.1%)
MAGNESCOPE	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

ATC class level 3 WHO-DDE drug name	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
ATC Class Level 3 not Available	0 (0.0%)	1 (14.3%)	1 (7.1%)
HERBAL PREPARATION	0 (0.0%)	1 (14.3%)	1 (7.1%)

SOURCE: Listing 16.2.4.6
WHO-DDE Version 01Sep2016 was used to code medications.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
ATC class = Anatomical Therapeutic Chemical class
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of treatment.

表 2.7.4.7-19　併用薬（210 試験）（安全性解析対象集団）

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
Number of subjects with at least one concomitant medication	23 (100.0%)
ADRENERGICS, INHALANTS	1 (4.3%)
FLUTICASONE;VILANTEROL	1 (4.3%)
AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISEASES	2 (8.7%)
SAMTIREL	2 (8.7%)
AGENTS FOR TREATMENT OF HEMORRHOIDS AND ANAL FISSURES FOR TOPICAL USE	1 (4.3%)
POSTERISAN FORTE /01567801/	1 (4.3%)
ALL OTHER THERAPEUTIC PRODUCTS	1 (4.3%)
CALCIUM POLYSTYRENE SULFONATE	1 (4.3%)
ANESTHETICS, LOCAL	3 (13.0%)
LIDOCAINE	1 (4.3%)
MEPIVACAINE HYDROCHLORIDE	1 (4.3%)
STROCAIN /00130301/	1 (4.3%)
XYLOCAINE /00033401/	1 (4.3%)
ANGIOTENSIN II ANTAGONISTS, PLAIN	1 (4.3%)
AZILVA	1 (4.3%)
ANTACIDS	2 (8.7%)
MAGMITT	2 (8.7%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
ANTI-ACNE PREPARATIONS FOR TOPICAL USE	2 (8.7%)
ACUATIM	1 (4.3%)
SAHNE	1 (4.3%)
ANTI-PARATHYROID AGENTS	2 (8.7%)
ELCITONIN	2 (8.7%)
ANTIDIARRHEAL MICROORGANISMS	3 (13.0%)
ANTIBIOTICS-RESISTANT LACTIC ACID BACTERIAE	1 (4.3%)
BIO-THREE	1 (4.3%)
BIOFERMIN R	1 (4.3%)
ANTIEMETICS AND ANTINAUSEANTS	3 (13.0%)
CEPHADOL	1 (4.3%)
DIFENIDOL	1 (4.3%)
TRAVELMIN /00517301/	1 (4.3%)
ANTIFUNGALS FOR TOPICAL USE	2 (8.7%)
KETOCONAZOLE	1 (4.3%)
NITRAZEN	1 (4.3%)

Source: Listing 16 2.4.5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
ANTIGLAUCOMA PREPARATIONS AND MIOTICS	2 (8.7%)
AIPHAGAN	1 (4.3%)
CARTEOLOL HYDROCHLORIDE	1 (4.3%)
COSOPT	1 (4.3%)
TAFLUPROST	1 (4.3%)
ANTIGOUT PREPARATIONS	10 (43.5%)
FEBURIC	8 (34.8%)
ALLOPURINOL	1 (4.3%)
FEBUXOSTAT	1 (4.3%)
ANTIHISTAMINES FOR SYSTEMIC USE	9 (39.1%)
OLOPATADINE HYDROCHLORIDE	5 (21.7%)
XYZAL	3 (13.0%)
ALLELOCK	1 (4.3%)
FEXOFENADINE	1 (4.3%)
FEXOFENADINE HYDROCHLORIDE	1 (4.3%)
LEVOCETIRIZINE HYDROCHLORIDE	1 (4.3%)
POLARAMINE	1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name		40 mg (N=23) n (%)
ANTIINFECTIVES		1 (4.3%)
CRAVIT		1 (4.3%)
TARIVID	/00731801/	1 (4.3%)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS		9 (39.1%)
LOXOPROFEN		3 (13.0%)
LOXOPROFEN SODIUM HYDRATE		2 (8.7%)
CELECOXIB		1 (4.3%)
DICLOFENAC SODIUM		1 (4.3%)
LOXONIN		1 (4.3%)
LOXOPROFEN NA		1 (4.3%)
SALAZOSULFAPYRIDINE		1 (4.3%)
ANTIMYCOTICS FOR SYSTEMIC USE		8 (34.8%)
ITRACONAZOLE		3 (13.0%)
FLUCONAZOLE		2 (8.7%)
ITRIZOLE		2 (8.7%)
FUNGIZONE		1 (4.3%)
ANTISEPTICS AND DISINFECTANTS		1 (4.3%)
ISODINE	/00080001/	1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
ANTITHROMBOTIC AGENTS	7 (30.4%)
BAYASPIRIN	2 (8.7%)
CLOPIDOGREL SULFATE	2 (8.7%)
ELIQUIS	1 (4.3%)
LIMAPROST ALFADEX	1 (4.3%)
SARPOGRELATE HYDROCHLORIDE	1 (4.3%)
ANXIOLYTICS	2 (8.7%)
ALPRAZOLAM	1 (4.3%)
DIAZEPAM	1 (4.3%)
BELLADONNA AND DERIVATIVES, PLAIN	1 (4.3%)
SCOPOLAMINE BUTYLBROMIDE	1 (4.3%)
BETA BLOCKING AGENTS	2 (8.7%)
ATENOLOL	1 (4.3%)
CARVEDILOL	1 (4.3%)
METOPROLOL TARTRATE	1 (4.3%)
BILE THERAPY	2 (8.7%)
URSO /00465701/	1 (4.3%)
URSODEOXYCHOLIC ACID	1 (4.3%)

Source: Listing 16.2.4 5
WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	5 (21.7%)
EQUA	2 (8.7%)
ACTOS	1 (4.3%)
GLUBES	1 (4.3%)
METFORMIN HYDROCHLORIDE	1 (4.3%)
SITAGLIPTIN PHOSPHATE MONOHYDRATE	1 (4.3%)
TENELIA	1 (4.3%)
TENELIGLIPTIN HYDROBROMIDE	1 (4.3%)
CALCIUM	1 (4.3%)
ASPARA-CA	1 (4.3%)
CHEMOTHERAPEUTICS FOR TOPICAL USE	1 (4.3%)
REFLAP	1 (4.3%)
CORTICOSTEROIDS FOR SYSTEMIC USE, COMBINATIONS	1 (4.3%)
CELESTAMINE /01221101/	1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN	9 (39.1%)
PREDNISOLONE	5 (21.7%)
PREDONINE /00016201/	3 (13.0%)
DEXAMETHASONE SODIUM PHOSPHATE	1 (4.3%)
SAXIZON	1 (4.3%)
CORTICOSTEROIDS, COMBINATIONS WITH ANTIBIOTICS	2 (8.7%)
DERMOSOL G	1 (4.3%)
RINDERON-VG	1 (4.3%)
CORTICOSTEROIDS, OTHER COMBINATIONS	1 (4.3%)
EURAX H	1 (4.3%)
CORTICOSTEROIDS, PLAIN	6 (26.1%)
METHADERM	2 (8.7%)
ANAMIDOL	1 (4.3%)
ANTEBATE	1 (4.3%)
BETAMETHASONE BUTYRATE PROPIONATE	1 (4.3%)
CLOBETASOL PROPIONATE	1 (4.3%)
DERMOVATE	1 (4.3%)
RINDERON-V	1 (4.3%)

Source: Listing 16 2.4.5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name		40 mg (N=23) n (%)
COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS		1 (4.3%)
CODEINE PHOSPHATE		1 (4.3%)
DECONGESTANTS AND ANTIALLERGICS		1 (4.3%)
LIVOSTIN		1 (4.3%)
DIRECT ACTING ANTIVIRALS		6 (26.1%)
ACICLOVIR		4 (17.4%)
ENTECAVIR		1 (4.3%)
VICCLOX	/00587301/	1 (4.3%)
DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION		1 (4.3%)
BENET		1 (4.3%)
DRUGS FOR CONSTIPATION		12 (52.2%)
MAGNESIUM OXIDE		9 (39.1%)
SENNOSIDE	/00571901/	4 (17.4%)
AMITIZA		2 (8.7%)
MAGMITT		2 (8.7%)
LINZESS		1 (4.3%)
PICOSULFATE		1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	20 (87.0%)
LANSOPRAZOLE	4 (17.4%)
OMEPRAZOLE	3 (13.0%)
RABEPRAZOLE SODIUM	3 (13.0%)
REBAMIPIDE	3 (13.0%)
TAKECAB	3 (13.0%)
ESOMEPRAZOLE	2 (8.7%)
RABEPRAZOLE	2 (8.7%)
ESOMEPRAZOLE MAGNESIUM	1 (4.3%)
IRSOGLADINE MALEATE	1 (4.3%)
LEVOGLUTAMIDE W/SODIUM GUALENATE HYDRATE	1 (4.3%)
PARIET	1 (4.3%)
DRUGS FOR TREATMENT OF TUBERCULOSIS	3 (13.0%)
ISONIAZID	2 (8.7%)
ISCOTIN /00030201/	1 (4.3%)
DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY	2 (8.7%)
TAMSULOSIN HYDROCHLORIDE	1 (4.3%)
URIEF	1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
EMOLLIENTS AND PROTECTIVES	13 (56.5%)
HIRUDOID	6 (26.1%)
HEPARINOID	5 (21.7%)
BESOFTEN	3 (13.0%)
PROPETO	3 (13.0%)
UREA	1 (4.3%)
VASELINE /00473501/	1 (4.3%)
EXPECTORANTS, EXCL. COMBINATIONS WITH COUGH SUPPRESSANTS	2 (8.7%)
L-CARBOCYSTEINE	1 (4.3%)
MUCODYNE	1 (4.3%)
RESPLEN	1 (4.3%)
HIGH-CEILING DIURETICS	6 (26.1%)
LUPRAC	3 (13.0%)
DIART	2 (8.7%)
AZOSEMIDE	1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
HYPNOTICS AND SEDATIVES	13 (56.5%)
BROTIZOLAM	5 (21.7%)
ZOLPIDEM TARTRATE	4 (17.4%)
ZOPICLONE	2 (8.7%)
ESTAZOLAM	1 (4.3%)
FLUNITRAZEPAM	1 (4.3%)
LUNESTA	1 (4.3%)
NITRAZEPAM	1 (4.3%)
RILMAZAFONE HYDROCHLORIDE	1 (4.3%)
ROZEREM	1 (4.3%)
ZOLPIDEM	1 (4.3%)
I.V. SOLUTION ADDITIVES	1 (4.3%)
ISOTONIC SODIUM CHLORIDE SOLUTION	1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name		40 mg (N=23) n (%)
I.V. SOLUTIONS		6 (26.1%)
BFLUID		4 (17.4%)
KCL		1 (4.3%)
SODIUM CHLORIDE		1 (4.3%)
SOLDEM		1 (4.3%)
SOLDEM 1		1 (4.3%)
YD SOLITA T NO.1		1 (4.3%)
YD SOLITA T NO.3G		1 (4.3%)
IMMUNOSTIMULANTS		6 (26.1%)
FILGRASTIM		4 (17.4%)
FILGRASTIM BS	/06441101/	2 (8.7%)
NEUTROGIN		1 (4.3%)
NEUTROPINE		1 (4.3%)
INSULINS AND ANALOGUES		2 (8.7%)
HUMALOG		1 (4.3%)
HUMULIN R		1 (4.3%)
INSULIN GLARGINE RECOMBINANT		1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
LIPID MODIFYING AGENTS, COMBINATIONS	1 (4.3%)
CADUET	1 (4.3%)
LIPID MODIFYING AGENTS, PLAIN	6 (26.1%)
ATORVASTATIN	1 (4.3%)
EPADEL-S	1 (4.3%)
FENOFIBRATE	1 (4.3%)
LIPIDIL	1 (4.3%)
LIVARO	1 (4.3%)
PRAVASTATIN SODIUM	1 (4.3%)
ROSUVASTATIN CALCIUM	1 (4.3%)
LOW-CEILING DIURETICS, THIAZIDES	1 (4.3%)
HYDROCHLOROTHIAZIDE	1 (4.3%)
OPIOIDS	1 (4.3%)
TRAMAL	1 (4.3%)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	3 (13.0%)
MIYA-BM	3 (13.0%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
OTHER ANALGESICS AND ANTIPYRETICS	8 (34.8%)
CALONAL	4 (17.4%)
ACETAMINOPHEN	3 (13.0%)
ACELIO	1 (4.3%)
LYRICA	1 (4.3%)
LYRICA OD	1 (4.3%)
OTHER BETA-LACTAM ANTIBACTERIALS	7 (30.4%)
CEFCAPENE PIVOXIL HYDROCHLORIDE	2 (8.7%)
CEFDITOREN PIVOXIL	1 (4.3%)
CEFON /00883901/	1 (4.3%)
CEFTRIAXONE	1 (4.3%)
FAROPENEM SODIUM	1 (4.3%)
MAXIPIME	1 (4.3%)
MEROPENEM	1 (4.3%)
OTHER CARDIAC PREPARATIONS	3 (13.0%)
UBIDECARENONE	2 (8.7%)
ADETPHOS	1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
OTHER DERMATOLOGICAL PREPARATIONS	1 (4.3%)
AZUNOL /00620101/	1 (4.3%)
OTHER NUTRIENTS	1 (4.3%)
SQUALENE	1 (4.3%)
OTHER OPHTHALMOLOGICALS	1 (4.3%)
DIQUAS	1 (4.3%)
TEARBALANCE	1 (4.3%)
OTHER PLAIN VITAMIN PREPARATIONS	2 (8.7%)
PANTOSIN	1 (4.3%)
PYRIDOXAL PHOSPHATE	1 (4.3%)
POTASSIUM	1 (4.3%)
K-SUPPLY	1 (4.3%)
POTASSIUM-SPARING AGENTS	2 (8.7%)
SPIRONOLACTONE	2 (8.7%)
PROPULSIVES	1 (4.3%)
DOMPERIDONE	1 (4.3%)
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS	1 (4.3%)
DILTIAZEM HYDROCHLORIDE	1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS	5 (21.7%)
AMLODIPINE	2 (8.7%)
AMLODIPINE BESILATE	2 (8.7%)
BENIDIPINE HYDROCHLORIDE	1 (4.3%)
STOMATOLOGICAL PREPARATIONS	6 (26.1%)
AZUNOL GARGLE LIQUID	2 (8.7%)
DEXALTIN	2 (8.7%)
AMPHOTERICIN B	1 (4.3%)
POPIYODON	1 (4.3%)
TRIAMCINOLONE ACETONIDE	1 (4.3%)
SULFONAMIDES AND TRIMETHOPRIM	14 (60.9%)
BAKTAR	7 (30.4%)
BACTRAMIN	3 (13.0%)
BACTAR	2 (8.7%)
SULFAMETHOXAZOLE W/TRIMETHOPRIM	2 (8.7%)
DAIPHEN	1 (4.3%)
THROAT PREPARATIONS	1 (4.3%)
SP TROCHES	1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
THYROID PREPARATIONS	2 (8.7%)
LEVOTHYROXINE SODIUM	1 (4.3%)
THYRADIN	1 (4.3%)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	6 (26.1%)
KETOPROFEN	2 (8.7%)
INDOMETACIN	1 (4.3%)
LOXOPROFEN SODIUM HYDRATE	1 (4.3%)
MOHRUS	1 (4.3%)
SALONPAS /07673501/	1 (4.3%)
VOLTAREN /00372301/	1 (4.3%)
VASODILATORS USED IN CARDIAC DISEASES	2 (8.7%)
FRANDOL	1 (4.3%)
ISOSORBIDE DINITRATE	1 (4.3%)
NICORANDIL	1 (4.3%)
VIRAL VACCINES	1 (4.3%)
INFLUENZA HA VACCINE	1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name	40 mg (N=23) n (%)
VITAMIN A AND D, INCL. COMBINATIONS OF THE TWO	4 (17.4%)
EDIROL	2 (8.7%)
ALFACALCIDOL	1 (4.3%)
CALFINA	1 (4.3%)
VITAMIN B12 AND FOLIC ACID	2 (8.7%)
MECOBALAMIN	1 (4.3%)
METHYCOBAL	1 (4.3%)
X-RAY CONTRAST MEDIA, IODINATED	6 (26.1%)
OMNIPAQUE	3 (13.0%)
IOVERIN	2 (8.7%)
IOPAMIDOL	1 (4.3%)
IOPROMIDE	1 (4.3%)
OYPALOMIN	1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

ATC class level 3 WHO-DDE drug name		40 mg (N=23) n (%)
ATC Class Level 3 not Available		6 (26.1%)
DIAMOX	/00016901/	1 (4.3%)
KAKKONTO	/07985901/	1 (4.3%)
KEISHIKAJUTSUBUTO		1 (4.3%)
NUTRIENTS NOS		1 (4.3%)
OPHTHALMOLOGICALS		1 (4.3%)
SOLACET F		1 (4.3%)

Source: Listing 16.2.4 5

WHO-DDE Version 01SEP2017 was used to code medications.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
ATC class = Anatomical Therapeutic Chemical class.
Concomitant medications = medications started prior to, on or after the first dose of study drug, and ended on or after the date of first dose of study drug or were ongoing at the end of the treatment. End of treatment is defined as end of treatment visit which is approximately 30 (± 3) days after the last dosing of study drug or before the initiation of new cancer treatment, whichever is earlier.

表 2.7.4.7-20　有害事象の概要（203 試験）（安全性解析対象集団）

Description	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Number of subjects with			
At least one TEAE	39 (100.0)	16 (100.0)	55 (100.0)
At least one TEAE related to the study drug	39 (100.0)	12 (75.0)	51 (92.7)
At least one serious TEAE	11 (28.2)	3 (18.8)	14 (25.5)
At least one serious TEAE related to the study drug	8 (20.5)	2 (12.5)	10 (18.2)
At least one TEAE leading to dose reduction or interruption	31 (79.5)	9 (56.3)	40 (72.7)
At least one TEAE leading to study drug discontinuation	15 (38.5)	3 (18.8)	18 (32.7)
At least one TEAE leading to death	0 (0.0)	1 (6.3)	1 (1.8)
At least one TEAE with grade 3 or higher	34 (87.2)	12 (75.0)	46 (83.6)
At least one TEAE with grade 3 or higher and related to the study drug	33 (84.6)	9 (56.3)	42 (76.4)

Source: Listing 16.2.6 1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE.　For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

表 2.7.4.7-21　有害事象の概要（201 試験）（安全性解析対象集団）

Description	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Number of patients with			
At least one TEAE	6 (85.7%)	7 (100.0%)	13 (92.9%)
At least one TEAE related to the study drug	6 (85.7%)	7 (100.0%)	13 (92.9%)
At least one serious TEAE	1 (14.3%)	1 (14.3%)	2 (14.3%)
At least one serious TEAE related to the study drug	0 (0.0%)	1 (14.3%)	1 (7.1%)
A TEAE leading to dose reduction or delay	4 (57.1%)	4 (57.1%)	8 (57.1%)
A TEAE leading to study drug discontinuation	2 (28.6%)	4 (57.1%)	6 (42.9%)
A TEAE leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity			
Grade 1: Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 2: Moderate	1 (14.3%)	1 (14.3%)	2 (14.3%)
Grade 3: Severe	5 (71.4%)	4 (57.1%)	9 (64.3%)
Grade 4: Life-Threatening	0 (0.0%)	2 (28.6%)	2 (14.3%)
Grade 5: Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 3 or higher	5 (71.4%)	6 (85.7%)	11 (78.6%)

SOURCE: Listing 16.2.6.3
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Description	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Causal relationship			
Unrelated	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unlikely	0 (0.0%)	0 (0.0%)	0 (0.0%)
Possible	0 (0.0%)	1 (14.3%)	1 (7.1%)
Probable	4 (57.1%)	3 (42.9%)	7 (50.0%)
Definite	2 (28.6%)	3 (42.9%)	5 (35.7%)

SOURCE: Listing 16.2.6.3
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

表 2.7.4.7-22　有害事象の概要（210 試験）（安全性解析対象集団）

Description	40 mg (N=23)
	n (%)
Number of subjects with	
At least one TEAE	23 (100.0%)
At least one TEAE related to the study drug	23 (100.0%)
At least one serious TEAE	7 (30.4%)
At least one serious TEAE related to the study drug	6 (26.1%)
At least one TEAE leading to dose reduction or interruption	16 (69.6%)
At least one TEAE leading to study drug discontinuation	9 (39.1%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	18 (78.3%)
At least one TEAE with grade 3 or higher and related to the study drug	18 (78.3%)

Source: Listing 16.2.6 1

Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

表 2.7.4.7-23　有害事象の発現割合（203 試験）（安全性解析対象集団）

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Number of subjects with at least one TEAE	39(100.0)	16(100.0)	55(100.0)
血液およびリンパ系障害	38(97.4)	14(87.5)	52(94.5)
血小板減少症*	35(89.7)	11(68.8)	46(83.6)
好中球減少症*	28(71.8)	3(18.8)	31(56.4)
白血球減少症*	24(61.5)	0	24(43.6)
貧血*	14(35.9)	4(25.0)	18(32.7)
リンパ球減少症*	16(41.0)	0	16(29.1)
発熱性好中球減少症	2(5.1)	1(6.3)	3(5.5)
再生不良性貧血	1(2.6)	0	1(1.8)
好酸球増加症	0	1(6.3)	1(1.8)
心臓障害	6(15.4)	1(6.3)	7(12.7)
動悸	3(7.7)	0	3(5.5)
心房細動	1(2.6)	1(6.3)	2(3.6)
不安定狭心症	1(2.6)	0	1(1.8)
不整脈	1(2.6)	0	1(1.8)
心嚢液貯留	1(2.6)	0	1(1.8)
耳および迷路障害	1(2.6)	1(6.3)	2(3.6)
回転性めまい	1(2.6)	0	1(1.8)
耳痛	0	1(6.3)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
眼障害	4(10.3)	1(6.3)	5(9.1)
ドライアイ	1(2.6)	0	1(1.8)
白内障	0	1(6.3)	1(1.8)
結膜出血	1(2.6)	0	1(1.8)
角膜炎	1(2.6)	0	1(1.8)
霧視	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
胃腸障害	25(64.1)	7(43.8)	32(58.2)
下痢	14(35.9)	3(18.8)	17(30.9)
悪心	9(23.1)	3(18.8)	12(21.8)
嘔吐	2(5.1)	1(6.3)	3(5.5)
腹痛	1(2.6)	2(12.5)	3(5.5)
上腹部痛	2(5.1)	0	2(3.6)
口内炎	0	2(12.5)	2(3.6)
齲歯	2(5.1)	0	2(3.6)
便秘	1(2.6)	0	1(1.8)
口腔粘膜血腫	1(2.6)	0	1(1.8)
心窩部不快感	1(2.6)	0	1(1.8)
歯痛	1(2.6)	0	1(1.8)
消化不良	1(2.6)	0	1(1.8)
痔出血	1(2.6)	0	1(1.8)
肛門出血	1(2.6)	0	1(1.8)
胃潰瘍	0	1(6.3)	1(1.8)
胃炎	0	1(6.3)	1(1.8)
腹部不快感	1(2.6)	0	1(1.8)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
一般・全身障害および投与部位の状態	19(48.7)	8(50.0)	27(49.1)
発熱	5(12.8)	6(37.5)	11(20.0)
倦怠感	8(20.5)	0	8(14.5)
疲労	4(10.3)	2(12.5)	6(10.9)
末梢性浮腫	2(5.1)	2(12.5)	4(7.3)
インフルエンザ様疾患	0	2(12.5)	2(3.6)
無力症	0	2(12.5)	2(3.6)
カテーテル留置部位腫脹	1(2.6)	0	1(1.8)
口渇	1(2.6)	0	1(1.8)
歩行障害	1(2.6)	0	1(1.8)
溢出	1(2.6)	0	1(1.8)
胸痛	1(2.6)	0	1(1.8)
胸部不快感	1(2.6)	0	1(1.8)
免疫系障害	1(2.6)	0	1(1.8)
薬物過敏症	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
感染症および寄生虫症	15(38.5)	4(25.0)	19(34.5)
上気道感染	2(5.1)	2(12.5)	4(7.3)
咽頭炎	3(7.7)	0	3(5.5)
インフルエンザ	2(5.1)	0	2(3.6)
上咽頭炎	2(5.1)	0	2(3.6)
気管支炎	2(5.1)	0	2(3.6)
結膜炎	2(5.1)	0	2(3.6)
サイトメガロウイルス感染	1(2.6)	0	1(1.8)
ニューモシスチス・イロベチイ肺炎	1(2.6)	0	1(1.8)
ブドウ球菌皮膚感染	0	1(6.3)	1(1.8)
帯状疱疹	1(2.6)	0	1(1.8)
感染性小腸結腸炎	0	1(6.3)	1(1.8)
肺炎	0	1(6.3)	1(1.8)
胃腸炎	0	1(6.3)	1(1.8)
膀胱炎	1(2.6)	0	1(1.8)
膿痂疹	1(2.6)	0	1(1.8)
鼻炎	1(2.6)	0	1(1.8)
傷害、中毒および処置合併症	1(2.6)	2(12.5)	3(5.5)
処置による疼痛	0	1(6.3)	1(1.8)
爪損傷	1(2.6)	0	1(1.8)
胃瘻管部合併症	0	1(6.3)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
臨床検査	24(61.5)	1(6.3)	25(45.5)
γ－グルタミルトランスフェラーゼ増加	8(20.5)	0	8(14.5)
血中アルカリホスファターゼ増加	8(20.5)	0	8(14.5)
アスパラギン酸アミノトランスフェラーゼ増加	7(17.9)	0	7(12.7)
体重減少	6(15.4)	0	6(10.9)
アラニンアミノトランスフェラーゼ増加	5(12.8)	0	5(9.1)
心電図ＱＴ延長	5(12.8)	0	5(9.1)
Ｃ－反応性蛋白増加	2(5.1)	1(6.3)	3(5.5)
好酸球数増加	2(5.1)	0	2(3.6)
脳性ナトリウム利尿ペプチド増加	2(5.1)	0	2(3.6)
血中クレアチニン増加	2(5.1)	0	2(3.6)
リパーゼ増加	1(2.6)	0	1(1.8)
体重増加	1(2.6)	0	1(1.8)
尿中血陽性	1(2.6)	0	1(1.8)
心胸郭比増加	1(2.6)	0	1(1.8)
心電図Ｔ波逆転	1(2.6)	0	1(1.8)
血中クレアチンホスホキナーゼ増加	1(2.6)	0	1(1.8)
血中クレアチンホスホキナーゼＭＢ増加	1(2.6)	0	1(1.8)
血中コレステロール増加	1(2.6)	0	1(1.8)
血中免疫グロブリンＡ減少	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
代謝および栄養障害	16(41.0)	9(56.3)	25(45.5)
食欲減退	8(20.5)	5(31.3)	13(23.6)
低アルブミン血症	4(10.3)	1(6.3)	5(9.1)
低カリウム血症	3(7.7)	2(12.5)	5(9.1)
低カルシウム血症	2(5.1)	1(6.3)	3(5.5)
低ナトリウム血症	2(5.1)	0	2(3.6)
低蛋白血症	1(2.6)	0	1(1.8)
糖尿病	1(2.6)	0	1(1.8)
高カリウム血症	1(2.6)	0	1(1.8)
高トリグリセリド血症	1(2.6)	0	1(1.8)
高マグネシウム血症	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
筋骨格系および結合組織障害	15(38.5)	4(25.0)	19(34.5)
筋痙縮	5(12.8)	0	5(9.1)
背部痛	4(10.3)	1(6.3)	5(9.1)
筋肉疲労	1(2.6)	1(6.3)	2(3.6)
筋肉痛	2(5.1)	0	2(3.6)
出血性関節症	1(2.6)	0	1(1.8)
四肢痛	1(2.6)	0	1(1.8)
筋力低下	0	1(6.3)	1(1.8)
筋骨格硬直	1(2.6)	0	1(1.8)
肩回旋筋腱板症候群	0	1(6.3)	1(1.8)
腱炎	1(2.6)	0	1(1.8)
関節炎	1(2.6)	0	1(1.8)
関節痛	1(2.6)	0	1(1.8)
関節腫脹	1(2.6)	0	1(1.8)
頚部痛	1(2.6)	0	1(1.8)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	3(7.7)	1(6.3)	4(7.3)
腫瘍疼痛	1(2.6)	1(6.3)	2(3.6)
末梢性Ｔ細胞性リンパ腫、組織型不明	1(2.6)	0	1(1.8)
皮膚乳頭腫	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
神経系障害	7(17.9)	2(12.5)	9(16.4)
頭痛	4(10.3)	2(12.5)	6(10.9)
味覚異常	2(5.1)	0	2(3.6)
失神寸前の状態	1(2.6)	0	1(1.8)
感覚鈍麻	1(2.6)	0	1(1.8)
末梢性感覚ニューロパチー	1(2.6)	0	1(1.8)
浮動性めまい	1(2.6)	0	1(1.8)
精神障害	4(10.3)	1(6.3)	5(9.1)
不眠症	3(7.7)	1(6.3)	4(7.3)
譫妄	2(5.1)	0	2(3.6)
腎および尿路障害	2(5.1)	0	2(3.6)
急性腎障害	1(2.6)	0	1(1.8)
蛋白尿	1(2.6)	0	1(1.8)
血尿	1(2.6)	0	1(1.8)
生殖系および乳房障害	0	1(6.3)	1(1.8)
陰嚢浮腫	0	1(6.3)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
呼吸器、胸郭および縦隔障害	14(35.9)	7(43.8)	21(38.2)
咳嗽	2(5.1)	4(25.0)	6(10.9)
呼吸困難	2(5.1)	2(12.5)	4(7.3)
肺臓炎	3(7.7)	1(6.3)	4(7.3)
口腔咽頭痛	2(5.1)	1(6.3)	3(5.5)
胸水	2(5.1)	0	2(3.6)
鼻出血	2(5.1)	0	2(3.6)
しゃっくり	0	1(6.3)	1(1.8)
アレルギー性鼻炎	0	1(6.3)	1(1.8)
上気道の炎症	1(2.6)	0	1(1.8)
労作性呼吸困難	0	1(6.3)	1(1.8)
咽頭知覚不全	1(2.6)	0	1(1.8)
湿性咳嗽	0	1(6.3)	1(1.8)
発声障害	0	1(6.3)	1(1.8)
間質性肺疾患	1(2.6)	0	1(1.8)
鼻漏	0	1(6.3)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
皮膚および皮下組織障害	18(46.2)	5(31.3)	23(41.8)
発疹	3(7.7)	2(12.5)	5(9.1)
蕁麻疹	3(7.7)	2(12.5)	5(9.1)
全身性そう痒症	1(2.6)	1(6.3)	2(3.6)
斑状丘疹状皮疹	2(5.1)	0	2(3.6)
紅斑	2(5.1)	0	2(3.6)
紫斑	2(5.1)	0	2(3.6)
ざ瘡様皮膚炎	1(2.6)	0	1(1.8)
そう痒性皮疹	1(2.6)	0	1(1.8)
全身性剥脱性皮膚炎	1(2.6)	0	1(1.8)
全身紅斑	1(2.6)	0	1(1.8)
多形紅斑	1(2.6)	0	1(1.8)
点状出血	1(2.6)	0	1(1.8)
皮脂欠乏性湿疹	1(2.6)	0	1(1.8)
皮膚乾燥	1(2.6)	0	1(1.8)
皮膚疼痛	1(2.6)	0	1(1.8)
色素沈着障害	1(2.6)	0	1(1.8)
褥瘡性潰瘍	1(2.6)	0	1(1.8)
血管障害	2(5.1)	1(6.3)	3(5.5)
低血圧	1(2.6)	0	1(1.8)
末梢動脈閉塞性疾患	1(2.6)	0	1(1.8)
深部静脈血栓症	0	1(6.3)	1(1.8)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-24　有害事象の発現割合（201 試験）（安全性解析対象集団）

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Number of patients with at least one TEAE	6 (85.7%)	7 (100.0%)	13 (92.9%)
血液およびリンパ系障害	5 (71.4%)	5 (71.4%)	10 (71.4%)
貧血	5 (71.4%)	0 (0.0%)	5 (35.7%)
白血球減少症	1 (14.3%)	0 (0.0%)	1 (7.1%)
好中球減少症	1 (14.3%)	2 (28.6%)	3 (21.4%)
血小板減少症	2 (28.6%)	4 (57.1%)	6 (42.9%)
先天性、家族性および遺伝性障害	1 (14.3%)	0 (0.0%)	1 (7.1%)
表皮融解	1 (14.3%)	0 (0.0%)	1 (7.1%)
耳および迷路障害	1 (14.3%)	0 (0.0%)	1 (7.1%)
回転性めまい	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
胃腸障害	3 (42.9%)	4 (57.1%)	7 (50.0%)
腹痛	1 (14.3%)	1 (14.3%)	2 (14.3%)
便秘	0 (0.0%)	1 (14.3%)	1 (7.1%)
下痢	3 (42.9%)	1 (14.3%)	4 (28.6%)
口内乾燥	0 (0.0%)	1 (14.3%)	1 (7.1%)
腸炎	0 (0.0%)	1 (14.3%)	1 (7.1%)
悪心	1 (14.3%)	2 (28.6%)	3 (21.4%)
口内炎	0 (0.0%)	1 (14.3%)	1 (7.1%)
嘔吐	1 (14.3%)	0 (0.0%)	1 (7.1%)
一般・全身障害および投与部位の状態	4 (57.1%)	3 (42.9%)	7 (50.0%)
疲労	3 (42.9%)	1 (14.3%)	4 (28.6%)
治癒不良	0 (0.0%)	1 (14.3%)	1 (7.1%)
末梢性浮腫	1 (14.3%)	0 (0.0%)	1 (7.1%)
発熱	1 (14.3%)	2 (28.6%)	3 (21.4%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
感染症および寄生虫症	2 (28.6%)	3 (42.9%)	5 (35.7%)
結膜炎	1 (14.3%)	0 (0.0%)	1 (7.1%)
膀胱炎	0 (0.0%)	1 (14.3%)	1 (7.1%)
鼻咽頭炎	0 (0.0%)	2 (28.6%)	2 (14.3%)
食道カンジダ症	0 (0.0%)	1 (14.3%)	1 (7.1%)
咽頭炎	1 (14.3%)	0 (0.0%)	1 (7.1%)
副鼻腔炎	1 (14.3%)	0 (0.0%)	1 (7.1%)
傷害、中毒および処置合併症	0 (0.0%)	1 (14.3%)	1 (7.1%)
挫傷	0 (0.0%)	1 (14.3%)	1 (7.1%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
臨床検査	4 (57.1%)	7 (100.0%)	11 (78.6%)
アラニンアミノトランスフェラーゼ増加	0 (0.0%)	1 (14.3%)	1 (7.1%)
アスパラギン酸アミノトランスフェラーゼ増加	0 (0.0%)	1 (14.3%)	1 (7.1%)
血中クレアチンホスホキナーゼ増加	1 (14.3%)	0 (0.0%)	1 (7.1%)
Ｃ－反応性蛋白増加	1 (14.3%)	1 (14.3%)	2 (14.3%)
低比重リポ蛋白増加	1 (14.3%)	0 (0.0%)	1 (7.1%)
リンパ球数減少	1 (14.3%)	0 (0.0%)	1 (7.1%)
好中球数減少	2 (28.6%)	0 (0.0%)	2 (14.3%)
血小板数減少	3 (42.9%)	3 (42.9%)	6 (42.9%)
体重減少	1 (14.3%)	2 (28.6%)	3 (21.4%)
体重増加	1 (14.3%)	0 (0.0%)	1 (7.1%)
白血球数減少	3 (42.9%)	1 (14.3%)	4 (28.6%)
トランスアミナーゼ上昇	0 (0.0%)	1 (14.3%)	1 (7.1%)
胸部コンピュータ断層撮影異常	0 (0.0%)	1 (14.3%)	1 (7.1%)
トロポニンＩ増加	1 (14.3%)	0 (0.0%)	1 (7.1%)
血中アルカリホスファターゼ増加	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
代謝および栄養障害	4 (57.1%)	6 (85.7%)	10 (71.4%)
糖尿病	0 (0.0%)	1 (14.3%)	1 (7.1%)
高血糖	0 (0.0%)	1 (14.3%)	1 (7.1%)
高マグネシウム血症	1 (14.3%)	0 (0.0%)	1 (7.1%)
高トリグリセリド血症	1 (14.3%)	1 (14.3%)	2 (14.3%)
高尿酸血症	2 (28.6%)	0 (0.0%)	2 (14.3%)
低カルシウム血症	0 (0.0%)	3 (42.9%)	3 (21.4%)
低カリウム血症	2 (28.6%)	1 (14.3%)	3 (21.4%)
低マグネシウム血症	0 (0.0%)	1 (14.3%)	1 (7.1%)
血液量減少症	0 (0.0%)	1 (14.3%)	1 (7.1%)
食欲減退	1 (14.3%)	2 (28.6%)	3 (21.4%)
筋骨格系および結合組織障害	1 (14.3%)	2 (28.6%)	3 (21.4%)
背部痛	0 (0.0%)	2 (28.6%)	2 (14.3%)
筋肉痛	1 (14.3%)	0 (0.0%)	1 (7.1%)
筋骨格系胸痛	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
神経系障害	3 (42.9%)	1 (14.3%)	4 (28.6%)
味覚異常	2 (28.6%)	1 (14.3%)	3 (21.4%)
頭痛	1 (14.3%)	1 (14.3%)	2 (14.3%)
パーキンソニズム	1 (14.3%)	0 (0.0%)	1 (7.1%)
精神障害	1 (14.3%)	1 (14.3%)	2 (14.3%)
不眠症	1 (14.3%)	1 (14.3%)	2 (14.3%)
腎および尿路障害	2 (28.6%)	1 (14.3%)	3 (21.4%)
血尿	1 (14.3%)	0 (0.0%)	1 (7.1%)
頻尿	1 (14.3%)	0 (0.0%)	1 (7.1%)
蛋白尿	1 (14.3%)	0 (0.0%)	1 (7.1%)
尿管結石症	0 (0.0%)	1 (14.3%)	1 (7.1%)
呼吸器、胸郭および縦隔障害	2 (28.6%)	0 (0.0%)	2 (14.3%)
胸水	1 (14.3%)	0 (0.0%)	1 (7.1%)
口腔咽頭不快感	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
皮膚および皮下組織障害	2 (28.6%)	1 (14.3%)	3 (21.4%)
多形紅斑	0 (0.0%)	1 (14.3%)	1 (7.1%)
結節性紅斑	0 (0.0%)	1 (14.3%)	1 (7.1%)
全身性皮疹	1 (14.3%)	0 (0.0%)	1 (7.1%)
斑状丘疹状皮疹	0 (0.0%)	1 (14.3%)	1 (7.1%)
不全角化	1 (14.3%)	0 (0.0%)	1 (7.1%)
血管周囲細胞浸潤性皮膚炎	1 (14.3%)	0 (0.0%)	1 (7.1%)
血管障害	1 (14.3%)	0 (0.0%)	1 (7.1%)
低血圧	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

表 2.7.4.7-25　有害事象の発現割合（210 試験）（安全性解析対象集団）

System organ class Preferred term	40 mg (N=23) n (%)
Number of subjects with at least one TEAE	23(100.0%)
血液およびリンパ系障害	19(82.6%)
血小板減少症*	18(78.3%)
好中球減少症*	12(52.2%)
白血球減少症*	10(43.5%)
貧血*	9(39.1%)
リンパ球減少症*	2(8.7%)
好酸球増加症	1(4.3%)
発熱性好中球減少症	1(4.3%)
心臓障害	2(8.7%)
第一度房室ブロック	1(4.3%)
動悸	1(4.3%)
眼障害	1(4.3%)
ドライアイ	1(4.3%)
胃腸障害	9(39.1%)
下痢	6(26.1%)
腹痛	3(13.0%)
悪心	3(13.0%)
口内炎	1(4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	40 mg (N=23) n (%)
一般・全身障害および投与部位の状態	13(56.5%)
倦怠感	7(30.4%)
疲労	3(13.0%)
発熱	3(13.0%)
悪寒	1(4.3%)
非心臓性胸痛	1(4.3%)
末梢性浮腫	1(4.3%)
感染症および寄生虫症	7(30.4%)
細菌感染	1(4.3%)
サイトメガロウイルス感染	1(4.3%)
医療機器関連感染	1(4.3%)
麦粒腫	1(4.3%)
口腔カンジダ症	1(4.3%)
ニューモシスチス・イロベチイ肺炎	1(4.3%)
皮膚感染	1(4.3%)
扁桃炎	1(4.3%)
上気道感染	1(4.3%)
尿路感染	1(4.3%)
傷害、中毒および処置合併症	1(4.3%)
挫傷	1(4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	40 mg (N=23) n (%)
臨床検査	10(43.5%)
体重減少	4(17.4%)
アスパラギン酸アミノトランスフェラーゼ増加	2(8.7%)
γ－グルタミルトランスフェラーゼ増加	2(8.7%)
アラニンアミノトランスフェラーゼ増加	1(4.3%)
血中アルカリホスファターゼ増加	1(4.3%)
血中乳酸脱水素酵素増加	1(4.3%)
脳性ナトリウム利尿ペプチド増加	1(4.3%)
好酸球数増加	1(4.3%)
リパーゼ増加	1(4.3%)
代謝および栄養障害	13(56.5%)
食欲減退	8(34.8%)
低アルブミン血症	3(13.0%)
低ナトリウム血症	2(8.7%)
高カルシウム血症	1(4.3%)
低カリウム血症	1(4.3%)
低リン酸血症	1(4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	40 mg (N=23) n (%)
筋骨格系および結合組織障害	7(30.4%)
背部痛	4(17.4%)
関節痛	1(4.3%)
脊椎すべり症	1(4.3%)
尺骨突き上げ症候群	1(4.3%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1(4.3%)
腫瘍疼痛	1(4.3%)
神経系障害	9(39.1%)
味覚異常	4(17.4%)
頭痛	2(8.7%)
味覚消失	1(4.3%)
認知障害	1(4.3%)
浮動性めまい	1(4.3%)
傾眠	1(4.3%)
腎および尿路障害	1(4.3%)
尿瘻	1(4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	40 mg (N=23) n (%)
呼吸器、胸郭および縦隔障害	4(17.4%)
急性呼吸不全	1(4.3%)
鼻出血	1(4.3%)
間質性肺疾患	1(4.3%)
口腔咽頭痛	1(4.3%)
皮膚および皮下組織障害	8(34.8%)
接触皮膚炎	1(4.3%)
湿疹	1(4.3%)
紅斑	1(4.3%)
多形紅斑	1(4.3%)
光線過敏性反応	1(4.3%)
そう痒症	1(4.3%)
発疹	1(4.3%)
皮膚剥脱	1(4.3%)
皮膚潰瘍	1(4.3%)
血管障害	1(4.3%)
高血圧	1(4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-26　治験薬と関連性のある有害事象（203 試験）（安全性解析対象集団）

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Number of subjects with at least one related TEAE	39(100.0)	12(75.0)	51(92.7)
血液およびリンパ系障害	38(97.4)	9(56.3)	47(85.5)
血小板減少症*	35(89.7)	7(43.8)	42(76.4)
好中球減少症*	28(71.8)	3(18.8)	31(56.4)
白血球減少症*	21(53.8)	0	21(38.2)
リンパ球減少症*	16(41.0)	0	16(29.1)
貧血*	11(28.2)	1(6.3)	12(21.8)
発熱性好中球減少症	2(5.1)	1(6.3)	3(5.5)
再生不良性貧血	1(2.6)	0	1(1.8)
心臓障害	4(10.3)	0	4(7.3)
動悸	2(5.1)	0	2(3.6)
不整脈	1(2.6)	0	1(1.8)
心嚢液貯留	1(2.6)	0	1(1.8)
心房細動	1(2.6)	0	1(1.8)
耳および迷路障害	1(2.6)	0	1(1.8)
回転性めまい	1(2.6)	0	1(1.8)
眼障害	1(2.6)	0	1(1.8)
結膜出血	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
胃腸障害	20(51.3)	5(31.3)	25(45.5)
悪心	9(23.1)	2(12.5)	11(20.0)
下痢	9(23.1)	1(6.3)	10(18.2)
便秘	1(2.6)	0	1(1.8)
嘔吐	1(2.6)	0	1(1.8)
心窩部不快感	1(2.6)	0	1(1.8)
消化不良	1(2.6)	0	1(1.8)
胃炎	0	1(6.3)	1(1.8)
腹痛	0	1(6.3)	1(1.8)
腹部不快感	1(2.6)	0	1(1.8)
齲歯	1(2.6)	0	1(1.8)
一般・全身障害および投与部位の状態	16(41.0)	1(6.3)	17(30.9)
倦怠感	8(20.5)	0	8(14.5)
疲労	4(10.3)	0	4(7.3)
末梢性浮腫	2(5.1)	0	2(3.6)
発熱	2(5.1)	0	2(3.6)
歩行障害	1(2.6)	0	1(1.8)
無力症	0	1(6.3)	1(1.8)
胸部不快感	1(2.6)	0	1(1.8)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
感染症および寄生虫症	7(17.9)	1(6.3)	8(14.5)
気管支炎	2(5.1)	0	2(3.6)
サイトメガロウイルス感染	1(2.6)	0	1(1.8)
ニューモシスチス・イロベチイ肺炎	1(2.6)	0	1(1.8)
上咽頭炎	1(2.6)	0	1(1.8)
肺炎	0	1(6.3)	1(1.8)
膀胱炎	1(2.6)	0	1(1.8)
膿痂疹	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
臨床検査	19(48.7)	1(6.3)	20(36.4)
γ－グルタミルトランスフェラーゼ増加	7(17.9)	0	7(12.7)
血中アルカリホスファターゼ増加	6(15.4)	0	6(10.9)
心電図ＱＴ延長	5(12.8)	0	5(9.1)
アスパラギン酸アミノトランスフェラーゼ増加	4(10.3)	0	4(7.3)
アラニンアミノトランスフェラーゼ増加	4(10.3)	0	4(7.3)
体重減少	2(5.1)	0	2(3.6)
好酸球数増加	2(5.1)	0	2(3.6)
血中クレアチニン増加	2(5.1)	0	2(3.6)
Ｃ－反応性蛋白増加	1(2.6)	1(6.3)	2(3.6)
リパーゼ増加	1(2.6)	0	1(1.8)
心胸郭比増加	1(2.6)	0	1(1.8)
心電図Ｔ波逆転	1(2.6)	0	1(1.8)
脳性ナトリウム利尿ペプチド増加	1(2.6)	0	1(1.8)
血中クレアチンホスホキナーゼ増加	1(2.6)	0	1(1.8)
血中クレアチンホスホキナーゼＭＢ増加	1(2.6)	0	1(1.8)
血中免疫グロブリンＡ減少	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
代謝および栄養障害	12(30.8)	4(25.0)	16(29.1)
食欲減退	8(20.5)	4(25.0)	12(21.8)
低アルブミン血症	2(5.1)	0	2(3.6)
低カリウム血症	2(5.1)	0	2(3.6)
低カルシウム血症	2(5.1)	0	2(3.6)
低ナトリウム血症	2(5.1)	0	2(3.6)
糖尿病	1(2.6)	0	1(1.8)
筋骨格系および結合組織障害	7(17.9)	0	7(12.7)
筋痙縮	3(7.7)	0	3(5.5)
四肢痛	1(2.6)	0	1(1.8)
筋肉疲労	1(2.6)	0	1(1.8)
筋骨格硬直	1(2.6)	0	1(1.8)
背部痛	1(2.6)	0	1(1.8)
関節炎	1(2.6)	0	1(1.8)
関節腫脹	1(2.6)	0	1(1.8)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1(2.6)	0	1(1.8)
末梢性Ｔ細胞性リンパ腫、組織型不明	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
神経系障害	4(10.3)	0	4(7.3)
味覚異常	2(5.1)	0	2(3.6)
頭痛	2(5.1)	0	2(3.6)
浮動性めまい	1(2.6)	0	1(1.8)
腎および尿路障害	1(2.6)	0	1(1.8)
蛋白尿	1(2.6)	0	1(1.8)
呼吸器、胸郭および縦隔障害	8(20.5)	1(6.3)	9(16.4)
肺臓炎	3(7.7)	1(6.3)	4(7.3)
呼吸困難	2(5.1)	0	2(3.6)
咳嗽	1(2.6)	0	1(1.8)
胸水	1(2.6)	0	1(1.8)
間質性肺疾患	1(2.6)	0	1(1.8)
鼻出血	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
皮膚および皮下組織障害	10(25.6)	2(12.5)	12(21.8)
発疹	2(5.1)	1(6.3)	3(5.5)
蕁麻疹	3(7.7)	0	3(5.5)
全身性そう痒症	1(2.6)	1(6.3)	2(3.6)
紫斑	2(5.1)	0	2(3.6)
ざ瘡様皮膚炎	1(2.6)	0	1(1.8)
全身性剥脱性皮膚炎	1(2.6)	0	1(1.8)
多形紅斑	1(2.6)	0	1(1.8)
斑状丘疹状皮疹	1(2.6)	0	1(1.8)
点状出血	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-27　治験薬と関連性のある有害事象（201 試験）（安全性解析対象集団）

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Number of patients with at least one related TEAE	6 (85.7%)	7 (100.0%)	13 (92.9%)
血液およびリンパ系障害	5 (71.4%)	5 (71.4%)	10 (71.4%)
貧血	5 (71.4%)	0 (0.0%)	5 (35.7%)
白血球減少症	1 (14.3%)	0 (0.0%)	1 (7.1%)
好中球減少症	1 (14.3%)	2 (28.6%)	3 (21.4%)
血小板減少症	2 (28.6%)	4 (57.1%)	6 (42.9%)
先天性、家族性および遺伝性障害	1 (14.3%)	0 (0.0%)	1 (7.1%)
表皮融解	1 (14.3%)	0 (0.0%)	1 (7.1%)
胃腸障害	3 (42.9%)	4 (57.1%)	7 (50.0%)
腹痛	1 (14.3%)	1 (14.3%)	2 (14.3%)
便秘	0 (0.0%)	1 (14.3%)	1 (7.1%)
下痢	2 (28.6%)	1 (14.3%)	3 (21.4%)
口内乾燥	0 (0.0%)	1 (14.3%)	1 (7.1%)
悪心	1 (14.3%)	2 (28.6%)	3 (21.4%)
口内炎	0 (0.0%)	1 (14.3%)	1 (7.1%)
嘔吐	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
一般・全身障害および投与部位の状態	3 (42.9%)	2 (28.6%)	5 (35.7%)
疲労	3 (42.9%)	1 (14.3%)	4 (28.6%)
発熱	1 (14.3%)	2 (28.6%)	3 (21.4%)
感染症および寄生虫症	2 (28.6%)	3 (42.9%)	5 (35.7%)
結膜炎	1 (14.3%)	0 (0.0%)	1 (7.1%)
膀胱炎	0 (0.0%)	1 (14.3%)	1 (7.1%)
鼻咽頭炎	0 (0.0%)	1 (14.3%)	1 (7.1%)
食道カンジダ症	0 (0.0%)	1 (14.3%)	1 (7.1%)
咽頭炎	1 (14.3%)	0 (0.0%)	1 (7.1%)
副鼻腔炎	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
臨床検査	4 (57.1%)	7 (100.0%)	11 (78.6%)
アラニンアミノトランスフェラーゼ増加	0 (0.0%)	1 (14.3%)	1 (7.1%)
アスパラギン酸アミノトランスフェラーゼ増加	0 (0.0%)	1 (14.3%)	1 (7.1%)
血中クレアチンホスホキナーゼ増加	1 (14.3%)	0 (0.0%)	1 (7.1%)
Ｃ－反応性蛋白増加	1 (14.3%)	1 (14.3%)	2 (14.3%)
低比重リポ蛋白増加	1 (14.3%)	0 (0.0%)	1 (7.1%)
リンパ球数減少	1 (14.3%)	0 (0.0%)	1 (7.1%)
好中球数減少	2 (28.6%)	0 (0.0%)	2 (14.3%)
血小板数減少	3 (42.9%)	3 (42.9%)	6 (42.9%)
体重減少	1 (14.3%)	2 (28.6%)	3 (21.4%)
白血球数減少	3 (42.9%)	1 (14.3%)	4 (28.6%)
トランスアミナーゼ上昇	0 (0.0%)	1 (14.3%)	1 (7.1%)
胸部コンピュータ断層撮影異常	0 (0.0%)	1 (14.3%)	1 (7.1%)
血中アルカリホスファターゼ増加	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
代謝および栄養障害	4 (57.1%)	4 (57.1%)	8 (57.1%)
糖尿病	0 (0.0%)	1 (14.3%)	1 (7.1%)
高トリグリセリド血症	1 (14.3%)	1 (14.3%)	2 (14.3%)
高尿酸血症	2 (28.6%)	0 (0.0%)	2 (14.3%)
低カルシウム血症	0 (0.0%)	2 (28.6%)	2 (14.3%)
低カリウム血症	2 (28.6%)	0 (0.0%)	2 (14.3%)
食欲減退	1 (14.3%)	2 (28.6%)	3 (21.4%)
筋骨格系および結合組織障害	1 (14.3%)	0 (0.0%)	1 (7.1%)
筋肉痛	1 (14.3%)	0 (0.0%)	1 (7.1%)
筋骨格系胸痛	1 (14.3%)	0 (0.0%)	1 (7.1%)
神経系障害	3 (42.9%)	1 (14.3%)	4 (28.6%)
味覚異常	2 (28.6%)	1 (14.3%)	3 (21.4%)
頭痛	1 (14.3%)	1 (14.3%)	2 (14.3%)
精神障害	0 (0.0%)	1 (14.3%)	1 (7.1%)
不眠症	0 (0.0%)	1 (14.3%)	1 (7.1%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
腎および尿路障害	2 (28.6%)	0 (0.0%)	2 (14.3%)
血尿	1 (14.3%)	0 (0.0%)	1 (7.1%)
頻尿	1 (14.3%)	0 (0.0%)	1 (7.1%)
蛋白尿	1 (14.3%)	0 (0.0%)	1 (7.1%)
呼吸器、胸郭および縦隔障害	1 (14.3%)	0 (0.0%)	1 (7.1%)
口腔咽頭不快感	1 (14.3%)	0 (0.0%)	1 (7.1%)
皮膚および皮下組織障害	2 (28.6%)	1 (14.3%)	3 (21.4%)
多形紅斑	0 (0.0%)	1 (14.3%)	1 (7.1%)
結節性紅斑	0 (0.0%)	1 (14.3%)	1 (7.1%)
全身性皮疹	1 (14.3%)	0 (0.0%)	1 (7.1%)
斑状丘疹状皮疹	0 (0.0%)	1 (14.3%)	1 (7.1%)
不全角化	1 (14.3%)	0 (0.0%)	1 (7.1%)
血管周囲細胞浸潤性皮膚炎	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

表 2.7.4.7-28　治験薬と関連性のある有害事象（210 試験）（安全性解析対象集団）

System organ class Preferred term	40 mg (N=23) n (%)
Number of subjects with at least one related TEAE	23(100.0%)
血液およびリンパ系障害	19(82.6%)
血小板減少症*	18(78.3%)
好中球減少症*	12(52.2%)
白血球減少症*	10(43.5%)
貧血*	9(39.1%)
リンパ球減少症*	2(8.7%)
好酸球増加症	1(4.3%)
発熱性好中球減少症	1(4.3%)
心臓障害	2(8.7%)
第一度房室ブロック	1(4.3%)
動悸	1(4.3%)
胃腸障害	7(30.4%)
下痢	5(21.7%)
悪心	3(13.0%)
腹痛	1(4.3%)
口内炎	1(4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	40 mg (N=23) n (%)
一般・全身障害および投与部位の状態	10(43.5%)
倦怠感	7(30.4%)
疲労	2(8.7%)
発熱	2(8.7%)
悪寒	1(4.3%)
末梢性浮腫	1(4.3%)
感染症および寄生虫症	5(21.7%)
サイトメガロウイルス感染	1(4.3%)
医療機器関連感染	1(4.3%)
口腔カンジダ症	1(4.3%)
ニューモシスチス・イロベチイ肺炎	1(4.3%)
皮膚感染	1(4.3%)
尿路感染	1(4.3%)
臨床検査	8(34.8%)
体重減少	4(17.4%)
アスパラギン酸アミノトランスフェラーゼ増加	2(8.7%)
γ－グルタミルトランスフェラーゼ増加	2(8.7%)
アラニンアミノトランスフェラーゼ増加	1(4.3%)
血中アルカリホスファターゼ増加	1(4.3%)
好酸球数増加	1(4.3%)
リパーゼ増加	1(4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	40 mg (N=23) n (%)
代謝および栄養障害	12(52.2%)
食欲減退	8(34.8%)
低アルブミン血症	3(13.0%)
低ナトリウム血症	2(8.7%)
低カリウム血症	1(4.3%)
低リン酸血症	1(4.3%)
筋骨格系および結合組織障害	1(4.3%)
関節痛	1(4.3%)
神経系障害	7(30.4%)
味覚異常	4(17.4%)
味覚消失	1(4.3%)
頭痛	1(4.3%)
傾眠	1(4.3%)
腎および尿路障害	1(4.3%)
尿瘻	1(4.3%)
呼吸器、胸郭および縦隔障害	2(8.7%)
鼻出血	1(4.3%)
間質性肺疾患	1(4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	40 mg (N=23) n (%)
皮膚および皮下組織障害	5(21.7%)
紅斑	1(4.3%)
多形紅斑	1(4.3%)
光線過敏性反応	1(4.3%)
そう痒症	1(4.3%)
発疹	1(4.3%)
皮膚潰瘍	1(4.3%)
血管障害	1(4.3%)
高血圧	1(4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-29　重症度別の有害事象（203 試験）（安全性解析対象集団）

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
Number of subjects with at least one TEAE	Any Grade	39(100.0)	31(79.5)	39(100.0)
	Grade 1	2(5.1)	5(12.8)	1(2.6)
	Grade 2	4(10.3)	15(38.5)	4(10.3)
	Grade 3	22(56.4)	10(25.6)	22(56.4)
	Grade 4	11(28.2)	1(2.6)	12(30.8)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	33(84.6)	11(28.2)	34(87.2)
血液およびリンパ系障害	Any Grade	38(97.4)	7(17.9)	38(97.4)
	Grade 1	1(2.6)	2(5.1)	1(2.6)
	Grade 2	6(15.4)	1(2.6)	6(15.4)
	Grade 3	20(51.3)	3(7.7)	19(48.7)
	Grade 4	11(28.2)	1(2.6)	12(30.8)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	31(79.5)	4(10.3)	31(79.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
血小板減少症*	Any Grade	35(89.7)	1(2.6)	35(89.7)
	Grade 1	7(17.9)	0(0.0)	6(15.4)
	Grade 2	7(17.9)	0(0.0)	7(17.9)
	Grade 3	14(35.9)	0(0.0)	14(35.9)
	Grade 4	7(17.9)	1(2.6)	8(20.5)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	21(53.8)	1(2.6)	22(56.4)
好中球減少症*	Any Grade	28(71.8)	0(0.0)	28(71.8)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	10(25.6)	0(0.0)	10(25.6)
	Grade 3	13(33.3)	0(0.0)	13(33.3)
	Grade 4	4(10.3)	0(0.0)	4(10.3)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	17(43.6)	0(0.0)	17(43.6)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
白血球減少症*	Any Grade	21(53.8)	3(7.7)	24(61.5)
	Grade 1	1(2.6)	1(2.6)	2(5.1)
	Grade 2	10(25.6)	1(2.6)	11(28.2)
	Grade 3	9(23.1)	1(2.6)	10(25.6)
	Grade 4	1(2.6)	0(0.0)	1(2.6)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	10(25.6)	1(2.6)	11(28.2)
リンパ球減少症*	Any Grade	16(41.0)	0(0.0)	16(41.0)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	3(7.7)	0(0.0)	3(7.7)
	Grade 3	10(25.6)	0(0.0)	10(25.6)
	Grade 4	2(5.1)	0(0.0)	2(5.1)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	12(30.8)	0(0.0)	12(30.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
貧血*	Any Grade	11(28.2)	3(7.7)	14(35.9)
	Grade 1	1(2.6)	1(2.6)	2(5.1)
	Grade 2	5(12.8)	0(0.0)	5(12.8)
	Grade 3	4(10.3)	2(5.1)	6(15.4)
	Grade 4	1(2.6)	0(0.0)	1(2.6)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	5(12.8)	2(5.1)	7(17.9)
発熱性好中球減少症	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(5.1)	0(0.0)	2(5.1)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(5.1)	0(0.0)	2(5.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
再生不良性貧血	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	1(2.6)	0(0.0)	1(2.6)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)
心臓障害	Any Grade	4(10.3)	2(5.1)	6(15.4)
	Grade 1	2(5.1)	1(2.6)	3(7.7)
	Grade 2	2(5.1)	0(0.0)	2(5.1)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
動悸	Any Grade	2(5.1)	1(2.6)	3(7.7)
	Grade 1	2(5.1)	1(2.6)	3(7.7)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
不安定狭心症	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
不整脈	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
心房細動	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
心嚢液貯留	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
耳および迷路障害	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
回転性めまい	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
眼障害	Any Grade	1(2.6)	3(7.7)	4(10.3)
	Grade 1	1(2.6)	2(5.1)	3(7.7)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
結膜出血	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
ドライアイ	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
角膜炎	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
霧視	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
胃腸障害	Any Grade	20(51.3)	13(33.3)	25(64.1)
	Grade 1	10(25.6)	11(28.2)	14(35.9)
	Grade 2	10(25.6)	1(2.6)	10(25.6)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)
下痢	Any Grade	9(23.1)	6(15.4)	14(35.9)
	Grade 1	5(12.8)	5(12.8)	9(23.1)
	Grade 2	4(10.3)	1(2.6)	5(12.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
悪心	Any Grade	9(23.1)	0(0.0)	9(23.1)
	Grade 1	4(10.3)	0(0.0)	4(10.3)
	Grade 2	5(12.8)	0(0.0)	5(12.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
上腹部痛	Any Grade	0(0.0)	2(5.1)	2(5.1)
	Grade 1	0(0.0)	2(5.1)	2(5.1)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
齲歯	Any Grade	1(2.6)	1(2.6)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)
嘔吐	Any Grade	1(2.6)	2(5.1)	2(5.1)
	Grade 1	1(2.6)	2(5.1)	2(5.1)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
腹部不快感	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
腹痛	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
肛門出血	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
便秘	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
消化不良	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
心窩部不快感	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
痔出血	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
口腔粘膜血腫	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
歯痛	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
一般・全身障害および投与部位の状態	Any Grade	16(41.0)	6(15.4)	19(48.7)
	Grade 1	9(23.1)	5(12.8)	11(28.2)
	Grade 2	6(15.4)	1(2.6)	7(17.9)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
倦怠感	Any Grade	8(20.5)	0(0.0)	8(20.5)
	Grade 1	5(12.8)	0(0.0)	5(12.8)
	Grade 2	3(7.7)	0(0.0)	3(7.7)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
発熱	Any Grade	2(5.1)	3(7.7)	5(12.8)
	Grade 1	1(2.6)	3(7.7)	4(10.3)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
疲労	Any Grade	4(10.3)	0(0.0)	4(10.3)
	Grade 1	3(7.7)	0(0.0)	3(7.7)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
末梢性浮腫	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
カテーテル留置部位腫脹	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
胸部不快感	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
胸痛	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
溢出	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
歩行障害	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
口渇	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
免疫系障害	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
薬物過敏症	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
感染症および寄生虫症	Any Grade	7(17.9)	11(28.2)	15(38.5)
	Grade 1	2(5.1)	2(5.1)	2(5.1)
	Grade 2	4(10.3)	8(20.5)	12(30.8)
	Grade 3	1(2.6)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	1(2.6)	1(2.6)
咽頭炎	Any Grade	0(0.0)	3(7.7)	3(7.7)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	2(5.1)	2(5.1)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
気管支炎	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	2(5.1)	0(0.0)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
結膜炎	Any Grade	0(0.0)	2(5.1)	2(5.1)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
インフルエンザ	Any Grade	0(0.0)	2(5.1)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	2(5.1)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
上咽頭炎	Any Grade	1(2.6)	2(5.1)	2(5.1)
	Grade 1	1(2.6)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
上気道感染	Any Grade	0(0.0)	2(5.1)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	2(5.1)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
膀胱炎	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
サイトメガロウイルス感染	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
帯状疱疹	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
膿痂疹	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
ニューモシスチス・イロベチイ肺炎	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
鼻炎	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
傷害、中毒および処置合併症	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
爪損傷	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
臨床検査	Any Grade	19(48.7)	11(28.2)	24(61.5)
	Grade 1	7(17.9)	6(15.4)	9(23.1)
	Grade 2	8(20.5)	4(10.3)	10(25.6)
	Grade 3	4(10.3)	1(2.6)	5(12.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	4(10.3)	1(2.6)	5(12.8)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
血中アルカリホスファターゼ増加	Any Grade	6(15.4)	2(5.1)	8(20.5)
	Grade 1	3(7.7)	1(2.6)	4(10.3)
	Grade 2	2(5.1)	1(2.6)	3(7.7)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)
γ－グルタミルトランスフェラーゼ増加	Any Grade	7(17.9)	1(2.6)	8(20.5)
	Grade 1	1(2.6)	1(2.6)	2(5.1)
	Grade 2	3(7.7)	0(0.0)	3(7.7)
	Grade 3	3(7.7)	0(0.0)	3(7.7)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(7.7)	0(0.0)	3(7.7)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
アスパラギン酸アミノトランスフェラーゼ増加	Any Grade	4(10.3)	4(10.3)	7(17.9)
	Grade 1	2(5.1)	4(10.3)	5(12.8)
	Grade 2	2(5.1)	0(0.0)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
体重減少	Any Grade	2(5.1)	4(10.3)	6(15.4)
	Grade 1	1(2.6)	2(5.1)	3(7.7)
	Grade 2	1(2.6)	1(2.6)	2(5.1)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
アラニンアミノトランスフェラーゼ増加	Any Grade	4(10.3)	3(7.7)	5(12.8)
	Grade 1	2(5.1)	3(7.7)	3(7.7)
	Grade 2	2(5.1)	0(0.0)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
心電図ＱＴ延長	Any Grade	5(12.8)	0(0.0)	5(12.8)
	Grade 1	4(10.3)	0(0.0)	4(10.3)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
血中クレアチニン増加	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
脳性ナトリウム利尿ペプチド増加	Any Grade	1(2.6)	1(2.6)	2(5.1)
	Grade 1	1(2.6)	1(2.6)	2(5.1)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
C－反応性蛋白増加	Any Grade	1(2.6)	1(2.6)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)
好酸球数増加	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
血中コレステロール増加	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
血中クレアチンホスホキナーゼＭＢ増加	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
血中クレアチンホスホキナーゼ増加	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
血中免疫グロブリンA減少	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=39) n (%)
尿中血陽性	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
心胸郭比増加	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
心電図Ｔ波逆転	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
リパーゼ増加	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
体重増加	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
代謝および栄養障害	Any Grade	12(30.8)	6(15.4)	16(41.0)
	Grade 1	2(5.1)	1(2.6)	2(5.1)
	Grade 2	7(17.9)	5(12.8)	11(28.2)
	Grade 3	2(5.1)	0(0.0)	2(5.1)
	Grade 4	1(2.6)	0(0.0)	1(2.6)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(7.7)	0(0.0)	3(7.7)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
食欲減退	Any Grade	8(20.5)	0(0.0)	8(20.5)
	Grade 1	2(5.1)	0(0.0)	2(5.1)
	Grade 2	4(10.3)	0(0.0)	4(10.3)
	Grade 3	2(5.1)	0(0.0)	2(5.1)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(5.1)	0(0.0)	2(5.1)
低アルブミン血症	Any Grade	2(5.1)	2(5.1)	4(10.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	2(5.1)	2(5.1)	4(10.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
低カリウム血症	Any Grade	2(5.1)	1(2.6)	3(7.7)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	1(2.6)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	1(2.6)	0(0.0)	1(2.6)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)
低カルシウム血症	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	2(5.1)	0(0.0)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
低ナトリウム血症	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(5.1)	0(0.0)	2(5.1)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(5.1)	0(0.0)	2(5.1)
糖尿病	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
高カリウム血症	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
高マグネシウム血症	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
高トリグリセリド血症	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
低蛋白血症	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
筋骨格系および結合組織障害	Any Grade	7(17.9)	11(28.2)	15(38.5)
	Grade 1	6(15.4)	6(15.4)	9(23.1)
	Grade 2	1(2.6)	5(12.8)	6(15.4)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
筋痙縮	Any Grade	3(7.7)	2(5.1)	5(12.8)
	Grade 1	3(7.7)	0(0.0)	3(7.7)
	Grade 2	0(0.0)	2(5.1)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
背部痛	Any Grade	1(2.6)	3(7.7)	4(10.3)
	Grade 1	0(0.0)	2(5.1)	2(5.1)
	Grade 2	1(2.6)	1(2.6)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
筋肉痛	Any Grade	0(0.0)	2(5.1)	2(5.1)
	Grade 1	0(0.0)	2(5.1)	2(5.1)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
関節痛	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
関節炎	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
出血性関節症	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
関節腫脹	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
筋肉疲労	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
筋骨格硬直	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
頚部痛	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
四肢痛	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
腱炎	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	Any Grade	1(2.6)	2(5.1)	3(7.7)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
末梢性Ｔ細胞性リンパ腫、組織型不明	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)
皮膚乳頭腫	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
腫瘍疼痛	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
神経系障害	Any Grade	4(10.3)	5(12.8)	7(17.9)
	Grade 1	3(7.7)	2(5.1)	4(10.3)
	Grade 2	1(2.6)	3(7.7)	3(7.7)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
頭痛	Any Grade	2(5.1)	2(5.1)	4(10.3)
	Grade 1	2(5.1)	1(2.6)	3(7.7)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
味覚異常	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
浮動性めまい	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
感覚鈍麻	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
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n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
末梢性感覚ニューロパチー	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
失神寸前の状態	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
精神障害	Any Grade	0(0.0)	4(10.3)	4(10.3)
	Grade 1	0(0.0)	3(7.7)	3(7.7)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
不眠症	Any Grade	0(0.0)	3(7.7)	3(7.7)
	Grade 1	0(0.0)	2(5.1)	2(5.1)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
譫妄	Any Grade	0(0.0)	2(5.1)	2(5.1)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
腎および尿路障害	Any Grade	1(2.6)	2(5.1)	2(5.1)
	Grade 1	0(0.0)	1(2.6)	0(0.0)
	Grade 2	1(2.6)	1(2.6)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
急性腎障害	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
血尿	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
蛋白尿	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
呼吸器、胸郭および縦隔障害	Any Grade	8(20.5)	7(17.9)	14(35.9)
	Grade 1	3(7.7)	2(5.1)	4(10.3)
	Grade 2	3(7.7)	3(7.7)	6(15.4)
	Grade 3	2(5.1)	2(5.1)	4(10.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(5.1)	2(5.1)	4(10.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
肺臓炎	Any Grade	3(7.7)	0(0.0)	3(7.7)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)
咳嗽	Any Grade	1(2.6)	1(2.6)	2(5.1)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=39) n (%)
呼吸困難	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
鼻出血	Any Grade	1(2.6)	1(2.6)	2(5.1)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
口腔咽頭痛	Any Grade	0(0.0)	2(5.1)	2(5.1)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
胸水	Any Grade	1(2.6)	1(2.6)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
咽頭知覚不全	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
間質性肺疾患	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
上気道の炎症	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)
皮膚および皮下組織障害	Any Grade	10(25.6)	10(25.6)	18(46.2)
	Grade 1	5(12.8)	6(15.4)	9(23.1)
	Grade 2	5(12.8)	4(10.3)	9(23.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
発疹	Any Grade	2(5.1)	1(2.6)	3(7.7)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	1(2.6)	1(2.6)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
蕁麻疹	Any Grade	3(7.7)	0(0.0)	3(7.7)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	3(7.7)	0(0.0)	3(7.7)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
紅斑	Any Grade	0(0.0)	2(5.1)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	2(5.1)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
紫斑	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	2(5.1)	0(0.0)	2(5.1)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
斑状丘疹状皮疹	Any Grade	1(2.6)	1(2.6)	2(5.1)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
褥瘡性潰瘍	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
ざ瘡様皮膚炎	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
全身性剥脱性皮膚炎	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
皮膚乾燥	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
皮脂欠乏性湿疹	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
多形紅斑	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
全身紅斑	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
皮膚疼痛	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
点状出血	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
色素沈着障害	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
全身性そう痒症	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
そう痒性皮疹	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
血管障害	Any Grade	0(0.0)	2(5.1)	2(5.1)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
低血圧	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
末梢動脈閉塞性疾患	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
Number of subjects with at least one TEAE	Any Grade	12(75.0)	14(87.5)	16(100.0)
	Grade 1	1(6.3)	2(12.5)	0(0.0)
	Grade 2	2(12.5)	7(43.8)	4(25.0)
	Grade 3	7(43.8)	3(18.8)	8(50.0)
	Grade 4	1(6.3)	2(12.5)	3(18.8)
	Grade 5	1(6.3)	0(0.0)	1(6.3)
	>=Grade 3	9(56.3)	5(31.3)	12(75.0)
血液およびリンパ系障害	Any Grade	9(56.3)	6(37.5)	14(87.5)
	Grade 1	1(6.3)	0(0.0)	1(6.3)
	Grade 2	2(12.5)	2(12.5)	3(18.8)
	Grade 3	5(31.3)	3(18.8)	8(50.0)
	Grade 4	1(6.3)	1(6.3)	2(12.5)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	6(37.5)	4(25.0)	10(62.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
血小板減少症*	Any Grade	7(43.8)	4(25.0)	11(68.8)
	Grade 1	2(12.5)	0(0.0)	2(12.5)
	Grade 2	2(12.5)	1(6.3)	3(18.8)
	Grade 3	3(18.8)	2(12.5)	5(31.3)
	Grade 4	0(0.0)	1(6.3)	1(6.3)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(18.8)	3(18.8)	6(37.5)
貧血*	Any Grade	1(6.3)	3(18.8)	4(25.0)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	2(12.5)	2(12.5)
	Grade 3	1(6.3)	1(6.3)	2(12.5)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	1(6.3)	2(12.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
好中球減少症*	Any Grade	3(18.8)	0(0.0)	3(18.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(12.5)	0(0.0)	2(12.5)
	Grade 4	1(6.3)	0(0.0)	1(6.3)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(18.8)	0(0.0)	3(18.8)
好酸球増加症	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
発熱性好中球減少症	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)
心臓障害	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
心房細動	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
耳および迷路障害	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
耳痛	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
眼障害	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
白内障	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
胃腸障害	Any Grade	5(31.3)	6(37.5)	7(43.8)
	Grade 1	0(0.0)	3(18.8)	1(6.3)
	Grade 2	4(25.0)	3(18.8)	5(31.3)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
下痢	Any Grade	1(6.3)	2(12.5)	3(18.8)
	Grade 1	0(0.0)	2(12.5)	2(12.5)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)
悪心	Any Grade	2(12.5)	1(6.3)	3(18.8)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	2(12.5)	0(0.0)	2(12.5)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
腹痛	Any Grade	1(6.3)	1(6.3)	2(12.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(6.3)	1(6.3)	2(12.5)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
口内炎	Any Grade	0(0.0)	2(12.5)	2(12.5)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
胃潰瘍	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
胃炎	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(6.3)	0(0.0)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
嘔吐	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
一般・全身障害および投与部位の状態	Any Grade	1(6.3)	7(43.8)	8(50.0)
	Grade 1	1(6.3)	3(18.8)	4(25.0)
	Grade 2	0(0.0)	4(25.0)	4(25.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
発熱	Any Grade	0(0.0)	6(37.5)	6(37.5)
	Grade 1	0(0.0)	6(37.5)	6(37.5)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
無力症	Any Grade	1(6.3)	1(6.3)	2(12.5)
	Grade 1	1(6.3)	0(0.0)	1(6.3)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
疲労	Any Grade	0(0.0)	2(12.5)	2(12.5)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
インフルエンザ様疾患	Any Grade	0(0.0)	2(12.5)	2(12.5)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
末梢性浮腫	Any Grade	0(0.0)	2(12.5)	2(12.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	2(12.5)	2(12.5)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
感染症および寄生虫症	Any Grade	1(6.3)	4(25.0)	4(25.0)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	2(12.5)	1(6.3)
	Grade 3	0(0.0)	1(6.3)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	1(6.3)	0(0.0)	1(6.3)
	>=Grade 3	1(6.3)	1(6.3)	2(12.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
上気道感染	Any Grade	0(0.0)	2(12.5)	2(12.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	2(12.5)	2(12.5)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
感染性小腸結腸炎	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(6.3)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(6.3)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
胃腸炎	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
肺炎	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	1(6.3)	0(0.0)	1(6.3)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
ブドウ球菌皮膚感染	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(6.3)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(6.3)	1(6.3)
傷害、中毒および処置合併症	Any Grade	0(0.0)	2(12.5)	2(12.5)
	Grade 1	0(0.0)	2(12.5)	2(12.5)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
胃瘻管部合併症	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
処置による疼痛	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
臨床検査	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)
C－反応性蛋白増加	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
代謝および栄養障害	Any Grade	4(25.0)	5(31.3)	9(56.3)
	Grade 1	2(12.5)	1(6.3)	3(18.8)
	Grade 2	2(12.5)	2(12.5)	4(25.0)
	Grade 3	0(0.0)	1(6.3)	1(6.3)
	Grade 4	0(0.0)	1(6.3)	1(6.3)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	2(12.5)	2(12.5)
食欲減退	Any Grade	4(25.0)	1(6.3)	5(31.3)
	Grade 1	2(12.5)	1(6.3)	3(18.8)
	Grade 2	2(12.5)	0(0.0)	2(12.5)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
低カリウム血症	Any Grade	0(0.0)	2(12.5)	2(12.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	1(6.3)	1(6.3)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(6.3)	1(6.3)
低アルブミン血症	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
低カルシウム血症	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(6.3)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(6.3)	1(6.3)
筋骨格系および結合組織障害	Any Grade	0(0.0)	4(25.0)	4(25.0)
	Grade 1	0(0.0)	2(12.5)	2(12.5)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	1(6.3)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(6.3)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
背部痛	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
筋肉疲労	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(6.3)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(6.3)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
筋力低下	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
肩回旋筋腱板症候群	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
腫瘍疼痛	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
神経系障害	Any Grade	0(0.0)	2(12.5)	2(12.5)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
頭痛	Any Grade	0(0.0)	2(12.5)	2(12.5)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
精神障害	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
不眠症	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
生殖系および乳房障害	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
陰嚢浮腫	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
呼吸器、胸郭および縦隔障害	Any Grade	1(6.3)	7(43.8)	7(43.8)
	Grade 1	0(0.0)	4(25.0)	3(18.8)
	Grade 2	0(0.0)	3(18.8)	3(18.8)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)
咳嗽	Any Grade	0(0.0)	4(25.0)	4(25.0)
	Grade 1	0(0.0)	4(25.0)	4(25.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
呼吸困難	Any Grade	0(0.0)	2(12.5)	2(12.5)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
発声障害	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
労作性呼吸困難	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
しゃっくり	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
口腔咽頭痛	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
肺臓炎	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
湿性咳嗽	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
アレルギー性鼻炎	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
鼻漏	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
皮膚および皮下組織障害	Any Grade	2(12.5)	3(18.8)	5(31.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	1(6.3)	2(12.5)	3(18.8)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
発疹	Any Grade	1(6.3)	1(6.3)	2(12.5)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)
蕁麻疹	Any Grade	0(0.0)	2(12.5)	2(12.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	2(12.5)	2(12.5)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
全身性そう痒症	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(6.3)	0(0.0)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
血管障害	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=16) n (%)
深部静脈血栓症	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(6.3)	1(6.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
Number of subjects with at least one TEAE	Any Grade	51(92.7)	45(81.8)	55(100.0)
	Grade 1	3(5.5)	7(12.7)	1(1.8)
	Grade 2	6(10.9)	22(40.0)	8(14.5)
	Grade 3	29(52.7)	13(23.6)	30(54.5)
	Grade 4	12(21.8)	3(5.5)	15(27.3)
	Grade 5	1(1.8)	0(0.0)	1(1.8)
	>=Grade 3	42(76.4)	16(29.1)	46(83.6)
血液およびリンパ系障害	Any Grade	47(85.5)	13(23.6)	52(94.5)
	Grade 1	2(3.6)	2(3.6)	2(3.6)
	Grade 2	8(14.5)	3(5.5)	9(16.4)
	Grade 3	25(45.5)	6(10.9)	27(49.1)
	Grade 4	12(21.8)	2(3.6)	14(25.5)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	37(67.3)	8(14.5)	41(74.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
血小板减少症*	Any Grade	42(76.4)	5(9.1)	46(83.6)
	Grade 1	9(16.4)	0(0.0)	8(14.5)
	Grade 2	9(16.4)	1(1.8)	10(18.2)
	Grade 3	17(30.9)	2(3.6)	19(34.5)
	Grade 4	7(12.7)	2(3.6)	9(16.4)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	24(43.6)	4(7.3)	28(50.9)
好中球减少症*	Any Grade	31(56.4)	0(0.0)	31(56.4)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	10(18.2)	0(0.0)	10(18.2)
	Grade 3	15(27.3)	0(0.0)	15(27.3)
	Grade 4	5(9.1)	0(0.0)	5(9.1)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	20(36.4)	0(0.0)	20(36.4)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
白血球減少症*	Any Grade	21(38.2)	3(5.5)	24(43.6)
	Grade 1	1(1.8)	1(1.8)	2(3.6)
	Grade 2	10(18.2)	1(1.8)	11(20.0)
	Grade 3	9(16.4)	1(1.8)	10(18.2)
	Grade 4	1(1.8)	0(0.0)	1(1.8)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	10(18.2)	1(1.8)	11(20.0)
貧血*	Any Grade	12(21.8)	6(10.9)	18(32.7)
	Grade 1	1(1.8)	1(1.8)	2(3.6)
	Grade 2	5(9.1)	2(3.6)	7(12.7)
	Grade 3	5(9.1)	3(5.5)	8(14.5)
	Grade 4	1(1.8)	0(0.0)	1(1.8)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	6(10.9)	3(5.5)	9(16.4)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
リンパ球減少症*	Any Grade	16(29.1)	0(0.0)	16(29.1)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	3(5.5)	0(0.0)	3(5.5)
	Grade 3	10(18.2)	0(0.0)	10(18.2)
	Grade 4	2(3.6)	0(0.0)	2(3.6)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	12(21.8)	0(0.0)	12(21.8)
発熱性好中球減少症	Any Grade	3(5.5)	0(0.0)	3(5.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	3(5.5)	0(0.0)	3(5.5)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(5.5)	0(0.0)	3(5.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
再生不良性貧血	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	1(1.8)	0(0.0)	1(1.8)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)
好酸球増加症	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
心臓障害	Any Grade	4(7.3)	3(5.5)	7(12.7)
	Grade 1	2(3.6)	1(1.8)	3(5.5)
	Grade 2	2(3.6)	1(1.8)	3(5.5)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)
動悸	Any Grade	2(3.6)	1(1.8)	3(5.5)
	Grade 1	2(3.6)	1(1.8)	3(5.5)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
心房細動	Any Grade	1(1.8)	1(1.8)	2(3.6)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
不安定狭心症	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
不整脈	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
心嚢液貯留	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
耳および迷路障害	Any Grade	1(1.8)	1(1.8)	2(3.6)
	Grade 1	1(1.8)	1(1.8)	2(3.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
耳痛	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
回転性めまい	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
眼障害	Any Grade	1(1.8)	4(7.3)	5(9.1)
	Grade 1	1(1.8)	3(5.5)	4(7.3)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
白内障	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
結膜出血	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
ドライアイ	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
角膜炎	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
霧視	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
胃腸障害	Any Grade	25(45.5)	19(34.5)	32(58.2)
	Grade 1	10(18.2)	14(25.5)	15(27.3)
	Grade 2	14(25.5)	4(7.3)	15(27.3)
	Grade 3	1(1.8)	1(1.8)	2(3.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	1(1.8)	2(3.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
下痢	Any Grade	10(18.2)	8(14.5)	17(30.9)
	Grade 1	5(9.1)	7(12.7)	11(20.0)
	Grade 2	4(7.3)	1(1.8)	5(9.1)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)
悪心	Any Grade	11(20.0)	1(1.8)	12(21.8)
	Grade 1	4(7.3)	1(1.8)	5(9.1)
	Grade 2	7(12.7)	0(0.0)	7(12.7)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
腹痛	Any Grade	1(1.8)	2(3.6)	3(5.5)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	1(1.8)	1(1.8)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
嘔吐	Any Grade	1(1.8)	3(5.5)	3(5.5)
	Grade 1	1(1.8)	2(3.6)	2(3.6)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
上腹部痛	Any Grade	0(0.0)	2(3.6)	2(3.6)
	Grade 1	0(0.0)	2(3.6)	2(3.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
齲歯	Any Grade	1(1.8)	1(1.8)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
口内炎	Any Grade	0(0.0)	2(3.6)	2(3.6)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
腹部不快感	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
肛門出血	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
便秘	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
消化不良	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
心窩部不快感	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
胃潰瘍	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
胃炎	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
痔出血	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
口腔粘膜血腫	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
歯痛	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
一般・全身障害および投与部位の状態	Any Grade	17(30.9)	13(23.6)	27(49.1)
	Grade 1	10(18.2)	8(14.5)	15(27.3)
	Grade 2	6(10.9)	5(9.1)	11(20.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
発熱	Any Grade	2(3.6)	9(16.4)	11(20.0)
	Grade 1	1(1.8)	9(16.4)	10(18.2)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
倦怠感	Any Grade	8(14.5)	0(0.0)	8(14.5)
	Grade 1	5(9.1)	0(0.0)	5(9.1)
	Grade 2	3(5.5)	0(0.0)	3(5.5)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
疲労	Any Grade	4(7.3)	2(3.6)	6(10.9)
	Grade 1	3(5.5)	1(1.8)	4(7.3)
	Grade 2	1(1.8)	1(1.8)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
末梢性浮腫	Any Grade	2(3.6)	2(3.6)	4(7.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	2(3.6)	3(5.5)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
無力症	Any Grade	1(1.8)	1(1.8)	2(3.6)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
インフルエンザ様疾患	Any Grade	0(0.0)	2(3.6)	2(3.6)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
カテーテル留置部位腫脹	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
胸部不快感	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
胸痛	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
溢出	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
歩行障害	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
口渇	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
免疫系障害	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
薬物過敏症	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
感染症および寄生虫症	Any Grade	8(14.5)	15(27.3)	19(34.5)
	Grade 1	2(3.6)	3(5.5)	3(5.5)
	Grade 2	4(7.3)	10(18.2)	13(23.6)
	Grade 3	1(1.8)	2(3.6)	2(3.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	1(1.8)	0(0.0)	1(1.8)
	>=Grade 3	2(3.6)	2(3.6)	3(5.5)
上気道感染	Any Grade	0(0.0)	4(7.3)	4(7.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	4(7.3)	4(7.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
咽頭炎	Any Grade	0(0.0)	3(5.5)	3(5.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	2(3.6)	2(3.6)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)
気管支炎	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	2(3.6)	0(0.0)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
結膜炎	Any Grade	0(0.0)	2(3.6)	2(3.6)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
インフルエンザ	Any Grade	0(0.0)	2(3.6)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	2(3.6)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
上咽頭炎	Any Grade	1(1.8)	2(3.6)	2(3.6)
	Grade 1	1(1.8)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
膀胱炎	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
サイトメガロウイルス感染	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
感染性小腸結腸炎	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
胃腸炎	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
帯状疱疹	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
膿痂疹	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
ニューモシスチス・イロベチイ肺炎	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
肺炎	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	1(1.8)	0(0.0)	1(1.8)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)
鼻炎	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
ブドウ球菌皮膚感染	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)
傷害、中毒および処置合併症	Any Grade	0(0.0)	3(5.5)	3(5.5)
	Grade 1	0(0.0)	2(3.6)	2(3.6)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
胃瘻管部合併症	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
爪損傷	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
処置による疼痛	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
臨床検査	Any Grade	20(36.4)	11(20.0)	25(45.5)
	Grade 1	7(12.7)	6(10.9)	9(16.4)
	Grade 2	8(14.5)	4(7.3)	10(18.2)
	Grade 3	5(9.1)	1(1.8)	6(10.9)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	5(9.1)	1(1.8)	6(10.9)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
血中アルカリホスファターゼ増加	Any Grade	6(10.9)	2(3.6)	8(14.5)
	Grade 1	3(5.5)	1(1.8)	4(7.3)
	Grade 2	2(3.6)	1(1.8)	3(5.5)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)
γーグルタミルトランスフェラーゼ増加	Any Grade	7(12.7)	1(1.8)	8(14.5)
	Grade 1	1(1.8)	1(1.8)	2(3.6)
	Grade 2	3(5.5)	0(0.0)	3(5.5)
	Grade 3	3(5.5)	0(0.0)	3(5.5)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(5.5)	0(0.0)	3(5.5)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
アスパラギン酸アミノトランスフェラーゼ増加	Any Grade	4(7.3)	4(7.3)	7(12.7)
	Grade 1	2(3.6)	4(7.3)	5(9.1)
	Grade 2	2(3.6)	0(0.0)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
体重減少	Any Grade	2(3.6)	4(7.3)	6(10.9)
	Grade 1	1(1.8)	2(3.6)	3(5.5)
	Grade 2	1(1.8)	1(1.8)	2(3.6)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
アラニンアミノトランスフェラーゼ増加	Any Grade	4(7.3)	3(5.5)	5(9.1)
	Grade 1	2(3.6)	3(5.5)	3(5.5)
	Grade 2	2(3.6)	0(0.0)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
心電図ＱＴ延長	Any Grade	5(9.1)	0(0.0)	5(9.1)
	Grade 1	4(7.3)	0(0.0)	4(7.3)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
C－反応性蛋白増加	Any Grade	2(3.6)	1(1.8)	3(5.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	2(3.6)	0(0.0)	2(3.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(3.6)	0(0.0)	2(3.6)
血中クレアチニン増加	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
脳性ナトリウム利尿ペプチド増加	Any Grade	1(1.8)	1(1.8)	2(3.6)
	Grade 1	1(1.8)	1(1.8)	2(3.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
好酸球数増加	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
血中コレステロール増加	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
血中クレアチンホスホキナーゼＭＢ増加	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
血中クレアチンホスホキナーゼ増加	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
血中免疫グロブリンA減少	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
尿中血陽性	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
心胸郭比増加	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
心電図Ｔ波逆転	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
リパーゼ増加	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
体重増加	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
代謝および栄養障害	Any Grade	16(29.1)	11(20.0)	25(45.5)
	Grade 1	4(7.3)	2(3.6)	5(9.1)
	Grade 2	9(16.4)	7(12.7)	15(27.3)
	Grade 3	2(3.6)	1(1.8)	3(5.5)
	Grade 4	1(1.8)	1(1.8)	2(3.6)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(5.5)	2(3.6)	5(9.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
食欲減退	Any Grade	12(21.8)	1(1.8)	13(23.6)
	Grade 1	4(7.3)	1(1.8)	5(9.1)
	Grade 2	6(10.9)	0(0.0)	6(10.9)
	Grade 3	2(3.6)	0(0.0)	2(3.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(3.6)	0(0.0)	2(3.6)
低アルブミン血症	Any Grade	2(3.6)	3(5.5)	5(9.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	2(3.6)	3(5.5)	5(9.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
低カリウム血症	Any Grade	2(3.6)	3(5.5)	5(9.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	2(3.6)	3(5.5)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	1(1.8)	1(1.8)	2(3.6)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	1(1.8)	2(3.6)
低カルシウム血症	Any Grade	2(3.6)	1(1.8)	3(5.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	2(3.6)	0(0.0)	2(3.6)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
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n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
低ナトリウム血症	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(3.6)	0(0.0)	2(3.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(3.6)	0(0.0)	2(3.6)
糖尿病	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
高カリウム血症	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
高マグネシウム血症	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
高トリグリセリド血症	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
低蛋白血症	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
筋骨格系および結合組織障害	Any Grade	7(12.7)	15(27.3)	19(34.5)
	Grade 1	6(10.9)	8(14.5)	11(20.0)
	Grade 2	1(1.8)	6(10.9)	7(12.7)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)
背部痛	Any Grade	1(1.8)	4(7.3)	5(9.1)
	Grade 1	0(0.0)	3(5.5)	3(5.5)
	Grade 2	1(1.8)	1(1.8)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
筋痙縮	Any Grade	3(5.5)	2(3.6)	5(9.1)
	Grade 1	3(5.5)	0(0.0)	3(5.5)
	Grade 2	0(0.0)	2(3.6)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
筋肉疲労	Any Grade	1(1.8)	1(1.8)	2(3.6)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
筋肉痛	Any Grade	0(0.0)	2(3.6)	2(3.6)
	Grade 1	0(0.0)	2(3.6)	2(3.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
関節痛	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
関節炎	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
出血性関節症	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
関節腫脹	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
筋力低下	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
筋骨格硬直	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
頚部痛	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
四肢痛	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
肩回旋筋腱板症候群	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
腱炎	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	Any Grade	1(1.8)	3(5.5)	4(7.3)
	Grade 1	0(0.0)	2(3.6)	2(3.6)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
腫瘍疼痛	Any Grade	0(0.0)	2(3.6)	2(3.6)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
末梢性Ｔ細胞性リンパ腫、組織型不明	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
皮膚乳頭腫	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
神経系障害	Any Grade	4(7.3)	7(12.7)	9(16.4)
	Grade 1	3(5.5)	3(5.5)	5(9.1)
	Grade 2	1(1.8)	4(7.3)	4(7.3)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
頭痛	Any Grade	2(3.6)	4(7.3)	6(10.9)
	Grade 1	2(3.6)	2(3.6)	4(7.3)
	Grade 2	0(0.0)	2(3.6)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
味覚異常	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
浮動性めまい	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
感覚鈍麻	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
末梢性感覚ニューロパチー	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
失神寸前の状態	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
精神障害	Any Grade	0(0.0)	5(9.1)	5(9.1)
	Grade 1	0(0.0)	3(5.5)	3(5.5)
	Grade 2	0(0.0)	2(3.6)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
不眠症	Any Grade	0(0.0)	4(7.3)	4(7.3)
	Grade 1	0(0.0)	2(3.6)	2(3.6)
	Grade 2	0(0.0)	2(3.6)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
譫妄	Any Grade	0(0.0)	2(3.6)	2(3.6)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
腎および尿路障害	Any Grade	1(1.8)	2(3.6)	2(3.6)
	Grade 1	0(0.0)	1(1.8)	0(0.0)
	Grade 2	1(1.8)	1(1.8)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
急性腎障害	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
血尿	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
蛋白尿	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
生殖系および乳房障害	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
陰嚢浮腫	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
呼吸器、胸郭および縦隔障害	Any Grade	9(16.4)	14(25.5)	21(38.2)
	Grade 1	3(5.5)	6(10.9)	7(12.7)
	Grade 2	3(5.5)	6(10.9)	9(16.4)
	Grade 3	3(5.5)	2(3.6)	5(9.1)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(5.5)	2(3.6)	5(9.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
咳嗽	Any Grade	1(1.8)	5(9.1)	6(10.9)
	Grade 1	1(1.8)	4(7.3)	5(9.1)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
呼吸困難	Any Grade	2(3.6)	2(3.6)	4(7.3)
	Grade 1	1(1.8)	1(1.8)	2(3.6)
	Grade 2	1(1.8)	1(1.8)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
肺臓炎	Any Grade	4(7.3)	0(0.0)	4(7.3)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	2(3.6)	0(0.0)	2(3.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(3.6)	0(0.0)	2(3.6)
口腔咽頭痛	Any Grade	0(0.0)	3(5.5)	3(5.5)
	Grade 1	0(0.0)	2(3.6)	2(3.6)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
鼻出血	Any Grade	1(1.8)	1(1.8)	2(3.6)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
胸水	Any Grade	1(1.8)	1(1.8)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
咽頭知覚不全	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
発声障害	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
労作性呼吸困難	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
しゃっくり	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
間質性肺疾患	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)
湿性咳嗽	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
アレルギー性鼻炎	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
鼻漏	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
上気道の炎症	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)
皮膚および皮下組織障害	Any Grade	12(21.8)	13(23.6)	23(41.8)
	Grade 1	5(9.1)	7(12.7)	10(18.2)
	Grade 2	6(10.9)	6(10.9)	12(21.8)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
発疹	Any Grade	3(5.5)	2(3.6)	5(9.1)
	Grade 1	1(1.8)	1(1.8)	2(3.6)
	Grade 2	1(1.8)	1(1.8)	2(3.6)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)
蕁麻疹	Any Grade	3(5.5)	2(3.6)	5(9.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	3(5.5)	2(3.6)	5(9.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
紅斑	Any Grade	0(0.0)	2(3.6)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	2(3.6)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
全身性そう痒症	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	2(3.6)	0(0.0)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
紫斑	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	2(3.6)	0(0.0)	2(3.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
斑状丘疹状皮疹	Any Grade	1(1.8)	1(1.8)	2(3.6)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
褥瘡性潰瘍	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
ざ瘡様皮膚炎	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
全身性剥脱性皮膚炎	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
皮膚乾燥	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
皮脂欠乏性湿疹	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
多形紅斑	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
全身紅斑	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
皮膚疼痛	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
点状出血	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
色素沈着障害	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
そう痒性皮疹	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
血管障害	Any Grade	0(0.0)	3(5.5)	3(5.5)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
深部静脈血栓症	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
低血圧	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
末梢動脈閉塞性疾患	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-30　重症度別の有害事象（201 試験）（安全性解析対象集団）

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Number of patients with at least one TEAE	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 3	5 (71.4%)	4 (57.1%)	9 (64.3%)
	Grade 4	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
血液およびリンパ系障害	Grade 1	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 2	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Grade 3	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Grade 4	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
貧血	Grade 1	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 2	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 3	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
白血球減少症	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
好中球減少症	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 4	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
血小板減少症	Grade 1	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 2	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Grade 3	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
先天性、家族性および遺伝性障害	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
表皮融解	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
耳および迷路障害	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
回転性めまい	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
胃腸障害	Grade 1	1 (14.3%)	3 (42.9%)	4 (28.6%)
	Grade 2	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 3	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
腹痛	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
便秘	Grade 1	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
下痢	Grade 1	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
口内乾燥	Grade 1	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
腸炎	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
悪心	Grade 1	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
口内炎	Grade 1	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
嘔吐	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
一般・全身障害および投与部位の状態	Grade 1	2 (28.6%)	2 (28.6%)	4 (28.6%)
	Grade 2	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 3	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
疲労	Grade 1	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
治癒不良	Grade 1	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
末梢性浮腫	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
発熱	Grade 1	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
感染症および寄生虫症	Grade 1	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 2	1 (14.3%)	2 (28.6%)	3 (21.4%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
結膜炎	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
膀胱炎	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
鼻咽頭炎	Grade 1	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
食道カンジダ症	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
咽頭炎	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
副鼻腔炎	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
傷害、中毒および処置合併症	Grade 1	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
挫傷	Grade 1	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
臨床検査	Grade 1	1 (14.3%)	2 (28.6%)	3 (21.4%)
	Grade 2	0 (0.0%)	3 (42.9%)	3 (21.4%)
	Grade 3	3 (42.9%)	2 (28.6%)	5 (35.7%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
アラニンアミノトランスフェラーゼ増加	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
アスパラギン酸アミノトランスフェラーゼ増加	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
血中クレアチンホスホキナーゼ増加	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ｃ－反応性蛋白増加	Grade 1	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
低比重リポ蛋白増加	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
リンパ球数減少	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
好中球数減少	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
血小板数減少	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	3 (42.9%)	3 (42.9%)	6 (42.9%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
体重减少	Grade 1	1 (14.3%)	2 (28.6%)	3 (21.4%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
体重增加	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
白血球数减少	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 3	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
トランスアミナーゼ上昇	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
胸部コンピュータ断層撮影異常	Grade 1	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
トロポニンＩ増加	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
血中アルカリホスファターゼ増加	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
代謝および栄養障害	Grade 1	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Grade 2	2 (28.6%)	3 (42.9%)	5 (35.7%)
	Grade 3	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
糖尿病	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
高血糖	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
高マグネシウム血症	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
高トリグリセリド血症	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
高尿酸血症	Grade 1	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
低カルシウム血症	Grade 1	0 (0.0%)	3 (42.9%)	3 (21.4%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
低カリウム血症	Grade 1	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
低マグネシウム血症	Grade 1	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
血液量減少症	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
食欲減退	Grade 1	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 2	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
筋骨格系および結合組織障害	Grade 1	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
背部痛	Grade 1	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
筋肉痛	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
筋骨格系胸痛	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
神経系障害	Grade 1	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
味覚異常	Grade 1	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
頭痛	Grade 1	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
パーキンソニズム	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
精神障害	Grade 1	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
不眠症	Grade 1	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
腎および尿路障害	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
血尿	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
頻尿	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
蛋白尿	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
尿管結石症	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
呼吸器、胸郭および縦隔障害	Grade 1	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
胸水	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
口腔咽頭不快感	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
皮膚および皮下組織障害	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
多形紅斑	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
結節性紅斑	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
全身性皮疹	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
斑状丘疹状皮疹	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
不全角化	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

System organ class Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
血管周囲細胞浸潤性皮膚炎	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
血管障害	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
低血圧	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Patients with more than one TEAE will be counted once in the worst severity category.

表 2.7.4.7-31　重症度別の有害事象（210 試験）（安全性解析対象集団）

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
Number of subjects with at least one TEAE	Any Grade	23(100.0%)	13(56.5%)	23(100.0%)
	Grade 1	3(13.0%)	2(8.7%)	1(4.3%)
	Grade 2	2(8.7%)	10(43.5%)	4(17.4%)
	Grade 3	9(39.1%)	0(0.0%)	9(39.1%)
	Grade 4	9(39.1%)	1(4.3%)	9(39.1%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	18(78.3%)	1(4.3%)	18(78.3%)
血液およびリンパ系障害	Any Grade	19(82.6%)	0(0.0%)	19(82.6%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 3	8(34.8%)	0(0.0%)	8(34.8%)
	Grade 4	8(34.8%)	0(0.0%)	8(34.8%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	16(69.6%)	0(0.0%)	16(69.6%)
血小板減少症*	Any Grade	18(78.3%)	0(0.0%)	18(78.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	5(21.7%)	0(0.0%)	5(21.7%)
	Grade 3	6(26.1%)	0(0.0%)	6(26.1%)
	Grade 4	6(26.1%)	0(0.0%)	6(26.1%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	12(52.2%)	0(0.0%)	12(52.2%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
好中球減少症*	Any Grade	12(52.2%)	0(0.0%)	12(52.2%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 3	7(30.4%)	0(0.0%)	7(30.4%)
	Grade 4	3(13.0%)	0(0.0%)	3(13.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	10(43.5%)	0(0.0%)	10(43.5%)
白血球減少症*	Any Grade	10(43.5%)	0(0.0%)	10(43.5%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 3	7(30.4%)	0(0.0%)	7(30.4%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	7(30.4%)	0(0.0%)	7(30.4%)
貧血*	Any Grade	9(39.1%)	0(0.0%)	9(39.1%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	3(13.0%)	0(0.0%)	3(13.0%)
	Grade 3	5(21.7%)	0(0.0%)	5(21.7%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	5(21.7%)	0(0.0%)	5(21.7%)

Source: Listing 16 2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

Subjects are counted only once for the worst grade under each relationship column.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
リンパ球減少症*	Any Grade	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
好酸球増加症	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
発熱性好中球減少症	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
心臓障害	Any Grade	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 1	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
第一度房室ブロック	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
動悸	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
眼障害	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
ドライアイ	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
胃腸障害	Any Grade	7(30.4%)	2(8.7%)	9(39.1%)
	Grade 1	6(26.1%)	1(4.3%)	7(30.4%)
	Grade 2	1(4.3%)	1(4.3%)	2(8.7%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16 2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
下痢	Any Grade	5(21.7%)	1(4.3%)	6(26.1%)
	Grade 1	4(17.4%)	1(4.3%)	5(21.7%)
	Grade 2	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
腹痛	Any Grade	1(4.3%)	2(8.7%)	3(13.0%)
	Grade 1	1(4.3%)	1(4.3%)	2(8.7%)
	Grade 2	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
悪心	Any Grade	3(13.0%)	0(0.0%)	3(13.0%)
	Grade 1	3(13.0%)	0(0.0%)	3(13.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

Subjects are counted only once for the worst grade under each relationship column.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
口内炎	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
一般・全身障害および投与部位の状態	Any Grade	10(43.5%)	3(13.0%)	13(56.5%)
	Grade 1	7(30.4%)	2(8.7%)	9(39.1%)
	Grade 2	1(4.3%)	1(4.3%)	2(8.7%)
	Grade 3	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	2(8.7%)	0(0.0%)	2(8.7%)
倦怠感	Any Grade	7(30.4%)	0(0.0%)	7(30.4%)
	Grade 1	5(21.7%)	0(0.0%)	5(21.7%)
	Grade 2	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
疲労	Any Grade	2(8.7%)	1(4.3%)	3(13.0%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 3	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	2(8.7%)	0(0.0%)	2(8.7%)
発熱	Any Grade	2(8.7%)	1(4.3%)	3(13.0%)
	Grade 1	2(8.7%)	1(4.3%)	3(13.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
悪寒	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

Subjects are counted only once for the worst grade under each relationship column.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
非心臓性胸痛	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
末梢性浮腫	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
感染症および寄生虫症	Any Grade	5(21.7%)	4(17.4%)	7(30.4%)
	Grade 1	1(4.3%)	1(4.3%)	1(4.3%)
	Grade 2	1(4.3%)	3(13.0%)	3(13.0%)
	Grade 3	3(13.0%)	0(0.0%)	3(13.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	3(13.0%)	0(0.0%)	3(13.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
細菌感染	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
サイトメガロウイルス感染	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
医療機器関連感染	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
麦粒腫	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
口腔カンジダ症	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
ニューモシスチス・イロベチイ肺炎	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
皮膚感染	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
扁桃炎	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
上気道感染	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

Subjects are counted only once for the worst grade under each relationship column.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
尿路感染	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
傷害、中毒および処置合併症	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
挫傷	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
臨床検査	Any Grade	8(34.8%)	2(8.7%)	10(43.5%)
	Grade 1	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 2	3(13.0%)	2(8.7%)	5(21.7%)
	Grade 3	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 4	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	3(13.0%)	0(0.0%)	3(13.0%)
体重減少	Any Grade	4(17.4%)	0(0.0%)	4(17.4%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	3(13.0%)	0(0.0%)	3(13.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
アスパラギン酸アミノトランスフェラーゼ増加	Any Grade	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 1	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
γーグルタミルトランスフェラーゼ増加	Any Grade	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
アラニンアミノトランスフェラーゼ増加	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
血中アルカリホスファターゼ増加	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
血中乳酸脱水素酵素増加	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
脳性ナトリウム利尿ペプチド増加	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
好酸球数増加	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
リパーゼ増加	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
代謝および栄養障害	Any Grade	12(52.2%)	1(4.3%)	13(56.5%)
	Grade 1	4(17.4%)	1(4.3%)	5(21.7%)
	Grade 2	6(26.1%)	0(0.0%)	6(26.1%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	2(8.7%)	0(0.0%)	2(8.7%)
食欲減退	Any Grade	8(34.8%)	0(0.0%)	8(34.8%)
	Grade 1	4(17.4%)	0(0.0%)	4(17.4%)
	Grade 2	4(17.4%)	0(0.0%)	4(17.4%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
低アルブミン血症	Any Grade	3(13.0%)	0(0.0%)	3(13.0%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	3(13.0%)	0(0.0%)	3(13.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
低ナトリウム血症	Any Grade	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
高カルシウム血症	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
低カリウム血症	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
低リン酸血症	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
筋骨格系および結合組織障害	Any Grade	1(4.3%)	6(26.1%)	7(30.4%)
	Grade 1	0(0.0%)	5(21.7%)	5(21.7%)
	Grade 2	1(4.3%)	1(4.3%)	2(8.7%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16 2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
背部痛	Any Grade	0(0.0%)	4(17.4%)	4(17.4%)
	Grade 1	0(0.0%)	3(13.0%)	3(13.0%)
	Grade 2	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
関節痛	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
脊椎すべり症	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

Subjects are counted only once for the worst grade under each relationship column.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
尺骨突き上げ症候群	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
腫瘍疼痛	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
神経系障害	Any Grade	7(30.4%)	3(13.0%)	9(39.1%)
	Grade 1	5(21.7%)	2(8.7%)	6(26.1%)
	Grade 2	2(8.7%)	1(4.3%)	3(13.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
味覚異常	Any Grade	4(17.4%)	0(0.0%)	4(17.4%)
	Grade 1	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 2	2(8.7%)	0(0.0%)	2(8.7%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
頭痛	Any Grade	1(4.3%)	1(4.3%)	2(8.7%)
	Grade 1	1(4.3%)	1(4.3%)	2(8.7%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
味覚消失	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
認知障害	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
浮動性めまい	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16 2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
傾眠	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
腎および尿路障害	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
尿瘻	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
呼吸器、胸郭および縦隔障害	Any Grade	2(8.7%)	2(8.7%)	4(17.4%)
	Grade 1	1(4.3%)	1(4.3%)	2(8.7%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	1(4.3%)	1(4.3%)	2(8.7%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	1(4.3%)	2(8.7%)
急性呼吸不全	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	1(4.3%)	1(4.3%)
鼻出血	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
間質性肺疾患	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
口腔咽頭痛	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
皮膚および皮下組織障害	Any Grade	5(21.7%)	3(13.0%)	8(34.8%)
	Grade 1	3(13.0%)	1(4.3%)	4(17.4%)
	Grade 2	2(8.7%)	2(8.7%)	4(17.4%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
接触皮膚炎	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
湿疹	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
紅斑	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
多形紅斑	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
光線過敏性反応	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
そう痒症	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16 2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
発疹	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
皮膚剥脱	Any Grade	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 1	0(0.0%)	1(4.3%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
皮膚潰瘍	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	0(0.0%)	0(0.0%)	0(0.0%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
血管障害	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
高血圧	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-32　発現時期別の有害事象（203 試験）（安全性解析対象集団）

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
Number of subjects with at least one TEAE	Any period	39	39 (100.0)	0 (0.0)	39 (100.0)
	<4 Weeks	39	36 (92.3)	1 (2.6)	37 (94.9)
	4 - <8 Weeks	37	29 (78.4)	5 (13.5)	34 (91.9)
	8 - <12 Weeks	29	22 (75.9)	4 (13.8)	26 (89.7)
	12 - <16 Weeks	23	14 (60.9)	2 (8.7)	16 (69.6)
	>=16 Weeks	18	14 (77.8)	1 (5.6)	15 (83.3)
血液およびリンパ系障害	Any period	39	38 (97.4)	0 (0.0)	38 (97.4)
	<4 Weeks	39	36 (92.3)	1 (2.6)	37 (94.9)
	4 - <8 Weeks	37	22 (59.5)	2 (5.4)	24 (64.9)
	8 - <12 Weeks	29	18 (62.1)	1 (3.4)	19 (65.5)
	12 - <16 Weeks	23	11 (47.8)	0 (0.0)	11 (47.8)
	>=16 Weeks	18	13 (72.2)	0 (0.0)	13 (72.2)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level.　Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
血小板減少症*	Any period	39	35 (89.7)	0 (0.0)	35 (89.7)
	<4 Weeks	39	29 (74.4)	0 (0.0)	29 (74.4)
	4 - <8 Weeks	37	10 (27.0)	0 (0.0)	10 (27.0)
	8 - <12 Weeks	29	4 (13.8)	0 (0.0)	4 (13.8)
	12 - <16 Weeks	23	8 (34.8)	0 (0.0)	8 (34.8)
	>=16 Weeks	18	10 (55.6)	0 (0.0)	10 (55.6)
好中球減少症*	Any period	39	28 (71.8)	0 (0.0)	28 (71.8)
	<4 Weeks	39	20 (51.3)	0 (0.0)	20 (51.3)
	4 - <8 Weeks	37	13 (35.1)	0 (0.0)	13 (35.1)
	8 - <12 Weeks	29	11 (37.9)	0 (0.0)	11 (37.9)
	12 - <16 Weeks	23	2 (8.7)	0 (0.0)	2 (8.7)
	>=16 Weeks	18	9 (50.0)	0 (0.0)	9 (50.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
白血球減少症*	Any period	39	21 (53.8)	3 (7.7)	24 (61.5)
	<4 Weeks	39	15 (38.5)	2 (5.1)	17 (43.6)
	4 - <8 Weeks	37	9 (24.3)	1 (2.7)	10 (27.0)
	8 - <12 Weeks	29	7 (24.1)	1 (3.4)	8 (27.6)
	12 - <16 Weeks	23	5 (21.7)	0 (0.0)	5 (21.7)
	>=16 Weeks	18	4 (22.2)	1 (5.6)	5 (27.8)
リンパ球減少症*	Any period	39	16 (41.0)	0 (0.0)	16 (41.0)
	<4 Weeks	39	7 (17.9)	0 (0.0)	7 (17.9)
	4 - <8 Weeks	37	6 (16.2)	0 (0.0)	6 (16.2)
	8 - <12 Weeks	29	5 (17.2)	0 (0.0)	5 (17.2)
	12 - <16 Weeks	23	3 (13.0)	0 (0.0)	3 (13.0)
	>=16 Weeks	18	5 (27.8)	0 (0.0)	5 (27.8)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
貧血*	Any period	39	11 (28.2)	3 (7.7)	14 (35.9)
	<4 Weeks	39	7 (17.9)	1 (2.6)	8 (20.5)
	4 - <8 Weeks	37	4 (10.8)	2 (5.4)	6 (16.2)
	8 - <12 Weeks	29	3 (10.3)	0 (0.0)	3 (10.3)
	12 - <16 Weeks	23	1 (4.3)	0 (0.0)	1 (4.3)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
発熱性好中球減少症	Any period	39	2 (5.1)	0 (0.0)	2 (5.1)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
再生不良性貧血	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
心臓障害	Any period	39	4 (10.3)	2 (5.1)	6 (15.4)
	<4 Weeks	39	2 (5.1)	1 (2.6)	3 (7.7)
	4 - <8 Weeks	37	2 (5.4)	1 (2.7)	3 (8.1)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	1 (5.6)	0 (0.0)	1 (5.6)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
動悸	Any period	39	2 (5.1)	1 (2.6)	3 (7.7)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	2 (5.4)	0 (0.0)	2 (5.4)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
不安定狭心症	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
不整脈	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
心房細動	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	1 (5.6)	0 (0.0)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
心嚢液貯留	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
耳および迷路障害	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
回転性めまい	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
眼障害	Any period	39	1 (2.6)	3 (7.7)	4 (10.3)
	<4 Weeks	39	1 (2.6)	2 (5.1)	3 (7.7)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
結膜出血	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
ドライアイ	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
角膜炎	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)
霧視	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
胃腸障害	Any period	39	20 (51.3)	5 (12.8)	25 (64.1)
	<4 Weeks	39	15 (38.5)	4 (10.3)	19 (48.7)
	4 - <8 Weeks	37	3 (8.1)	4 (10.8)	7 (18.9)
	8 - <12 Weeks	29	1 (3.4)	1 (3.4)	2 (6.9)
	12 - <16 Weeks	23	0 (0.0)	1 (4.3)	1 (4.3)
	>=16 Weeks	18	3 (16.7)	3 (16.7)	6 (33.3)
下痢	Any period	39	9 (23.1)	5 (12.8)	14 (35.9)
	<4 Weeks	39	7 (17.9)	3 (7.7)	10 (25.6)
	4 - <8 Weeks	37	3 (8.1)	1 (2.7)	4 (10.8)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	1 (4.3)	1 (4.3)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
悪心	Any period	39	9 (23.1)	0 (0.0)	9 (23.1)
	<4 Weeks	39	6 (15.4)	0 (0.0)	6 (15.4)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	2 (11.1)	0 (0.0)	2 (11.1)
上腹部痛	Any period	39	0 (0.0)	2 (5.1)	2 (5.1)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
齲歯	Any period	39	1 (2.6)	1 (2.6)	2 (5.1)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	1 (5.6)	1 (5.6)	2 (11.1)
嘔吐	Any period	39	1 (2.6)	1 (2.6)	2 (5.1)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
腹部不快感	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
腹痛	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
肛門出血	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)
便秘	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
消化不良	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
心窩部不快感	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
痔出血	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)
口腔粘膜血腫	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
歯痛	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)
一般・全身障害および投与部位の状態	Any period	39	16 (41.0)	3 (7.7)	19 (48.7)
	<4 Weeks	39	12 (30.8)	1 (2.6)	13 (33.3)
	4 - <8 Weeks	37	3 (8.1)	2 (5.4)	5 (13.5)
	8 - <12 Weeks	29	2 (6.9)	1 (3.4)	3 (10.3)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	2 (11.1)	1 (5.6)	3 (16.7)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
倦怠感	Any period	39	8 (20.5)	0 (0.0)	8 (20.5)
	<4 Weeks	39	7 (17.9)	0 (0.0)	7 (17.9)
	4 - <8 Weeks	37	2 (5.4)	0 (0.0)	2 (5.4)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
発熱	Any period	39	2 (5.1)	3 (7.7)	5 (12.8)
	<4 Weeks	39	1 (2.6)	2 (5.1)	3 (7.7)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	1 (3.4)	1 (3.4)	2 (6.9)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
疲労	Any period	39	4 (10.3)	0 (0.0)	4 (10.3)
	<4 Weeks	39	3 (7.7)	0 (0.0)	3 (7.7)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	1 (5.6)	0 (0.0)	1 (5.6)
末梢性浮腫	Any period	39	2 (5.1)	0 (0.0)	2 (5.1)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	1 (5.6)	0 (0.0)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
カテーテル留置部位腫脹	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
胸部不快感	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
胸痛	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
溢出	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
歩行障害	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
口渇	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
免疫系障害	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
薬物過敏症	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
感染症および寄生虫症	Any period	39	7 (17.9)	8 (20.5)	15 (38.5)
	<4 Weeks	39	1 (2.6)	3 (7.7)	4 (10.3)
	4 - <8 Weeks	37	3 (8.1)	1 (2.7)	4 (10.8)
	8 - <12 Weeks	29	0 (0.0)	2 (6.9)	2 (6.9)
	12 - <16 Weeks	23	2 (8.7)	0 (0.0)	2 (8.7)
	>=16 Weeks	18	1 (5.6)	5 (27.8)	6 (33.3)
咽頭炎	Any period	39	0 (0.0)	3 (7.7)	3 (7.7)
	<4 Weeks	39	0 (0.0)	2 (5.1)	2 (5.1)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
気管支炎	Any period	39	2 (5.1)	0 (0.0)	2 (5.1)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	2 (5.4)	0 (0.0)	2 (5.4)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
結膜炎	Any period	39	0 (0.0)	2 (5.1)	2 (5.1)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
インフルエンザ	Any period	39	0 (0.0)	2 (5.1)	2 (5.1)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)
上咽頭炎	Any period	39	1 (2.6)	1 (2.6)	2 (5.1)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	1 (4.3)	0 (0.0)	1 (4.3)
	>=16 Weeks	18	0 (0.0)	2 (11.1)	2 (11.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
上気道感染	Any period	39	0 (0.0)	2 (5.1)	2 (5.1)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)
膀胱炎	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	1 (5.6)	0 (0.0)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
サイトメガロウイルス感染	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
帯状疱疹	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
膿痂疹	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	1 (4.3)	0 (0.0)	1 (4.3)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
ニューモシスチス・イロベチイ肺炎	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
鼻炎	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
傷害、中毒および処置合併症	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
爪損傷	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)
臨床検査	Any period	39	19 (48.7)	5 (12.8)	24 (61.5)
	<4 Weeks	39	10 (25.6)	2 (5.1)	12 (30.8)
	4 - <8 Weeks	37	6 (16.2)	4 (10.8)	10 (27.0)
	8 - <12 Weeks	29	3 (10.3)	4 (13.8)	7 (24.1)
	12 - <16 Weeks	23	5 (21.7)	2 (8.7)	7 (30.4)
	>=16 Weeks	18	6 (33.3)	1 (5.6)	7 (38.9)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
血中アルカリホスファターゼ増加	Any period	39	6 (15.4)	2 (5.1)	8 (20.5)
	<4 Weeks	39	2 (5.1)	1 (2.6)	3 (7.7)
	4 - <8 Weeks	37	3 (8.1)	0 (0.0)	3 (8.1)
	8 - <12 Weeks	29	1 (3.4)	1 (3.4)	2 (6.9)
	12 - <16 Weeks	23	1 (4.3)	0 (0.0)	1 (4.3)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)
γーグルタミルトランスフェラーゼ増加	Any period	39	7 (17.9)	1 (2.6)	8 (20.5)
	<4 Weeks	39	5 (12.8)	0 (0.0)	5 (12.8)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	1 (4.3)	0 (0.0)	1 (4.3)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
アスパラギン酸アミノトランスフェラーゼ増加	Any period	39	4 (10.3)	3 (7.7)	7 (17.9)
	<4 Weeks	39	1 (2.6)	1 (2.6)	2 (5.1)
	4 - <8 Weeks	37	3 (8.1)	1 (2.7)	4 (10.8)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	2 (8.7)	0 (0.0)	2 (8.7)
	>=16 Weeks	18	1 (5.6)	1 (5.6)	2 (11.1)
体重減少	Any period	39	2 (5.1)	4 (10.3)	6 (15.4)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	1 (3.4)	1 (3.4)	2 (6.9)
	12 - <16 Weeks	23	0 (0.0)	1 (4.3)	1 (4.3)
	>=16 Weeks	18	1 (5.6)	1 (5.6)	2 (11.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
アラニンアミノトランスフェラーゼ増加	Any period	39	4 (10.3)	1 (2.6)	5 (12.8)
	<4 Weeks	39	3 (7.7)	0 (0.0)	3 (7.7)
	4 - <8 Weeks	37	2 (5.4)	0 (0.0)	2 (5.4)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)
心電図ＱＴ延長	Any period	39	5 (12.8)	0 (0.0)	5 (12.8)
	<4 Weeks	39	2 (5.1)	0 (0.0)	2 (5.1)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	1 (4.3)	0 (0.0)	1 (4.3)
	>=16 Weeks	18	2 (11.1)	0 (0.0)	2 (11.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
血中クレアチニン増加	Any period	39	2 (5.1)	0 (0.0)	2 (5.1)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	2 (8.7)	0 (0.0)	2 (8.7)
	>=16 Weeks	18	1 (5.6)	0 (0.0)	1 (5.6)
脳性ナトリウム利尿ペプチド増加	Any period	39	1 (2.6)	1 (2.6)	2 (5.1)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
C－反応性蛋白増加	Any period	39	1 (2.6)	1 (2.6)	2 (5.1)
	<4 Weeks	39	1 (2.6)	1 (2.6)	2 (5.1)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
好酸球数増加	Any period	39	2 (5.1)	0 (0.0)	2 (5.1)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
血中コレステロール増加	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
血中クレアチンホスホキナーゼＭＢ増加	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	1 (5.6)	0 (0.0)	1 (5.6)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
血中クレアチンホスホキナーゼ増加	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
血中免疫グロブリンA減少	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
尿中血陽性	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	1 (4.3)	1 (4.3)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
心胸郭比増加	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
心電図Ｔ波逆転	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
リパーゼ増加	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
体重増加	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
代謝および栄養障害	Any period	39	12 (30.8)	4 (10.3)	16 (41.0)
	<4 Weeks	39	9 (23.1)	3 (7.7)	12 (30.8)
	4 - <8 Weeks	37	1 (2.7)	1 (2.7)	2 (5.4)
	8 - <12 Weeks	29	3 (10.3)	1 (3.4)	4 (13.8)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
食欲減退	Any period	39	8 (20.5)	0 (0.0)	8 (20.5)
	<4 Weeks	39	7 (17.9)	0 (0.0)	7 (17.9)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
低アルブミン血症	Any period	39	2 (5.1)	2 (5.1)	4 (10.3)
	<4 Weeks	39	1 (2.6)	1 (2.6)	2 (5.1)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
低カリウム血症	Any period	39	2 (5.1)	1 (2.6)	3 (7.7)
	<4 Weeks	39	1 (2.6)	1 (2.6)	2 (5.1)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
低カルシウム血症	Any period	39	2 (5.1)	0 (0.0)	2 (5.1)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
低ナトリウム血症	Any period	39	2 (5.1)	0 (0.0)	2 (5.1)
	<4 Weeks	39	2 (5.1)	0 (0.0)	2 (5.1)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
糖尿病	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
高カリウム血症	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
高マグネシウム血症	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
高トリグリセリド血症	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)
低蛋白血症	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
筋骨格系および結合組織障害	Any period	39	7 (17.9)	8 (20.5)	15 (38.5)
	<4 Weeks	39	3 (7.7)	3 (7.7)	6 (15.4)
	4 - <8 Weeks	37	4 (10.8)	1 (2.7)	5 (13.5)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	2 (8.7)	2 (8.7)
	>=16 Weeks	18	2 (11.1)	3 (16.7)	5 (27.8)
筋痙縮	Any period	39	3 (7.7)	2 (5.1)	5 (12.8)
	<4 Weeks	39	2 (5.1)	0 (0.0)	2 (5.1)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	1 (5.6)	1 (5.6)	2 (11.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
背部痛	Any period	39	1 (2.6)	3 (7.7)	4 (10.3)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	2 (11.1)	2 (11.1)
筋肉痛	Any period	39	0 (0.0)	2 (5.1)	2 (5.1)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	1 (4.3)	1 (4.3)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
関節痛	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
関節炎	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
出血性関節症	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	1 (4.3)	1 (4.3)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
関節腫脹	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	1 (5.6)	0 (0.0)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
筋肉疲労	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
筋骨格硬直	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
頚部痛	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
四肢痛	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
腱炎	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	Any period	39	1 (2.6)	2 (5.1)	3 (7.7)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	2 (5.4)	2 (5.4)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	1 (4.3)	0 (0.0)	1 (4.3)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
末梢性Ｔ細胞性リンパ腫、組織型不明	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	1 (4.3)	0 (0.0)	1 (4.3)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
皮膚乳頭腫	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
腫瘍疼痛	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
神経系障害	Any period	39	4 (10.3)	3 (7.7)	7 (17.9)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	3 (8.1)	1 (2.7)	4 (10.8)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	2 (11.1)	2 (11.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
頭痛	Any period	39	2 (5.1)	2 (5.1)	4 (10.3)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	1 (2.7)	1 (2.7)	2 (5.4)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)
味覚異常	Any period	39	2 (5.1)	0 (0.0)	2 (5.1)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	2 (5.4)	0 (0.0)	2 (5.4)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
浮動性めまい	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
感覚鈍麻	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
末梢性感覚ニューロパチー	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)
失神寸前の状態	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
精神障害	Any period	39	0 (0.0)	4 (10.3)	4 (10.3)
	<4 Weeks	39	0 (0.0)	2 (5.1)	2 (5.1)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
不眠症	Any period	39	0 (0.0)	3 (7.7)	3 (7.7)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
譫妄	Any period	39	0 (0.0)	2 (5.1)	2 (5.1)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
腎および尿路障害	Any period	39	1 (2.6)	1 (2.6)	2 (5.1)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
急性腎障害	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
血尿	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
蛋白尿	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
呼吸器、胸郭および縦隔障害	Any period	39	8 (20.5)	6 (15.4)	14 (35.9)
	<4 Weeks	39	2 (5.1)	3 (7.7)	5 (12.8)
	4 - <8 Weeks	37	1 (2.7)	1 (2.7)	2 (5.4)
	8 - <12 Weeks	29	3 (10.3)	1 (3.4)	4 (13.8)
	12 - <16 Weeks	23	1 (4.3)	0 (0.0)	1 (4.3)
	>=16 Weeks	18	2 (11.1)	1 (5.6)	3 (16.7)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
肺臓炎	Any period	39	3 (7.7)	0 (0.0)	3 (7.7)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	12 - <16 Weeks	23	1 (4.3)	0 (0.0)	1 (4.3)
	>=16 Weeks	18	1 (5.6)	0 (0.0)	1 (5.6)
咳嗽	Any period	39	1 (2.6)	1 (2.6)	2 (5.1)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	1 (5.6)	0 (0.0)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
呼吸困難	Any period	39	2 (5.1)	0 (0.0)	2 (5.1)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
鼻出血	Any period	39	1 (2.6)	1 (2.6)	2 (5.1)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
口腔咽頭痛	Any period	39	0 (0.0)	2 (5.1)	2 (5.1)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)
胸水	Any period	39	1 (2.6)	1 (2.6)	2 (5.1)
	<4 Weeks	39	1 (2.6)	1 (2.6)	2 (5.1)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
咽頭知覚不全	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
間質性肺疾患	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
上気道の炎症	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
皮膚および皮下組織障害	Any period	39	10 (25.6)	8 (20.5)	18 (46.2)
	<4 Weeks	39	5 (12.8)	2 (5.1)	7 (17.9)
	4 - <8 Weeks	37	2 (5.4)	6 (16.2)	8 (21.6)
	8 - <12 Weeks	29	4 (13.8)	2 (6.9)	6 (20.7)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	1 (5.6)	0 (0.0)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
発疹	Any period	39	2 (5.1)	1 (2.6)	3 (7.7)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
蕁麻疹	Any period	39	3 (7.7)	0 (0.0)	3 (7.7)
	<4 Weeks	39	2 (5.1)	0 (0.0)	2 (5.1)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
紅斑	Any period	39	0 (0.0)	2 (5.1)	2 (5.1)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
紫斑	Any period	39	2 (5.1)	0 (0.0)	2 (5.1)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	1 (2.7)	0 (0.0)	1 (2.7)
	8 - <12 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
斑状丘疹状皮疹	Any period	39	1 (2.6)	1 (2.6)	2 (5.1)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	1 (3.4)	1 (3.4)	2 (6.9)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
褥瘡性潰瘍	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
ざ瘡様皮膚炎	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
全身性剥脱性皮膚炎	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	1 (5.6)	0 (0.0)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
皮膚乾燥	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
皮脂欠乏性湿疹	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
多形紅斑	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
全身紅斑	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
皮膚疼痛	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
点状出血	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
色素沈着障害	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
全身性そう痒症	Any period	39	1 (2.6)	0 (0.0)	1 (2.6)
	<4 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
そう痒性皮疹	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
血管障害	Any period	39	0 (0.0)	2 (5.1)	2 (5.1)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Japan

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=39)
			n (%)	n (%)	n (%)
低血圧	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	1 (2.7)	1 (2.7)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	0 (0.0)	0 (0.0)
末梢動脈閉塞性疾患	Any period	39	0 (0.0)	1 (2.6)	1 (2.6)
	<4 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	37	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	23	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	18	0 (0.0)	1 (5.6)	1 (5.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
Number of subjects with at least one TEAE	Any period	16	12 (75.0)	4 (25.0)	16 (100.0)
	<4 Weeks	16	9 (56.3)	6 (37.5)	15 (93.8)
	4 - <8 Weeks	15	8 (53.3)	4 (26.7)	12 (80.0)
	8 - <12 Weeks	10	3 (30.0)	1 (10.0)	4 (40.0)
	12 - <16 Weeks	6	1 (16.7)	0 (0.0)	1 (16.7)
	>=16 Weeks	4	3 (75.0)	1 (25.0)	4 (100.0)
血液およびリンパ系障害	Any period	16	9 (56.3)	5 (31.3)	14 (87.5)
	<4 Weeks	16	8 (50.0)	3 (18.8)	11 (68.8)
	4 - <8 Weeks	15	5 (33.3)	3 (20.0)	8 (53.3)
	8 - <12 Weeks	10	3 (30.0)	0 (0.0)	3 (30.0)
	12 - <16 Weeks	6	1 (16.7)	0 (0.0)	1 (16.7)
	>=16 Weeks	4	2 (50.0)	0 (0.0)	2 (50.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
血小板減少症*	Any period	16	7 (43.8)	4 (25.0)	11 (68.8)
	<4 Weeks	16	7 (43.8)	2 (12.5)	9 (56.3)
	4 - <8 Weeks	15	2 (13.3)	3 (20.0)	5 (33.3)
	8 - <12 Weeks	10	2 (20.0)	0 (0.0)	2 (20.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	1 (25.0)	0 (0.0)	1 (25.0)
貧血*	Any period	16	1 (6.3)	3 (18.8)	4 (25.0)
	<4 Weeks	16	1 (6.3)	1 (6.3)	2 (12.5)
	4 - <8 Weeks	15	0 (0.0)	2 (13.3)	2 (13.3)
	8 - <12 Weeks	10	1 (10.0)	0 (0.0)	1 (10.0)
	12 - <16 Weeks	6	1 (16.7)	0 (0.0)	1 (16.7)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
好中球減少症*	Any period	16	3 (18.8)	0 (0.0)	3 (18.8)
	<4 Weeks	16	2 (12.5)	0 (0.0)	2 (12.5)
	4 - <8 Weeks	15	3 (20.0)	0 (0.0)	3 (20.0)
	8 - <12 Weeks	10	1 (10.0)	0 (0.0)	1 (10.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	1 (25.0)	0 (0.0)	1 (25.0)
好酸球増加症	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
発熱性好中球減少症	Any period	16	1 (6.3)	0 (0.0)	1 (6.3)
	<4 Weeks	16	1 (6.3)	0 (0.0)	1 (6.3)
	4 - <8 Weeks	15	1 (6.7)	0 (0.0)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
心臓障害	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
心房細動	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
耳および迷路障害	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
耳痛	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
眼障害	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
白内障	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
胃腸障害	Any period	16	5 (31.3)	2 (12.5)	7 (43.8)
	<4 Weeks	16	5 (31.3)	1 (6.3)	6 (37.5)
	4 - <8 Weeks	15	1 (6.7)	4 (26.7)	5 (33.3)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	1 (25.0)	1 (25.0)	2 (50.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
下痢	Any period	16	1 (6.3)	2 (12.5)	3 (18.8)
	<4 Weeks	16	1 (6.3)	0 (0.0)	1 (6.3)
	4 - <8 Weeks	15	1 (6.7)	2 (13.3)	3 (20.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	1 (25.0)	0 (0.0)	1 (25.0)
悪心	Any period	16	2 (12.5)	1 (6.3)	3 (18.8)
	<4 Weeks	16	2 (12.5)	1 (6.3)	3 (18.8)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
腹痛	Any period	16	1 (6.3)	1 (6.3)	2 (12.5)
	<4 Weeks	16	1 (6.3)	0 (0.0)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
口内炎	Any period	16	0 (0.0)	2 (12.5)	2 (12.5)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
胃潰瘍	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	1 (25.0)	1 (25.0)
胃炎	Any period	16	1 (6.3)	0 (0.0)	1 (6.3)
	<4 Weeks	16	1 (6.3)	0 (0.0)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
嘔吐	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
一般・全身障害および投与部位の状態	Any period	16	1 (6.3)	7 (43.8)	8 (50.0)
	<4 Weeks	16	1 (6.3)	4 (25.0)	5 (31.3)
	4 - <8 Weeks	15	0 (0.0)	5 (33.3)	5 (33.3)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
発熱	Any period	16	0 (0.0)	6 (37.5)	6 (37.5)
	<4 Weeks	16	0 (0.0)	2 (12.5)	2 (12.5)
	4 - <8 Weeks	15	0 (0.0)	4 (26.7)	4 (26.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
無力症	Any period	16	1 (6.3)	1 (6.3)	2 (12.5)
	<4 Weeks	16	1 (6.3)	0 (0.0)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
疲労	Any period	16	0 (0.0)	2 (12.5)	2 (12.5)
	<4 Weeks	16	0 (0.0)	2 (12.5)	2 (12.5)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
インフルエンザ様疾患	Any period	16	0 (0.0)	2 (12.5)	2 (12.5)
	<4 Weeks	16	0 (0.0)	2 (12.5)	2 (12.5)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
末梢性浮腫	Any period	16	0 (0.0)	2 (12.5)	2 (12.5)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	2 (13.3)	2 (13.3)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
感染症および寄生虫症	Any period	16	1 (6.3)	3 (18.8)	4 (25.0)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	1 (6.7)	0 (0.0)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	1 (10.0)	1 (10.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	2 (50.0)	2 (50.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
上気道感染	Any period	16	0 (0.0)	2 (12.5)	2 (12.5)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	1 (25.0)	1 (25.0)
感染性小腸結腸炎	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	1 (10.0)	1 (10.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
胃腸炎	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	1 (25.0)	1 (25.0)
肺炎	Any period	16	1 (6.3)	0 (0.0)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	1 (6.7)	0 (0.0)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
ブドウ球菌皮膚感染	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	1 (10.0)	1 (10.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
傷害、中毒および処置合併症	Any period	16	0 (0.0)	2 (12.5)	2 (12.5)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	1 (10.0)	1 (10.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	1 (25.0)	1 (25.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
胃瘻管部合併症	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	1 (10.0)	1 (10.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
処置による疼痛	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	1 (25.0)	1 (25.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

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TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
臨床検査	Any period	16	1 (6.3)	0 (0.0)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	1 (6.7)	0 (0.0)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
Ｃ－反応性蛋白増加	Any period	16	1 (6.3)	0 (0.0)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	1 (6.7)	0 (0.0)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
代謝および栄養障害	Any period	16	4 (25.0)	5 (31.3)	9 (56.3)
	<4 Weeks	16	2 (12.5)	1 (6.3)	3 (18.8)
	4 - <8 Weeks	15	2 (13.3)	2 (13.3)	4 (26.7)
	8 - <12 Weeks	10	1 (10.0)	1 (10.0)	2 (20.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	1 (25.0)	1 (25.0)	2 (50.0)
食欲減退	Any period	16	4 (25.0)	1 (6.3)	5 (31.3)
	<4 Weeks	16	2 (12.5)	0 (0.0)	2 (12.5)
	4 - <8 Weeks	15	2 (13.3)	0 (0.0)	2 (13.3)
	8 - <12 Weeks	10	1 (10.0)	0 (0.0)	1 (10.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	1 (25.0)	1 (25.0)	2 (50.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
低カリウム血症	Any period	16	0 (0.0)	2 (12.5)	2 (12.5)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	1 (10.0)	1 (10.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
低アルブミン血症	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
低カルシウム血症	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
筋骨格系および結合組織障害	Any period	16	0 (0.0)	4 (25.0)	4 (25.0)
	<4 Weeks	16	0 (0.0)	3 (18.8)	3 (18.8)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
背部痛	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
筋肉疲労	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
筋力低下	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
肩回旋筋腱板症候群	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
腫瘍疼痛	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
神経系障害	Any period	16	0 (0.0)	2 (12.5)	2 (12.5)
	<4 Weeks	16	0 (0.0)	2 (12.5)	2 (12.5)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
頭痛	Any period	16	0 (0.0)	2 (12.5)	2 (12.5)
	<4 Weeks	16	0 (0.0)	2 (12.5)	2 (12.5)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
精神障害	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
不眠症	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
生殖系および乳房障害	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
陰嚢浮腫	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
呼吸器、胸郭および縦隔障害	Any period	16	1 (6.3)	6 (37.5)	7 (43.8)
	<4 Weeks	16	0 (0.0)	5 (31.3)	5 (31.3)
	4 - <8 Weeks	15	0 (0.0)	3 (20.0)	3 (20.0)
	8 - <12 Weeks	10	0 (0.0)	1 (10.0)	1 (10.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	1 (25.0)	1 (25.0)	2 (50.0)
咳嗽	Any period	16	0 (0.0)	4 (25.0)	4 (25.0)
	<4 Weeks	16	0 (0.0)	2 (12.5)	2 (12.5)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	1 (25.0)	1 (25.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
呼吸困難	Any period	16	0 (0.0)	2 (12.5)	2 (12.5)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	1 (10.0)	1 (10.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	1 (25.0)	1 (25.0)
発声障害	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
労作性呼吸困難	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	1 (25.0)	1 (25.0)
しゃっくり	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
口腔咽頭痛	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
肺臓炎	Any period	16	1 (6.3)	0 (0.0)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	1 (25.0)	0 (0.0)	1 (25.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
湿性咳嗽	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
アレルギー性鼻炎	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	1 (25.0)	1 (25.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
鼻漏	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
皮膚および皮下組織障害	Any period	16	2 (12.5)	3 (18.8)	5 (31.3)
	<4 Weeks	16	1 (6.3)	1 (6.3)	2 (12.5)
	4 - <8 Weeks	15	1 (6.7)	1 (6.7)	2 (13.3)
	8 - <12 Weeks	10	0 (0.0)	1 (10.0)	1 (10.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
発疹	Any period	16	1 (6.3)	1 (6.3)	2 (12.5)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	1 (6.7)	0 (0.0)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	1 (10.0)	1 (10.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
蕁麻疹	Any period	16	0 (0.0)	2 (12.5)	2 (12.5)
	<4 Weeks	16	0 (0.0)	1 (6.3)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
全身性そう痒症	Any period	16	1 (6.3)	0 (0.0)	1 (6.3)
	<4 Weeks	16	1 (6.3)	0 (0.0)	1 (6.3)
	4 - <8 Weeks	15	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)
血管障害	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Korea

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=16)
			n (%)	n (%)	n (%)
深部静脈血栓症	Any period	16	0 (0.0)	1 (6.3)	1 (6.3)
	<4 Weeks	16	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	15	0 (0.0)	1 (6.7)	1 (6.7)
	8 - <12 Weeks	10	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	6	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	4	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
Number of subjects with at least one TEAE	Any period	55	51 (92.7)	4 (7.3)	55 (100.0)
	<4 Weeks	55	45 (81.8)	7 (12.7)	52 (94.5)
	4 - <8 Weeks	52	37 (71.2)	9 (17.3)	46 (88.5)
	8 - <12 Weeks	39	25 (64.1)	5 (12.8)	30 (76.9)
	12 - <16 Weeks	29	15 (51.7)	2 (6.9)	17 (58.6)
	>=16 Weeks	22	17 (77.3)	2 (9.1)	19 (86.4)
血液およびリンパ系障害	Any period	55	47 (85.5)	5 (9.1)	52 (94.5)
	<4 Weeks	55	44 (80.0)	4 (7.3)	48 (87.3)
	4 - <8 Weeks	52	27 (51.9)	5 (9.6)	32 (61.5)
	8 - <12 Weeks	39	21 (53.8)	1 (2.6)	22 (56.4)
	12 - <16 Weeks	29	12 (41.4)	0 (0.0)	12 (41.4)
	>=16 Weeks	22	15 (68.2)	0 (0.0)	15 (68.2)
血小板減少症*	Any period	55	42 (76.4)	4 (7.3)	46 (83.6)
	<4 Weeks	55	36 (65.5)	2 (3.6)	38 (69.1)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
血小板减少症*	4 - <8 Weeks	52	12 (23.1)	3 (5.8)	15 (28.8)
	8 - <12 Weeks	39	6 (15.4)	0 (0.0)	6 (15.4)
	12 - <16 Weeks	29	8 (27.6)	0 (0.0)	8 (27.6)
	>=16 Weeks	22	11 (50.0)	0 (0.0)	11 (50.0)
好中球减少症*	Any period	55	31 (56.4)	0 (0.0)	31 (56.4)
	<4 Weeks	55	22 (40.0)	0 (0.0)	22 (40.0)
	4 - <8 Weeks	52	16 (30.8)	0 (0.0)	16 (30.8)
	8 - <12 Weeks	39	12 (30.8)	0 (0.0)	12 (30.8)
	12 - <16 Weeks	29	2 (6.9)	0 (0.0)	2 (6.9)
	>=16 Weeks	22	10 (45.5)	0 (0.0)	10 (45.5)
白血球减少症*	Any period	55	21 (38.2)	3 (5.5)	24 (43.6)
	<4 Weeks	55	15 (27.3)	2 (3.6)	17 (30.9)
	4 - <8 Weeks	52	9 (17.3)	1 (1.9)	10 (19.2)
	8 - <12 Weeks	39	7 (17.9)	1 (2.6)	8 (20.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
白血球減少症*	12 - <16 Weeks	29	5 (17.2)	0 (0.0)	5 (17.2)
	>=16 Weeks	22	4 (18.2)	1 (4.5)	5 (22.7)
貧血*	Any period	55	12 (21.8)	6 (10.9)	18 (32.7)
	<4 Weeks	55	8 (14.5)	2 (3.6)	10 (18.2)
	4 - <8 Weeks	52	4 (7.7)	4 (7.7)	8 (15.4)
	8 - <12 Weeks	39	4 (10.3)	0 (0.0)	4 (10.3)
	12 - <16 Weeks	29	2 (6.9)	0 (0.0)	2 (6.9)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
リンパ球減少症*	Any period	55	16 (29.1)	0 (0.0)	16 (29.1)
	<4 Weeks	55	7 (12.7)	0 (0.0)	7 (12.7)
	4 - <8 Weeks	52	6 (11.5)	0 (0.0)	6 (11.5)
	8 - <12 Weeks	39	5 (12.8)	0 (0.0)	5 (12.8)
	12 - <16 Weeks	29	3 (10.3)	0 (0.0)	3 (10.3)
	>=16 Weeks	22	5 (22.7)	0 (0.0)	5 (22.7)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
発熱性好中球減少症	Any period	55	3 (5.5)	0 (0.0)	3 (5.5)
	<4 Weeks	55	2 (3.6)	0 (0.0)	2 (3.6)
	4 - <8 Weeks	52	2 (3.8)	0 (0.0)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
再生不良性貧血	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
好酸球増加症	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
好酸球増加症	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
心臓障害	Any period	55	4 (7.3)	3 (5.5)	7 (12.7)
	<4 Weeks	55	2 (3.6)	2 (3.6)	4 (7.3)
	4 - <8 Weeks	52	2 (3.8)	1 (1.9)	3 (5.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	0 (0.0)	1 (4.5)
動悸	Any period	55	2 (3.6)	1 (1.8)	3 (5.5)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	2 (3.8)	0 (0.0)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
動悸	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
心房細動	Any period	55	1 (1.8)	1 (1.8)	2 (3.6)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	0 (0.0)	1 (4.5)
不安定狭心症	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
不整脈	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
心嚢液貯留	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
耳および迷路障害	Any period	55	1 (1.8)	1 (1.8)	2 (3.6)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
耳および迷路障害	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
耳痛	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
回転性めまい	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related n (%)	Not Related n (%)	Total (N=55) n (%)
回転性めまい	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
眼障害	Any period	55	1 (1.8)	4 (7.3)	5 (9.1)
	<4 Weeks	55	1 (1.8)	3 (5.5)	4 (7.3)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
白内障	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
結膜出血	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
ドライアイ	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
角膜炎	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
角膜炎	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
霧視	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
胃腸障害	Any period	55	25 (45.5)	7 (12.7)	32 (58.2)
	<4 Weeks	55	20 (36.4)	5 (9.1)	25 (45.5)
	4 - <8 Weeks	52	4 (7.7)	8 (15.4)	12 (23.1)
	8 - <12 Weeks	39	1 (2.6)	1 (2.6)	2 (5.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
胃腸障害	12 - <16 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	>=16 Weeks	22	4 (18.2)	4 (18.2)	8 (36.4)
下痢	Any period	55	10 (18.2)	7 (12.7)	17 (30.9)
	<4 Weeks	55	8 (14.5)	3 (5.5)	11 (20.0)
	4 - <8 Weeks	52	4 (7.7)	3 (5.8)	7 (13.5)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	>=16 Weeks	22	1 (4.5)	0 (0.0)	1 (4.5)
悪心	Any period	55	11 (20.0)	1 (1.8)	12 (21.8)
	<4 Weeks	55	8 (14.5)	1 (1.8)	9 (16.4)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	2 (9.1)	0 (0.0)	2 (9.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
腹痛	Any period	55	1 (1.8)	2 (3.6)	3 (5.5)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	2 (3.8)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
嘔吐	Any period	55	1 (1.8)	2 (3.6)	3 (5.5)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
上腹部痛	Any period	55	0 (0.0)	2 (3.6)	2 (3.6)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
上腹部痛	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
齲歯	Any period	55	1 (1.8)	1 (1.8)	2 (3.6)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	1 (4.5)	2 (9.1)
口内炎	Any period	55	0 (0.0)	2 (3.6)	2 (3.6)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related n (%)	Not Related n (%)	Total (N=55) n (%)
口内炎	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
腹部不快感	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
肛門出血	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
便秘	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
消化不良	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
心窩部不快感	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
心窩部不快感	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
胃潰瘍	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
胃炎	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
胃炎	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
痔出血	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
口腔粘膜血腫	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
歯痛	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
一般・全身障害および投与部位の状態	Any period	55	17 (30.9)	10 (18.2)	27 (49.1)
	<4 Weeks	55	13 (23.6)	5 (9.1)	18 (32.7)
	4 - <8 Weeks	52	3 (5.8)	7 (13.5)	10 (19.2)
	8 - <12 Weeks	39	2 (5.1)	1 (2.6)	3 (7.7)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	2 (9.1)	1 (4.5)	3 (13.6)
発熱	Any period	55	2 (3.6)	9 (16.4)	11 (20.0)
	<4 Weeks	55	1 (1.8)	4 (7.3)	5 (9.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
発熱	4 - <8 Weeks	52	1 (1.9)	4 (7.7)	5 (9.6)
	8 - <12 Weeks	39	1 (2.6)	1 (2.6)	2 (5.1)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
倦怠感	Any period	55	8 (14.5)	0 (0.0)	8 (14.5)
	<4 Weeks	55	7 (12.7)	0 (0.0)	7 (12.7)
	4 - <8 Weeks	52	2 (3.8)	0 (0.0)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
疲労	Any period	55	4 (7.3)	2 (3.6)	6 (10.9)
	<4 Weeks	55	3 (5.5)	2 (3.6)	5 (9.1)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
疲労	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	0 (0.0)	1 (4.5)
末梢性浮腫	Any period	55	2 (3.6)	2 (3.6)	4 (7.3)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	1 (1.9)	2 (3.8)	3 (5.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	0 (0.0)	1 (4.5)
無力症	Any period	55	1 (1.8)	1 (1.8)	2 (3.6)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
インフルエンザ様疾患	Any period	55	0 (0.0)	2 (3.6)	2 (3.6)
	<4 Weeks	55	0 (0.0)	2 (3.6)	2 (3.6)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
カテーテル留置部位腫脹	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
胸部不快感	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
胸部不快感	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
胸痛	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
溢出	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related n (%)	Not Related n (%)	Total (N=55) n (%)
溢出	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
歩行障害	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
口渇	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
免疫系障害	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
薬物過敏症	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
感染症および寄生虫症	Any period	55	8 (14.5)	11 (20.0)	19 (34.5)
	<4 Weeks	55	1 (1.8)	4 (7.3)	5 (9.1)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
感染症および寄生虫症	4 - <8 Weeks	52	4 (7.7)	1 (1.9)	5 (9.6)
	8 - <12 Weeks	39	0 (0.0)	3 (7.7)	3 (7.7)
	12 - <16 Weeks	29	2 (6.9)	0 (0.0)	2 (6.9)
	>=16 Weeks	22	1 (4.5)	7 (31.8)	8 (36.4)
上気道感染	Any period	55	0 (0.0)	4 (7.3)	4 (7.3)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	2 (9.1)	2 (9.1)
咽頭炎	Any period	55	0 (0.0)	3 (5.5)	3 (5.5)
	<4 Weeks	55	0 (0.0)	2 (3.6)	2 (3.6)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related n (%)	Not Related n (%)	Total (N=55) n (%)
咽頭炎	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
気管支炎	Any period	55	2 (3.6)	0 (0.0)	2 (3.6)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	2 (3.8)	0 (0.0)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
結膜炎	Any period	55	0 (0.0)	2 (3.6)	2 (3.6)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
インフルエンザ	Any period	55	0 (0.0)	2 (3.6)	2 (3.6)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
上咽頭炎	Any period	55	1 (1.8)	1 (1.8)	2 (3.6)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	>=16 Weeks	22	0 (0.0)	2 (9.1)	2 (9.1)
膀胱炎	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related n (%)	Not Related n (%)	Total (N=55) n (%)
膀胱炎	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	0 (0.0)	1 (4.5)
サイトメガロウイルス感染	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
感染性小腸結腸炎	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related n (%)	Not Related n (%)	Total (N=55) n (%)
感染性小腸結腸炎	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
胃腸炎	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
帯状疱疹	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
膿痂疹	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
ニューモシスチス・イロベチイ肺炎	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
肺炎	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
肺炎	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
鼻炎	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
ブドウ球菌皮膚感染	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
ブドウ球菌皮膚感染	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
傷害、中毒および処置合併症	Any period	55	0 (0.0)	3 (5.5)	3 (5.5)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	2 (9.1)	2 (9.1)
胃瘻管部合併症	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
爪損傷	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
処置による疼痛	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
臨床検査	Any period	55	20 (36.4)	5 (9.1)	25 (45.5)
	<4 Weeks	55	10 (18.2)	2 (3.6)	12 (21.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
臨床検査	4 - <8 Weeks	52	7 (13.5)	4 (7.7)	11 (21.2)
	8 - <12 Weeks	39	3 (7.7)	4 (10.3)	7 (17.9)
	12 - <16 Weeks	29	5 (17.2)	2 (6.9)	7 (24.1)
	>=16 Weeks	22	6 (27.3)	1 (4.5)	7 (31.8)
血中アルカリホスファターゼ増加	Any period	55	6 (10.9)	2 (3.6)	8 (14.5)
	<4 Weeks	55	2 (3.6)	1 (1.8)	3 (5.5)
	4 - <8 Weeks	52	3 (5.8)	0 (0.0)	3 (5.8)
	8 - <12 Weeks	39	1 (2.6)	1 (2.6)	2 (5.1)
	12 - <16 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
γ－グルタミルトランスフェラーゼ増加	Any period	55	7 (12.7)	1 (1.8)	8 (14.5)
	<4 Weeks	55	5 (9.1)	0 (0.0)	5 (9.1)
	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
γーグルタミルトランスフェラーゼ増加	12 - <16 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
アスパラギン酸アミノトランスフェラーゼ増加	Any period	55	4 (7.3)	3 (5.5)	7 (12.7)
	<4 Weeks	55	1 (1.8)	1 (1.8)	2 (3.6)
	4 - <8 Weeks	52	3 (5.8)	1 (1.9)	4 (7.7)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	2 (6.9)	0 (0.0)	2 (6.9)
	>=16 Weeks	22	1 (4.5)	1 (4.5)	2 (9.1)
体重減少	Any period	55	2 (3.6)	4 (7.3)	6 (10.9)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	1 (2.6)	1 (2.6)	2 (5.1)
	12 - <16 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	>=16 Weeks	22	1 (4.5)	1 (4.5)	2 (9.1)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
アラニンアミノトランスフェラーゼ増加	Any period	55	4 (7.3)	1 (1.8)	5 (9.1)
	<4 Weeks	55	3 (5.5)	0 (0.0)	3 (5.5)
	4 - <8 Weeks	52	2 (3.8)	0 (0.0)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
心電図ＱＴ延長	Any period	55	5 (9.1)	0 (0.0)	5 (9.1)
	<4 Weeks	55	2 (3.6)	0 (0.0)	2 (3.6)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	>=16 Weeks	22	2 (9.1)	0 (0.0)	2 (9.1)
Ｃ－反応性蛋白増加	Any period	55	2 (3.6)	1 (1.8)	3 (5.5)
	<4 Weeks	55	1 (1.8)	1 (1.8)	2 (3.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
Ｃ－反応性蛋白増加	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
血中クレアチニン増加	Any period	55	2 (3.6)	0 (0.0)	2 (3.6)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	2 (6.9)	0 (0.0)	2 (6.9)
	>=16 Weeks	22	1 (4.5)	0 (0.0)	1 (4.5)
脳性ナトリウム利尿ペプチド増加	Any period	55	1 (1.8)	1 (1.8)	2 (3.6)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
脳性ナトリウム利尿ペプチド増加	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
好酸球数増加	Any period	55	2 (3.6)	0 (0.0)	2 (3.6)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
血中コレステロール増加	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related n (%)	Not Related n (%)	Total (N=55) n (%)
血中クレアチンホスホキナーゼＭＢ増加	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	0 (0.0)	1 (4.5)
血中クレアチンホスホキナーゼ増加	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
血中免疫グロブリンＡ減少	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
血中免疫グロブリンA減少	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
尿中血陽性	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
心胸郭比増加	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
心胸郭比増加	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
心電図Ｔ波逆転	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
リパーゼ増加	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
体重増加	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
代謝および栄養障害	Any period	55	16 (29.1)	9 (16.4)	25 (45.5)
	<4 Weeks	55	11 (20.0)	4 (7.3)	15 (27.3)
	4 - <8 Weeks	52	3 (5.8)	3 (5.8)	6 (11.5)
	8 - <12 Weeks	39	4 (10.3)	2 (5.1)	6 (15.4)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	2 (9.1)	3 (13.6)
食欲減退	Any period	55	12 (21.8)	1 (1.8)	13 (23.6)
	<4 Weeks	55	9 (16.4)	0 (0.0)	9 (16.4)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
食欲減退	4 - <8 Weeks	52	2 (3.8)	0 (0.0)	2 (3.8)
	8 - <12 Weeks	39	2 (5.1)	0 (0.0)	2 (5.1)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	1 (4.5)	2 (9.1)
低アルブミン血症	Any period	55	2 (3.6)	3 (5.5)	5 (9.1)
	<4 Weeks	55	1 (1.8)	1 (1.8)	2 (3.6)
	4 - <8 Weeks	52	1 (1.9)	1 (1.9)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
低カリウム血症	Any period	55	2 (3.6)	3 (5.5)	5 (9.1)
	<4 Weeks	55	1 (1.8)	1 (1.8)	2 (3.6)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	1 (2.6)	1 (2.6)	2 (5.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
低カリウム血症	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
低カルシウム血症	Any period	55	2 (3.6)	1 (1.8)	3 (5.5)
	<4 Weeks	55	1 (1.8)	1 (1.8)	2 (3.6)
	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
低ナトリウム血症	Any period	55	2 (3.6)	0 (0.0)	2 (3.6)
	<4 Weeks	55	2 (3.6)	0 (0.0)	2 (3.6)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
糖尿病	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
高カリウム血症	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
高マグネシウム血症	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
高マグネシウム血症	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
高トリグリセリド血症	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
低蛋白血症	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
低蛋白血症	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
筋骨格系および結合組織障害	Any period	55	7 (12.7)	12 (21.8)	19 (34.5)
	<4 Weeks	55	3 (5.5)	6 (10.9)	9 (16.4)
	4 - <8 Weeks	52	4 (7.7)	2 (3.8)	6 (11.5)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	2 (6.9)	2 (6.9)
	>=16 Weeks	22	2 (9.1)	3 (13.6)	5 (22.7)
背部痛	Any period	55	1 (1.8)	4 (7.3)	5 (9.1)
	<4 Weeks	55	0 (0.0)	2 (3.6)	2 (3.6)
	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	2 (9.1)	2 (9.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
筋痙縮	Any period	55	3 (5.5)	2 (3.6)	5 (9.1)
	<4 Weeks	55	2 (3.6)	0 (0.0)	2 (3.6)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	1 (4.5)	2 (9.1)
筋肉疲労	Any period	55	1 (1.8)	1 (1.8)	2 (3.6)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	1 (1.9)	1 (1.9)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
筋肉痛	Any period	55	0 (0.0)	2 (3.6)	2 (3.6)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
筋肉痛	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
関節痛	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
関節炎	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related n (%)	Not Related n (%)	Total (N=55) n (%)
関節炎	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
出血性関節症	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	1 (3.4)	1 (3.4)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
関節腫脹	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	0 (0.0)	1 (4.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related n (%)	Not Related n (%)	Total (N=55) n (%)
筋力低下	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
筋骨格硬直	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
頚部痛	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
頚部痛	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
四肢痛	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
肩回旋筋腱板症候群	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related n (%)	Not Related n (%)	Total (N=55) n (%)
肩回旋筋腱板症候群	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
腱炎	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	Any period	55	1 (1.8)	3 (5.5)	4 (7.3)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	2 (3.8)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in ‘Any Period’ level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
腫瘍疼痛	Any period	55	0 (0.0)	2 (3.6)	2 (3.6)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
末梢性Ｔ細胞性リンパ腫、組織型不明	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
皮膚乳頭腫	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
皮膚乳頭腫	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
神経系障害	Any period	55	4 (7.3)	5 (9.1)	9 (16.4)
	<4 Weeks	55	1 (1.8)	2 (3.6)	3 (5.5)
	4 - <8 Weeks	52	3 (5.8)	1 (1.9)	4 (7.7)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	2 (9.1)	2 (9.1)
頭痛	Any period	55	2 (3.6)	4 (7.3)	6 (10.9)
	<4 Weeks	55	1 (1.8)	2 (3.6)	3 (5.5)
	4 - <8 Weeks	52	1 (1.9)	1 (1.9)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
頭痛	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
味覚異常	Any period	55	2 (3.6)	0 (0.0)	2 (3.6)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	2 (3.8)	0 (0.0)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
浮動性めまい	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
感覚鈍麻	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
末梢性感覚ニューロパチー	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
失神寸前の状態	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
失神寸前の状態	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
精神障害	Any period	55	0 (0.0)	5 (9.1)	5 (9.1)
	<4 Weeks	55	0 (0.0)	3 (5.5)	3 (5.5)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
不眠症	Any period	55	0 (0.0)	4 (7.3)	4 (7.3)
	<4 Weeks	55	0 (0.0)	2 (3.6)	2 (3.6)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
不眠症	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
譫妄	Any period	55	0 (0.0)	2 (3.6)	2 (3.6)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
腎および尿路障害	Any period	55	1 (1.8)	1 (1.8)	2 (3.6)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
急性腎障害	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
血尿	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
蛋白尿	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
蛋白尿	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
生殖系および乳房障害	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
陰嚢浮腫	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related n (%)	Not Related n (%)	Total (N=55) n (%)
陰嚢浮腫	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
呼吸器、胸郭および縦隔障害	Any period	55	9 (16.4)	12 (21.8)	21 (38.2)
	<4 Weeks	55	2 (3.6)	8 (14.5)	10 (18.2)
	4 - <8 Weeks	52	1 (1.9)	4 (7.7)	5 (9.6)
	8 - <12 Weeks	39	3 (7.7)	2 (5.1)	5 (12.8)
	12 - <16 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	>=16 Weeks	22	3 (13.6)	2 (9.1)	5 (22.7)
咳嗽	Any period	55	1 (1.8)	5 (9.1)	6 (10.9)
	<4 Weeks	55	0 (0.0)	2 (3.6)	2 (3.6)
	4 - <8 Weeks	52	0 (0.0)	2 (3.8)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	1 (4.5)	2 (9.1)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
呼吸困難	Any period	55	2 (3.6)	2 (3.6)	4 (7.3)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	1 (2.6)	1 (2.6)	2 (5.1)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
肺臓炎	Any period	55	4 (7.3)	0 (0.0)	4 (7.3)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	12 - <16 Weeks	29	1 (3.4)	0 (0.0)	1 (3.4)
	>=16 Weeks	22	2 (9.1)	0 (0.0)	2 (9.1)
口腔咽頭痛	Any period	55	0 (0.0)	3 (5.5)	3 (5.5)
	<4 Weeks	55	0 (0.0)	2 (3.6)	2 (3.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
口腔咽頭痛	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
鼻出血	Any period	55	1 (1.8)	1 (1.8)	2 (3.6)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
胸水	Any period	55	1 (1.8)	1 (1.8)	2 (3.6)
	<4 Weeks	55	1 (1.8)	1 (1.8)	2 (3.6)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related n (%)	Not Related n (%)	Total (N=55) n (%)
胸水	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
咽頭知覚不全	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
発声障害	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
労作性呼吸困難	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
しゃっくり	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
間質性肺疾患	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
間質性肺疾患	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
湿性咳嗽	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
アレルギー性鼻炎	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
アレルギー性鼻炎	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
鼻漏	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
上気道の炎症	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
皮膚および皮下組織障害	Any period	55	12 (21.8)	11 (20.0)	23 (41.8)
	<4 Weeks	55	6 (10.9)	3 (5.5)	9 (16.4)
	4 - <8 Weeks	52	3 (5.8)	7 (13.5)	10 (19.2)
	8 - <12 Weeks	39	4 (10.3)	3 (7.7)	7 (17.9)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	0 (0.0)	1 (4.5)
発疹	Any period	55	3 (5.5)	2 (3.6)	5 (9.1)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	1 (1.9)	1 (1.9)	2 (3.8)
	8 - <12 Weeks	39	1 (2.6)	1 (2.6)	2 (5.1)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
蕁麻疹	Any period	55	3 (5.5)	2 (3.6)	5 (9.1)
	<4 Weeks	55	2 (3.6)	1 (1.8)	3 (5.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
蕁麻疹	4 - <8 Weeks	52	1 (1.9)	1 (1.9)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
紅斑	Any period	55	0 (0.0)	2 (3.6)	2 (3.6)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
全身性そう痒症	Any period	55	2 (3.6)	0 (0.0)	2 (3.6)
	<4 Weeks	55	2 (3.6)	0 (0.0)	2 (3.6)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
全身性そう痒症	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
紫斑	Any period	55	2 (3.6)	0 (0.0)	2 (3.6)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	1 (1.9)	0 (0.0)	1 (1.9)
	8 - <12 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
斑状丘疹状皮疹	Any period	55	1 (1.8)	1 (1.8)	2 (3.6)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	1 (2.6)	1 (2.6)	2 (5.1)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
褥瘡性潰瘍	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
ざ瘡様皮膚炎	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
全身性剥脱性皮膚炎	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
全身性剥脱性皮膚炎	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	1 (2.6)	0 (0.0)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	1 (4.5)	0 (0.0)	1 (4.5)
皮膚乾燥	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
皮脂欠乏性湿疹	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related n (%)	Not Related n (%)	Total (N=55) n (%)
皮脂欠乏性湿疹	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
多形紅斑	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
全身紅斑	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
皮膚疼痛	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	1 (1.8)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
点状出血	Any period	55	1 (1.8)	0 (0.0)	1 (1.8)
	<4 Weeks	55	1 (1.8)	0 (0.0)	1 (1.8)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
色素沈着障害	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
色素沈着障害	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	1 (2.6)	1 (2.6)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
そう痒性皮疹	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
血管障害	Any period	55	0 (0.0)	3 (5.5)	3 (5.5)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	2 (3.8)	2 (3.8)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
血管障害	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)
深部静脈血栓症	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)
低血圧	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	1 (1.9)	1 (1.9)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;

Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.

Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

Country: Overall

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total (N=55)
			n (%)	n (%)	n (%)
末梢動脈閉塞性疾患	Any period	55	0 (0.0)	1 (1.8)	1 (1.8)
	<4 Weeks	55	0 (0.0)	0 (0.0)	0 (0.0)
	4 - <8 Weeks	52	0 (0.0)	0 (0.0)	0 (0.0)
	8 - <12 Weeks	39	0 (0.0)	0 (0.0)	0 (0.0)
	12 - <16 Weeks	29	0 (0.0)	0 (0.0)	0 (0.0)
	>=16 Weeks	22	0 (0.0)	1 (4.5)	1 (4.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.; n = number of subjects; % = percentages are based on number of subjects in a country at risk at the particular interval;
Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period.
Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-33　発現時期別の有害事象（210 試験）（安全性解析対象集団）

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
Number of subjects with at least one TEAE	Any period	23	23 (100.0%)	0 (0.0%)	23 (100.0%)
	<4 Weeks	23	23 (100.0%)	0 (0.0%)	23 (100.0%)
	4 - <8 Weeks	17	13 (76.5%)	0 (0.0%)	13 (76.5%)
	8 - <12 Weeks	12	7 (58.3%)	1 (8.3%)	8 (66.7%)
	12 - <16 Weeks	6	6 (100.0%)	0 (0.0%)	6 (100.0%)
	>=16 Weeks	3	3 (100.0%)	0 (0.0%)	3 (100.0%)
血液およびリンパ系障害	Any period	23	19 (82.6%)	0 (0.0%)	19 (82.6%)
	<4 Weeks	23	19 (82.6%)	0 (0.0%)	19 (82.6%)
	4 - <8 Weeks	17	13 (76.5%)	0 (0.0%)	13 (76.5%)
	8 - <12 Weeks	12	6 (50.0%)	0 (0.0%)	6 (50.0%)
	12 - <16 Weeks	6	5 (83.3%)	0 (0.0%)	5 (83.3%)
	>=16 Weeks	3	3 (100.0%)	0 (0.0%)	3 (100.0%)
血小板減少症*	Any period	23	18 (78.3%)	0 (0.0%)	18 (78.3%)
	<4 Weeks	23	18 (78.3%)	0 (0.0%)	18 (78.3%)
	4 - <8 Weeks	17	7 (41.2%)	0 (0.0%)	7 (41.2%)
	8 - <12 Weeks	12	3 (25.0%)	0 (0.0%)	3 (25.0%)
	12 - <16 Weeks	6	2 (33.3%)	0 (0.0%)	2 (33.3%)
	>=16 Weeks	3	1 (33.3%)	0 (0.0%)	1 (33.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
好中球減少症*	Any period	23	12 (52.2%)	0 (0.0%)	12 (52.2%)
	<4 Weeks	23	10 (43.5%)	0 (0.0%)	10 (43.5%)
	4 - <8 Weeks	17	9 (52.9%)	0 (0.0%)	9 (52.9%)
	8 - <12 Weeks	12	4 (33.3%)	0 (0.0%)	4 (33.3%)
	12 - <16 Weeks	6	3 (50.0%)	0 (0.0%)	3 (50.0%)
	>=16 Weeks	3	2 (66.7%)	0 (0.0%)	2 (66.7%)
白血球減少症*	Any period	23	10 (43.5%)	0 (0.0%)	10 (43.5%)
	<4 Weeks	23	8 (34.8%)	0 (0.0%)	8 (34.8%)
	4 - <8 Weeks	17	9 (52.9%)	0 (0.0%)	9 (52.9%)
	8 - <12 Weeks	12	5 (41.7%)	0 (0.0%)	5 (41.7%)
	12 - <16 Weeks	6	2 (33.3%)	0 (0.0%)	2 (33.3%)
	>=16 Weeks	3	2 (66.7%)	0 (0.0%)	2 (66.7%)
貧血*	Any period	23	9 (39.1%)	0 (0.0%)	9 (39.1%)
	<4 Weeks	23	4 (17.4%)	0 (0.0%)	4 (17.4%)
	4 - <8 Weeks	17	6 (35.3%)	0 (0.0%)	6 (35.3%)
	8 - <12 Weeks	12	1 (8.3%)	0 (0.0%)	1 (8.3%)
	12 - <16 Weeks	6	1 (16.7%)	0 (0.0%)	1 (16.7%)
	>=16 Weeks	3	1 (33.3%)	0 (0.0%)	1 (33.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
リンパ球減少症*	Any period	23	2 (8.7%)	0 (0.0%)	2 (8.7%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	2 (11.8%)	0 (0.0%)	2 (11.8%)
	8 - <12 Weeks	12	1 (8.3%)	0 (0.0%)	1 (8.3%)
	12 - <16 Weeks	6	1 (16.7%)	0 (0.0%)	1 (16.7%)
	>=16 Weeks	3	1 (33.3%)	0 (0.0%)	1 (33.3%)
好酸球増加症	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
発熱性好中球減少症	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
心臓障害	Any period	23	2 (8.7%)	0 (0.0%)	2 (8.7%)
	<4 Weeks	23	2 (8.7%)	0 (0.0%)	2 (8.7%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
第一度房室ブロック	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
動悸	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Study week = (start date of adverse event – date of first study drug + 1)/7.
Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
眼障害	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	1 (8.3%)	1 (8.3%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
ドライアイ	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	1 (8.3%)	1 (8.3%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
胃腸障害	Any period	23	7 (30.4%)	2 (8.7%)	9 (39.1%)
	<4 Weeks	23	6 (26.1%)	1 (4.3%)	7 (30.4%)
	4 - <8 Weeks	17	2 (11.8%)	1 (5.9%)	3 (17.6%)
	8 - <12 Weeks	12	1 (8.3%)	0 (0.0%)	1 (8.3%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	1 (33.3%)	0 (0.0%)	1 (33.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
下痢	Any period	23	5 (21.7%)	1 (4.3%)	6 (26.1%)
	<4 Weeks	23	3 (13.0%)	1 (4.3%)	4 (17.4%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	1 (8.3%)	0 (0.0%)	1 (8.3%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	1 (33.3%)	0 (0.0%)	1 (33.3%)
腹痛	Any period	23	1 (4.3%)	2 (8.7%)	3 (13.0%)
	<4 Weeks	23	1 (4.3%)	1 (4.3%)	2 (8.7%)
	4 - <8 Weeks	17	0 (0.0%)	1 (5.9%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
悪心	Any period	23	3 (13.0%)	0 (0.0%)	3 (13.0%)
	<4 Weeks	23	3 (13.0%)	0 (0.0%)	3 (13.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
口内炎	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
一般・全身障害および投与部位の状態	Any period	23	10 (43.5%)	3 (13.0%)	13 (56.5%)
	<4 Weeks	23	7 (30.4%)	3 (13.0%)	10 (43.5%)
	4 - <8 Weeks	17	4 (23.5%)	0 (0.0%)	4 (23.5%)
	8 - <12 Weeks	12	1 (8.3%)	0 (0.0%)	1 (8.3%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	1 (33.3%)	0 (0.0%)	1 (33.3%)
倦怠感	Any period	23	7 (30.4%)	0 (0.0%)	7 (30.4%)
	<4 Weeks	23	6 (26.1%)	0 (0.0%)	6 (26.1%)
	4 - <8 Weeks	17	2 (11.8%)	0 (0.0%)	2 (11.8%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
疲労	Any period	23	2 (8.7%)	1 (4.3%)	3 (13.0%)
	<4 Weeks	23	1 (4.3%)	1 (4.3%)	2 (8.7%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	1 (33.3%)	0 (0.0%)	1 (33.3%)
発熱	Any period	23	2 (8.7%)	1 (4.3%)	3 (13.0%)
	<4 Weeks	23	1 (4.3%)	1 (4.3%)	2 (8.7%)
	4 - <8 Weeks	17	2 (11.8%)	0 (0.0%)	2 (11.8%)
	8 - <12 Weeks	12	1 (8.3%)	0 (0.0%)	1 (8.3%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
悪寒	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
非心臓性胸痛	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
末梢性浮腫	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
感染症および寄生虫症	Any period	23	5 (21.7%)	2 (8.7%)	7 (30.4%)
	<4 Weeks	23	1 (4.3%)	2 (8.7%)	3 (13.0%)
	4 - <8 Weeks	17	3 (17.6%)	1 (5.9%)	4 (23.5%)
	8 - <12 Weeks	12	2 (16.7%)	0 (0.0%)	2 (16.7%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	1 (33.3%)	0 (0.0%)	1 (33.3%)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
細菌感染	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
サイトメガロウイルス感染	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
医療機器関連感染	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
麦粒腫	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	1 (33.3%)	1 (33.3%)
口腔カンジダ症	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	1 (8.3%)	0 (0.0%)	1 (8.3%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
ニューモシスチス・イロベチイ肺炎	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	1 (8.3%)	0 (0.0%)	1 (8.3%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
皮膚感染	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
扁桃炎	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
上気道感染	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	0 (0.0%)	1 (5.9%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
尿路感染	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	1 (33.3%)	0 (0.0%)	1 (33.3%)
傷害、中毒および処置合併症	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
挫傷	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
臨床検査	Any period	23	8 (34.8%)	2 (8.7%)	10 (43.5%)
	<4 Weeks	23	6 (26.1%)	1 (4.3%)	7 (30.4%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	1 (8.3%)	0 (0.0%)	1 (8.3%)
	12 - <16 Weeks	6	1 (16.7%)	0 (0.0%)	1 (16.7%)
	>=16 Weeks	3	0 (0.0%)	1 (33.3%)	1 (33.3%)
体重減少	Any period	23	4 (17.4%)	0 (0.0%)	4 (17.4%)
	<4 Weeks	23	2 (8.7%)	0 (0.0%)	2 (8.7%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	1 (8.3%)	0 (0.0%)	1 (8.3%)
	12 - <16 Weeks	6	1 (16.7%)	0 (0.0%)	1 (16.7%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
アスパラギン酸アミノトランスフェラーゼ増加	Any period	23	2 (8.7%)	0 (0.0%)	2 (8.7%)
	<4 Weeks	23	2 (8.7%)	0 (0.0%)	2 (8.7%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
γーグルタミルトランスフェラーゼ増加	Any period	23	2 (8.7%)	0 (0.0%)	2 (8.7%)
	<4 Weeks	23	2 (8.7%)	0 (0.0%)	2 (8.7%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
アラニンアミノトランスフェラーゼ増加	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
血中アルカリホスファターゼ増加	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
血中乳酸脱水素酵素増加	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
脳性ナトリウム利尿ペプチド増加	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	1 (33.3%)	1 (33.3%)
好酸球数増加	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
リパーゼ増加	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
代謝および栄養障害	Any period	23	12 (52.2%)	1 (4.3%)	13 (56.5%)
	<4 Weeks	23	12 (52.2%)	1 (4.3%)	13 (56.5%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
食欲減退	Any period	23	8 (34.8%)	0 (0.0%)	8 (34.8%)
	<4 Weeks	23	8 (34.8%)	0 (0.0%)	8 (34.8%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
低アルブミン血症	Any period	23	3 (13.0%)	0 (0.0%)	3 (13.0%)
	<4 Weeks	23	3 (13.0%)	0 (0.0%)	3 (13.0%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
低ナトリウム血症	Any period	23	2 (8.7%)	0 (0.0%)	2 (8.7%)
	<4 Weeks	23	2 (8.7%)	0 (0.0%)	2 (8.7%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
高カルシウム血症	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
低カリウム血症	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
低リン酸血症	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
筋骨格系および結合組織障害	Any period	23	1 (4.3%)	6 (26.1%)	7 (30.4%)
	<4 Weeks	23	0 (0.0%)	4 (17.4%)	4 (17.4%)
	4 - <8 Weeks	17	0 (0.0%)	1 (5.9%)	1 (5.9%)
	8 - <12 Weeks	12	1 (8.3%)	1 (8.3%)	2 (16.7%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
背部痛	Any period	23	0 (0.0%)	4 (17.4%)	4 (17.4%)
	<4 Weeks	23	0 (0.0%)	3 (13.0%)	3 (13.0%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	1 (8.3%)	1 (8.3%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
関節痛	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	1 (8.3%)	0 (0.0%)	1 (8.3%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
脊椎すべり症	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	0 (0.0%)	1 (5.9%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
尺骨突き上げ症候群	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
腫瘍疼痛	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
神経系障害	Any period	23	7 (30.4%)	2 (8.7%)	9 (39.1%)
	<4 Weeks	23	6 (26.1%)	1 (4.3%)	7 (30.4%)
	4 - <8 Weeks	17	0 (0.0%)	1 (5.9%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	1 (16.7%)	0 (0.0%)	1 (16.7%)
	>=16 Weeks	3	0 (0.0%)	1 (33.3%)	1 (33.3%)
味覚異常	Any period	23	4 (17.4%)	0 (0.0%)	4 (17.4%)
	<4 Weeks	23	3 (13.0%)	0 (0.0%)	3 (13.0%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	1 (16.7%)	0 (0.0%)	1 (16.7%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
頭痛	Any period	23	1 (4.3%)	1 (4.3%)	2 (8.7%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	1 (33.3%)	1 (33.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
味覚消失	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
認知障害	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
浮動性めまい	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	0 (0.0%)	1 (5.9%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
傾眠	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
腎および尿路障害	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
尿瘻	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
呼吸器、胸郭および縦隔障害	Any period	23	2 (8.7%)	2 (8.7%)	4 (17.4%)
	<4 Weeks	23	1 (4.3%)	1 (4.3%)	2 (8.7%)
	4 - <8 Weeks	17	1 (5.9%)	1 (5.9%)	2 (11.8%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
急性呼吸不全	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
鼻出血	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
間質性肺疾患	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
口腔咽頭痛	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	0 (0.0%)	1 (5.9%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
皮膚および皮下組織障害	Any period	23	5 (21.7%)	3 (13.0%)	8 (34.8%)
	<4 Weeks	23	2 (8.7%)	2 (8.7%)	4 (17.4%)
	4 - <8 Weeks	17	3 (17.6%)	0 (0.0%)	3 (17.6%)
	8 - <12 Weeks	12	1 (8.3%)	1 (8.3%)	2 (16.7%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
接触皮膚炎	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
湿疹	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	1 (8.3%)	1 (8.3%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
紅斑	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
多形紅斑	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
光線過敏性反応	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
そう痒症	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
発疹	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
皮膚剥脱	Any period	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	1 (4.3%)	1 (4.3%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
皮膚潰瘍	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8 - <12 Weeks	12	1 (8.3%)	0 (0.0%)	1 (8.3%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	Study Week	Subject at Risk	Related	Not Related	Total
			n (%)	n (%)	n (%)
血管障害	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
高血圧	Any period	23	1 (4.3%)	0 (0.0%)	1 (4.3%)
	<4 Weeks	23	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4 - <8 Weeks	17	1 (5.9%)	0 (0.0%)	1 (5.9%)
	8 - <12 Weeks	12	0 (0.0%)	0 (0.0%)	0 (0.0%)
	12 - <16 Weeks	6	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=16 Weeks	3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. n = number of subjects; % = percentages are based on number of subjects at risk at the particular interval; Number of subjects at risk is defined as subjects on treatment at a particular study week.

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

Study week = (start date of adverse event – date of first study drug + 1)/7.

Subjects whose TEAEs occurred more than once in the same PT and in the same period are counted once in that particular PT and period. Subjects who had more than one AEs occurring at different period within the same PT are counted once in 'Any Period' level. Subjects with more than one TEAE in a particular period are counted once in the worst relationship.

TEAE of overdose is not included in this analysis.

表 2.7.4.7-34　死亡に至った有害事象（203 試験）（安全性解析対象集団）

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Number of subjects with TEAE leading to death	0	1(6.3)	1(1.8)
感染症および寄生虫症	0	1(6.3)	1(1.8)
肺炎	0	1(6.3)	1(1.8)

Source: Listing 16.2.6.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-35　死亡に至った有害事象（201 試験）（安全性解析対象集団）

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Not Applicable			

SOURCE: Listing 16.2.6.6
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

表 2.7.4.7-36　死亡に至った有害事象（210 試験）（安全性解析対象集団）

System organ class Preferred term	40 mg (N=23) n (%)
No observation.	

Source: Listing 16.2.6.4
MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-37　重篤な有害事象（203 試験）（安全性解析対象集団）

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Number of subjects with at least one serious TEAE	11(28.2)	3(18.8)	14(25.5)
血液およびリンパ系障害	2(5.1)	1(6.3)	3(5.5)
発熱性好中球減少症	1(2.6)	1(6.3)	2(3.6)
再生不良性貧血	1(2.6)	0	1(1.8)
心臓障害	1(2.6)	0	1(1.8)
不安定狭心症	1(2.6)	0	1(1.8)
一般・全身障害および投与部位の状態	0	2(12.5)	2(3.6)
疲労	0	1(6.3)	1(1.8)
発熱	0	1(6.3)	1(1.8)
感染症および寄生虫症	1(2.6)	1(6.3)	2(3.6)
ニューモシスチス・イロベチイ肺炎	1(2.6)	0	1(1.8)
咽頭炎	1(2.6)	0	1(1.8)
肺炎	0	1(6.3)	1(1.8)
臨床検査	1(2.6)	0	1(1.8)
Ｃ－反応性蛋白増加	1(2.6)	0	1(1.8)
代謝および栄養障害	1(2.6)	0	1(1.8)
低ナトリウム血症	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 3

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1(2.6)	0	1(1.8)
末梢性Ｔ細胞性リンパ腫、組織型不明	1(2.6)	0	1(1.8)
腎および尿路障害	1(2.6)	0	1(1.8)
急性腎障害	1(2.6)	0	1(1.8)
呼吸器、胸郭および縦隔障害	3(7.7)	0	3(5.5)
上気道の炎症	1(2.6)	0	1(1.8)
肺臓炎	1(2.6)	0	1(1.8)
間質性肺疾患	1(2.6)	0	1(1.8)
血管障害	1(2.6)	0	1(1.8)
末梢動脈閉塞性疾患	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 3

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-38　重篤な有害事象（201 試験）（安全性解析対象集団）

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Number of patients with at least one serious TEAE	1 (14.3%)	1 (14.3%)	2 (14.3%)
胃腸障害	0 (0.0%)	1 (14.3%)	1 (7.1%)
腹痛	0 (0.0%)	1 (14.3%)	1 (7.1%)
腸炎	0 (0.0%)	1 (14.3%)	1 (7.1%)
神経系障害	1 (14.3%)	0 (0.0%)	1 (7.1%)
パーキンソニズム	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.6.5
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

表 2.7.4.7-39　重篤な有害事象（210 試験）（安全性解析対象集団）

System organ class Preferred term	40 mg (N=23) n (%)
Number of subjects with at least one serious TEAE	7(30.4%)
血液およびリンパ系障害	2(8.7%)
血小板減少症*	2(8.7%)
好中球減少症*	1(4.3%)
心臓障害	1(4.3%)
動悸	1(4.3%)
感染症および寄生虫症	2(8.7%)
ニューモシスチス・イロベチイ肺炎	1(4.3%)
尿路感染	1(4.3%)
呼吸器、胸郭および縦隔障害	2(8.7%)
急性呼吸不全	1(4.3%)
間質性肺疾患	1(4.3%)

Source: Listing 16.2.6 3

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-40　治験薬の投与中止に至った有害事象（203 試験）（安全性解析対象集団）

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Number of subjects with at least one TEAE leading to study drug discontinuation	15(38.5)	3(18.8)	18(32.7)
血液およびリンパ系障害	8(20.5)	1(6.3)	9(16.4)
好中球減少症*	4(10.3)	1(6.3)	5(9.1)
血小板減少症*	4(10.3)	0	4(7.3)
リンパ球減少症*	2(5.1)	0	2(3.6)
白血球減少症*	1(2.6)	0	1(1.8)
感染症および寄生虫症	1(2.6)	1(6.3)	2(3.6)
ニューモシスチス・イロベチイ肺炎	1(2.6)	0	1(1.8)
肺炎	0	1(6.3)	1(1.8)
臨床検査	3(7.7)	0	3(5.5)
γーグルタミルトランスフェラーゼ増加	2(5.1)	0	2(3.6)
脳性ナトリウム利尿ペプチド増加	1(2.6)	0	1(1.8)
血中アルカリホスファターゼ増加	1(2.6)	0	1(1.8)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1(2.6)	0	1(1.8)
末梢性Ｔ細胞性リンパ腫、組織型不明	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 2

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE.　For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
呼吸器、胸郭および縦隔障害	2(5.1)	1(6.3)	3(5.5)
肺臓炎	1(2.6)	1(6.3)	2(3.6)
呼吸困難	0	1(6.3)	1(1.8)
間質性肺疾患	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 2

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

表 2.7.4.7-41　重症度別関連性別治験薬の投与中止に至った有害事象（203 試験）（安全性解析対象集団）

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
Number of subjects with at least one TEAE leading to study drug discontinuation	Any Grade	14(35.9)	1(2.6)	15(38.5)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	12(30.8)	0(0.0)	12(30.8)
	Grade 4	2(5.1)	0(0.0)	2(5.1)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	14(35.9)	0(0.0)	14(35.9)
血液およびリンパ系障害	Any Grade	8(20.5)	0(0.0)	8(20.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	6(15.4)	0(0.0)	6(15.4)
	Grade 4	2(5.1)	0(0.0)	2(5.1)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	8(20.5)	0(0.0)	8(20.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE.　For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
好中球減少症*	Any Grade	4(10.3)	0(0.0)	4(10.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	4(10.3)	0(0.0)	4(10.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	4(10.3)	0(0.0)	4(10.3)
血小板減少症*	Any Grade	4(10.3)	0(0.0)	4(10.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(5.1)	0(0.0)	2(5.1)
	Grade 4	2(5.1)	0(0.0)	2(5.1)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	4(10.3)	0(0.0)	4(10.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
リンパ球減少症*	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(5.1)	0(0.0)	2(5.1)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(5.1)	0(0.0)	2(5.1)
白血球減少症*	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
感染症および寄生虫症	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)
ニューモシスチス・イロベチイ肺炎	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
臨床検査	Any Grade	2(5.1)	1(2.6)	3(7.7)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(5.1)	0(0.0)	2(5.1)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(5.1)	0(0.0)	2(5.1)
γーグルタミルトランスフェラーゼ増加	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(5.1)	0(0.0)	2(5.1)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(5.1)	0(0.0)	2(5.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
血中アルカリホスファターゼ増加	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)
脳性ナトリウム利尿ペプチド増加	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	1(2.6)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)
末梢性Ｔ細胞性リンパ腫、組織型不明	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
呼吸器、胸郭および縦隔障害	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(5.1)	0(0.0)	2(5.1)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(5.1)	0(0.0)	2(5.1)
間質性肺疾患	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
肺臓炎	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
Number of subjects with at least one TEAE leading to study drug discontinuation	Any Grade	3(18.8)	1(6.3)	3(18.8)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(12.5)	0(0.0)	2(12.5)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	1(6.3)	0(0.0)	1(6.3)
	>=Grade 3	3(18.8)	0(0.0)	3(18.8)
血液およびリンパ系障害	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
好中球減少症*	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)
感染症および寄生虫症	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	1(6.3)	0(0.0)	1(6.3)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Korea

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=16) n (%)
肺炎	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	1(6.3)	0(0.0)	1(6.3)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)
呼吸器、胸郭および縦隔障害	Any Grade	1(6.3)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
呼吸困難	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
肺臓炎	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
Number of subjects with at least one TEAE leading to study drug discontinuation	Any Grade	17(30.9)	2(3.6)	18(32.7)
	Grade 1	0(0.0)	2(3.6)	2(3.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	14(25.5)	0(0.0)	14(25.5)
	Grade 4	2(3.6)	0(0.0)	2(3.6)
	Grade 5	1(1.8)	0(0.0)	1(1.8)
	>=Grade 3	17(30.9)	0(0.0)	17(30.9)
血液およびリンパ系障害	Any Grade	9(16.4)	0(0.0)	9(16.4)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	7(12.7)	0(0.0)	7(12.7)
	Grade 4	2(3.6)	0(0.0)	2(3.6)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	9(16.4)	0(0.0)	9(16.4)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
好中球減少症*	Any Grade	5(9.1)	0(0.0)	5(9.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	5(9.1)	0(0.0)	5(9.1)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	5(9.1)	0(0.0)	5(9.1)
血小板減少症*	Any Grade	4(7.3)	0(0.0)	4(7.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(3.6)	0(0.0)	2(3.6)
	Grade 4	2(3.6)	0(0.0)	2(3.6)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	4(7.3)	0(0.0)	4(7.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
リンパ球減少症*	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(3.6)	0(0.0)	2(3.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(3.6)	0(0.0)	2(3.6)
白血球減少症*	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
感染症および寄生虫症	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	1(1.8)	0(0.0)	1(1.8)
	>=Grade 3	2(3.6)	0(0.0)	2(3.6)
ニューモシスチス・イロベチイ肺炎	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
肺炎	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	1(1.8)	0(0.0)	1(1.8)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)
臨床検査	Any Grade	2(3.6)	1(1.8)	3(5.5)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(3.6)	0(0.0)	2(3.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(3.6)	0(0.0)	2(3.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
γーグルタミルトランスフェラーゼ増加	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(3.6)	0(0.0)	2(3.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(3.6)	0(0.0)	2(3.6)
血中アルカリホスファターゼ増加	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6.1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
脳性ナトリウム利尿ペプチド増加	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
末梢性Ｔ細胞性リンパ腫、組織型不明	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)
呼吸器、胸郭および縦隔障害	Any Grade	3(5.5)	1(1.8)	3(5.5)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	3(5.5)	0(0.0)	3(5.5)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(5.5)	0(0.0)	3(5.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
肺臓炎	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(3.6)	0(0.0)	2(3.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(3.6)	0(0.0)	2(3.6)
呼吸困難	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
間質性肺疾患	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

表 2.7.4.7-42　治験薬の投与中止に至った有害事象（201 試験）（安全性解析対象集団）

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Number of patients with TEAE leading to study drug discontinuation	2 (28.6%)	4 (57.1%)	6 (42.9%)
血液およびリンパ系障害	0 (0.0%)	1 (14.3%)	1 (7.1%)
好中球減少症	0 (0.0%)	1 (14.3%)	1 (7.1%)
胃腸障害	0 (0.0%)	1 (14.3%)	1 (7.1%)
腹痛	0 (0.0%)	1 (14.3%)	1 (7.1%)
臨床検査	1 (14.3%)	1 (14.3%)	2 (14.3%)
血中クレアチンホスホキナーゼ増加	1 (14.3%)	0 (0.0%)	1 (7.1%)
胸部コンピュータ断層撮影異常	0 (0.0%)	1 (14.3%)	1 (7.1%)
皮膚および皮下組織障害	1 (14.3%)	1 (14.3%)	2 (14.3%)
多形紅斑	0 (0.0%)	1 (14.3%)	1 (7.1%)
血管周囲細胞浸潤性皮膚炎	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.6.4
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

表 2.7.4.7-43　治験薬の投与中止に至った有害事象（210 試験）（安全性解析対象集団）

System organ class Preferred term	40 mg (N=23) n (%)
Number of subjects with at least one TEAE leading to study drug discontinuation	9(39.1%)
血液およびリンパ系障害	5(21.7%)
血小板減少症*	4(17.4%)
好中球減少症*	3(13.0%)
一般・全身障害および投与部位の状態	1(4.3%)
疲労	1(4.3%)
感染症および寄生虫症	1(4.3%)
ニューモシスチス・イロベチイ肺炎	1(4.3%)
臨床検査	1(4.3%)
血中アルカリホスファターゼ増加	1(4.3%)
γーグルタミルトランスフェラーゼ増加	1(4.3%)
呼吸器、胸郭および縦隔障害	1(4.3%)
間質性肺疾患	1(4.3%)

Source: Listing 16.2.6 2

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

表 2.7.4.7-44　重症度別関連性別治験薬の投与中止に至った有害事象（210 試験）（安全性解析対象集団）

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
Number of subjects with at least one TEAE leading to study drug discontinuation	Any Grade	9 (39.1%)	0 (0.0%)	9 (39.1%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	6 (26.1%)	0 (0.0%)	6 (26.1%)
	Grade 4	3 (13.0%)	0 (0.0%)	3 (13.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=Grade 3	9 (39.1%)	0 (0.0%)	9 (39.1%)
血液およびリンパ系障害	Any Grade	5 (21.7%)	0 (0.0%)	5 (21.7%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	3 (13.0%)	0 (0.0%)	3 (13.0%)
	Grade 4	2 (8.7%)	0 (0.0%)	2 (8.7%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=Grade 3	5 (21.7%)	0 (0.0%)	5 (21.7%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
血小板减少症*	Any Grade	4 (17.4%)	0 (0.0%)	4 (17.4%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	2 (8.7%)	0 (0.0%)	2 (8.7%)
	Grade 4	2 (8.7%)	0 (0.0%)	2 (8.7%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=Grade 3	4 (17.4%)	0 (0.0%)	4 (17.4%)
好中球减少症*	Any Grade	3 (13.0%)	0 (0.0%)	3 (13.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 3	2 (8.7%)	0 (0.0%)	2 (8.7%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=Grade 3	2 (8.7%)	0 (0.0%)	2 (8.7%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI CTCAE Version 4.03.

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

Subjects are counted only once for the worst grade under each column.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

TEAE of overdose is not included in this analysis.

For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
一般・全身障害および投与部位の状態	Any Grade	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)
疲労	Any Grade	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI CTCAE Version 4.03.

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

Subjects are counted only once for the worst grade under each column.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

TEAE of overdose is not included in this analysis.

For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
感染症および寄生虫症	Any Grade	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)
ニューモシスチス・イロベチイ肺炎	Any Grade	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI CTCAE Version 4.03.

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

Subjects are counted only once for the worst grade under each column.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

TEAE of overdose is not included in this analysis.

For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
臨床検査	Any Grade	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)
血中アルカリホスファターゼ増加	Any Grade	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
γーグルタミルトランスフェラーゼ増加	Any Grade	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
呼吸器、胸郭および縦隔障害	Any Grade	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)
間質性肺疾患	Any Grade	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	1 (4.3%)	0 (0.0%)	1 (4.3%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>=Grade 3	1 (4.3%)	0 (0.0%)	1 (4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

表 2.7.4.7-45　治験薬の休薬又は減量に至った有害事象（203 試験）（安全性解析対象集団）

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Number of subjects with at least one dose reduction or dose interruption due to TEAE	31(79.5)	9(56.3)	40(72.7)
血液およびリンパ系障害	28(71.8)	6(37.5)	34(61.8)
血小板減少症*	18(46.2)	3(18.8)	21(38.2)
好中球減少症*	16(41.0)	3(18.8)	19(34.5)
発熱性好中球減少症	2(5.1)	1(6.3)	3(5.5)
白血球減少症*	2(5.1)	0	2(3.6)
心臓障害	1(2.6)	0	1(1.8)
不安定狭心症	1(2.6)	0	1(1.8)
耳および迷路障害	1(2.6)	0	1(1.8)
回転性めまい	1(2.6)	0	1(1.8)
胃腸障害	1(2.6)	1(6.3)	2(3.6)
下痢	0	1(6.3)	1(1.8)
悪心	1(2.6)	0	1(1.8)
一般・全身障害および投与部位の状態	2(5.1)	1(6.3)	3(5.5)
発熱	1(2.6)	1(6.3)	2(3.6)
末梢性浮腫	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE.　For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

System organ class Preferred term	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
感染症および寄生虫症	2(5.1)	0	2(3.6)
上咽頭炎	1(2.6)	0	1(1.8)
気管支炎	1(2.6)	0	1(1.8)
臨床検査	2(5.1)	1(6.3)	3(5.5)
Ｃ－反応性蛋白増加	1(2.6)	1(6.3)	2(3.6)
心電図ＱＴ延長	1(2.6)	0	1(1.8)
心電図Ｔ波逆転	1(2.6)	0	1(1.8)
代謝および栄養障害	4(10.3)	0	4(7.3)
食欲減退	3(7.7)	0	3(5.5)
低ナトリウム血症	2(5.1)	0	2(3.6)
皮膚および皮下組織障害	1(2.6)	1(6.3)	2(3.6)
発疹	0	1(6.3)	1(1.8)
蕁麻疹	1(2.6)	0	1(1.8)
血管障害	1(2.6)	0	1(1.8)
末梢動脈閉塞性疾患	1(2.6)	0	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

表 2.7.4.7-46　重症度別関連性別治験薬の休薬又は減量に至った有害事象（203 試験）（安全性解析対象集団）

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
Number of subjects with at least one TEAE leading to dose reduction or interruption	Any Grade	29(74.4)	5(12.8)	31(79.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	2(5.1)	2(5.1)	3(7.7)
	Grade 3	19(48.7)	2(5.1)	20(51.3)
	Grade 4	8(20.5)	1(2.6)	9(23.1)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	27(69.2)	3(7.7)	28(71.8)
血液およびリンパ系障害	Any Grade	27(69.2)	1(2.6)	28(71.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	18(46.2)	0(0.0)	18(46.2)
	Grade 4	8(20.5)	1(2.6)	9(23.1)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	26(66.7)	1(2.6)	27(69.2)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE.　For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
血小板減少症*	Any Grade	17(43.6)	1(2.6)	18(46.2)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	12(30.8)	0(0.0)	12(30.8)
	Grade 4	4(10.3)	1(2.6)	5(12.8)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	16(41.0)	1(2.6)	17(43.6)
好中球減少症*	Any Grade	16(41.0)	0(0.0)	16(41.0)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	12(30.8)	0(0.0)	12(30.8)
	Grade 4	4(10.3)	0(0.0)	4(10.3)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	16(41.0)	0(0.0)	16(41.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
発熱性好中球減少症	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(5.1)	0(0.0)	2(5.1)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(5.1)	0(0.0)	2(5.1)
白血球減少症*	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(5.1)	0(0.0)	2(5.1)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(5.1)	0(0.0)	2(5.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
心臓障害	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)
不安定狭心症	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
耳および迷路障害	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
回転性めまい	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
胃腸障害	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
悪心	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=39) n (%)
一般・全身障害および投与部位の状態	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)
末梢性浮腫	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(2.6)	0(0.0)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(2.6)	0(0.0)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
発熱	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
感染症および寄生虫症	Any Grade	1(2.6)	1(2.6)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	1(2.6)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
気管支炎	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
上咽頭炎	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
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Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
臨床検査	Any Grade	2(5.1)	1(2.6)	2(5.1)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	1(2.6)	1(2.6)	2(5.1)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
C－反応性蛋白増加	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(2.6)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
心電図ＱＴ延長	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
心電図Ｔ波逆転	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	1(2.6)	0(0.0)	1(2.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
代謝および栄養障害	Any Grade	4(10.3)	0(0.0)	4(10.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	3(7.7)	0(0.0)	3(7.7)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(7.7)	0(0.0)	3(7.7)
食欲減退	Any Grade	3(7.7)	0(0.0)	3(7.7)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	2(5.1)	0(0.0)	2(5.1)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(5.1)	0(0.0)	2(5.1)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
低ナトリウム血症	Any Grade	2(5.1)	0(0.0)	2(5.1)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(5.1)	0(0.0)	2(5.1)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(5.1)	0(0.0)	2(5.1)
皮膚および皮下組織障害	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
蕁麻疹	Any Grade	1(2.6)	0(0.0)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(2.6)	0(0.0)	1(2.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
血管障害	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Japan

System organ class Preferred term	Severity	Related	Not Related	Total (N=39)
		n (%)	n (%)	n (%)
末梢動脈閉塞性疾患	Any Grade	0(0.0)	1(2.6)	1(2.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(2.6)	1(2.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(2.6)	1(2.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
Number of subjects with at least one TEAE leading to dose reduction or interruption	Any Grade	8(50.0)	1(6.3)	9(56.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	7(43.8)	0(0.0)	7(43.8)
	Grade 4	1(6.3)	0(0.0)	1(6.3)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	8(50.0)	0(0.0)	8(50.0)
血液およびリンパ系障害	Any Grade	6(37.5)	0(0.0)	6(37.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	5(31.3)	0(0.0)	5(31.3)
	Grade 4	1(6.3)	0(0.0)	1(6.3)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	6(37.5)	0(0.0)	6(37.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
好中球減少症*	Any Grade	3(18.8)	0(0.0)	3(18.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(12.5)	0(0.0)	2(12.5)
	Grade 4	1(6.3)	0(0.0)	1(6.3)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(18.8)	0(0.0)	3(18.8)
血小板減少症*	Any Grade	3(18.8)	0(0.0)	3(18.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	3(18.8)	0(0.0)	3(18.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(18.8)	0(0.0)	3(18.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
発熱性好中球減少症	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)
胃腸障害	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
下痢	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)
一般・全身障害および投与部位の状態	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
発熱	Any Grade	0(0.0)	1(6.3)	1(6.3)
	Grade 1	0(0.0)	1(6.3)	1(6.3)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
臨床検査	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
C－反応性蛋白増加	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)
皮膚および皮下組織障害	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Korea

System organ class Preferred term	Severity	Related	Not Related	Total (N=16)
		n (%)	n (%)	n (%)
発疹	Any Grade	1(6.3)	0(0.0)	1(6.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(6.3)	0(0.0)	1(6.3)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(6.3)	0(0.0)	1(6.3)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
Number of subjects with at least one TEAE leading to dose reduction or interruption	Any Grade	37(67.3)	6(10.9)	40(72.7)
	Grade 1	0(0.0)	1(1.8)	1(1.8)
	Grade 2	2(3.6)	2(3.6)	3(5.5)
	Grade 3	26(47.3)	2(3.6)	27(49.1)
	Grade 4	9(16.4)	1(1.8)	10(18.2)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	35(63.6)	3(5.5)	36(65.5)
血液およびリンパ系障害	Any Grade	33(60.0)	1(1.8)	34(61.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	23(41.8)	0(0.0)	23(41.8)
	Grade 4	9(16.4)	1(1.8)	10(18.2)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	32(58.2)	1(1.8)	33(60.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
血小板减少症*	Any Grade	20(36.4)	1(1.8)	21(38.2)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	15(27.3)	0(0.0)	15(27.3)
	Grade 4	4(7.3)	1(1.8)	5(9.1)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	19(34.5)	1(1.8)	20(36.4)
好中球减少症*	Any Grade	19(34.5)	0(0.0)	19(34.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	14(25.5)	0(0.0)	14(25.5)
	Grade 4	5(9.1)	0(0.0)	5(9.1)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	19(34.5)	0(0.0)	19(34.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
発熱性好中球減少症	Any Grade	3(5.5)	0(0.0)	3(5.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	3(5.5)	0(0.0)	3(5.5)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(5.5)	0(0.0)	3(5.5)
白血球減少症*	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(3.6)	0(0.0)	2(3.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(3.6)	0(0.0)	2(3.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
心臓障害	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)
不安定狭心症	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
耳および迷路障害	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
回転性めまい	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
胃腸障害	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)
下痢	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
悪心	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
一般・全身障害および投与部位の状態	Any Grade	2(3.6)	1(1.8)	3(5.5)
	Grade 1	1(1.8)	1(1.8)	2(3.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
発熱	Any Grade	1(1.8)	1(1.8)	2(3.6)
	Grade 1	1(1.8)	1(1.8)	2(3.6)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
末梢性浮腫	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
感染症および寄生虫症	Any Grade	1(1.8)	1(1.8)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	1(1.8)	2(3.6)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
気管支炎	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
上咽頭炎	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
臨床検査	Any Grade	3(5.5)	1(1.8)	3(5.5)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	1(1.8)	1(1.8)	2(3.6)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
Ｃ－反応性蛋白増加	Any Grade	1(1.8)	1(1.8)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	1(1.8)	1(1.8)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)
心電図ＱＴ延長	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
心電図Ｔ波逆転	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	1(1.8)	0(0.0)	1(1.8)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
代謝および栄養障害	Any Grade	4(7.3)	0(0.0)	4(7.3)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	3(5.5)	0(0.0)	3(5.5)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	3(5.5)	0(0.0)	3(5.5)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
食欲減退	Any Grade	3(5.5)	0(0.0)	3(5.5)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	2(3.6)	0(0.0)	2(3.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(3.6)	0(0.0)	2(3.6)
低ナトリウム血症	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	2(3.6)	0(0.0)	2(3.6)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	2(3.6)	0(0.0)	2(3.6)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
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Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
皮膚および皮下組織障害	Any Grade	2(3.6)	0(0.0)	2(3.6)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)
発疹	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	1(1.8)	0(0.0)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	1(1.8)	0(0.0)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related n (%)	Not Related n (%)	Total (N=55) n (%)
蕁麻疹	Any Grade	1(1.8)	0(0.0)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	1(1.8)	0(0.0)	1(1.8)
	Grade 3	0(0.0)	0(0.0)	0(0.0)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	0(0.0)	0(0.0)
血管障害	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

Country: Overall

System organ class Preferred term	Severity	Related	Not Related	Total (N=55)
		n (%)	n (%)	n (%)
末梢動脈閉塞性疾患	Any Grade	0(0.0)	1(1.8)	1(1.8)
	Grade 1	0(0.0)	0(0.0)	0(0.0)
	Grade 2	0(0.0)	0(0.0)	0(0.0)
	Grade 3	0(0.0)	1(1.8)	1(1.8)
	Grade 4	0(0.0)	0(0.0)	0(0.0)
	Grade 5	0(0.0)	0(0.0)	0(0.0)
	>=Grade 3	0(0.0)	1(1.8)	1(1.8)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each relationship column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

表 2.7.4.7-47　治験薬の休薬又は減量に至った有害事象（201 試験）（安全性解析対象集団）

System organ class Preferred term	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Number of patients with TEAE leading to dose reduction or delay	4 (57.1%)	4 (57.1%)	8 (57.1%)
血液およびリンパ系障害	1 (14.3%)	1 (14.3%)	2 (14.3%)
貧血	1 (14.3%)	0 (0.0%)	1 (7.1%)
好中球減少症	0 (0.0%)	1 (14.3%)	1 (7.1%)
血小板減少症	0 (0.0%)	1 (14.3%)	1 (7.1%)
一般・全身障害および投与部位の状態	1 (14.3%)	0 (0.0%)	1 (7.1%)
疲労	1 (14.3%)	0 (0.0%)	1 (7.1%)
感染症および寄生虫症	1 (14.3%)	0 (0.0%)	1 (7.1%)
副鼻腔炎	1 (14.3%)	0 (0.0%)	1 (7.1%)
臨床検査	2 (28.6%)	3 (42.9%)	5 (35.7%)
アラニンアミノトランスフェラーゼ増加	0 (0.0%)	1 (14.3%)	1 (7.1%)
好中球数減少	2 (28.6%)	0 (0.0%)	2 (14.3%)
血小板数減少	2 (28.6%)	2 (28.6%)	4 (28.6%)
代謝および栄養障害	0 (0.0%)	1 (14.3%)	1 (7.1%)
高トリグリセリド血症	0 (0.0%)	1 (14.3%)	1 (7.1%)
皮膚および皮下組織障害	1 (14.3%)	1 (14.3%)	2 (14.3%)
結節性紅斑	0 (0.0%)	1 (14.3%)	1 (7.1%)
全身性皮疹	1 (14.3%)	0 (0.0%)	1 (7.1%)

SOURCE: Listing 16.2.6.3
MedDRA Version 19.1 was used to code adverse events.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

表 2.7.4.7-48　治験薬の休薬又は減量に至った有害事象（210 試験）（安全性解析対象集団）

System organ class Preferred term	40 mg (N=23) n (%)
Number of subjects with at least one dose reduction or dose interruption due to TEAE	16(69.6%)
血液およびリンパ系障害	15(65.2%)
好中球減少症*	10(43.5%)
血小板減少症*	10(43.5%)
一般・全身障害および投与部位の状態	1(4.3%)
疲労	1(4.3%)
感染症および寄生虫症	1(4.3%)
尿路感染	1(4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

表 2.7.4.7-49　重症度別関連性別治験薬の休薬又は減量に至った有害事象（210 試験）（安全性解析対象集団）

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
Number of subjects with at least one TEAE leading to dose reduction or interruption	Any Grade	16(69.6%)	0(0.0%)	16(69.6%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	10(43.5%)	0(0.0%)	10(43.5%)
	Grade 4	6(26.1%)	0(0.0%)	6(26.1%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	16(69.6%)	0(0.0%)	16(69.6%)
血液およびリンパ系障害	Any Grade	15(65.2%)	0(0.0%)	15(65.2%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	9(39.1%)	0(0.0%)	9(39.1%)
	Grade 4	6(26.1%)	0(0.0%)	6(26.1%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	15(65.2%)	0(0.0%)	15(65.2%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI CTCAE Version 4.03.

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

Subjects are counted only once for the worst grade under each column.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

TEAE of overdose is not included in this analysis.

For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
好中球减少症*	Any Grade	10(43.5%)	0(0.0%)	10(43.5%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	7(30.4%)	0(0.0%)	7(30.4%)
	Grade 4	3(13.0%)	0(0.0%)	3(13.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	10(43.5%)	0(0.0%)	10(43.5%)
血小板减少症*	Any Grade	10(43.5%)	0(0.0%)	10(43.5%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	6(26.1%)	0(0.0%)	6(26.1%)
	Grade 4	4(17.4%)	0(0.0%)	4(17.4%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	10(43.5%)	0(0.0%)	10(43.5%)

Source: Listing 16 2.6.1

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI CTCAE Version 4.03.

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

Subjects are counted only once for the worst grade under each column.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

TEAE of overdose is not included in this analysis.

For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
一般・全身障害および投与部位の状態	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
疲労	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI CTCAE Version 4.03.

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

Subjects are counted only once for the worst grade under each column.

TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.

TEAE of overdose is not included in this analysis.

For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

System organ class Preferred term	Severity	Related	Not Related	Total (N=23)
		n (%)	n (%)	n (%)
感染症および寄生虫症	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
尿路感染	Any Grade	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 1	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 2	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 3	1(4.3%)	0(0.0%)	1(4.3%)
	Grade 4	0(0.0%)	0(0.0%)	0(0.0%)
	Grade 5	0(0.0%)	0(0.0%)	0(0.0%)
	>=Grade 3	1(4.3%)	0(0.0%)	1(4.3%)

Source: Listing 16.2.6 1

MedDRA Version 21.1 was used to code adverse events. Severities are graded using NCI CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Subjects are counted only once for the worst grade under each column.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.

表 2.7.4.7-50　注目すべき有害事象（203 試験）（安全性解析対象集団）

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
Number of subjects with at least one Adverse Event of Special Interest		53(96.4%)
「貧血」	Any Grade	18(32.7%)
	Grade 1	2(3.6%)
	Grade 2	7(12.7%)
	Grade 3	8(14.5%)
	Grade 4	1(1.8%)
	Grade 5	0(0.0%)
	>=Grade 3	9(16.4%)
貧血	Any Grade	18(32.7%)
	Grade 1	2(3.6%)
	Grade 2	7(12.7%)
	Grade 3	8(14.5%)
	Grade 4	1(1.8%)
	Grade 5	0(0.0%)
	>=Grade 3	9(16.4%)
貧血+ヘモグロビン減少	Any Grade	18(32.7%)
	Grade 1	2(3.6%)
	Grade 2	7(12.7%)
	Grade 3	8(14.5%)
	Grade 4	1(1.8%)
	Grade 5	0(0.0%)
	>=Grade 3	9(16.4%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
「心臓障害」	Any Grade	7(12.7%)
	Grade 1	3(5.5%)
	Grade 2	3(5.5%)
	Grade 3	1(1.8%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(1.8%)
動悸	Any Grade	3(5.5%)
	Grade 1	3(5.5%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
心房細動	Any Grade	2(3.6%)
	Grade 1	1(1.8%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
不安定狭心症	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(1.8%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(1.8%)
不整脈	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
心嚢液貯留	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
「ウイルス再活性化を除く肝障害」	Any Grade	10(18.2%)
	Grade 1	3(5.5%)
	Grade 2	4(7.3%)
	Grade 3	3(5.5%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	3(5.5%)
γーグルタミルトランスフェラーゼ増加	Any Grade	8(14.5%)
	Grade 1	2(3.6%)
	Grade 2	3(5.5%)
	Grade 3	3(5.5%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	3(5.5%)
アスパラギン酸アミノトランスフェラーゼ増加	Any Grade	7(12.7%)
	Grade 1	5(9.1%)
	Grade 2	2(3.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
アラニンアミノトランスフェラーゼ増加	Any Grade	5(9.1%)
	Grade 1	3(5.5%)
	Grade 2	2(3.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
「過敏症」	Any Grade	3(5.5%)
	Grade 1	2(3.6%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
全身性剥脱性皮膚炎	Any Grade	1(1.8%)
	Grade 1	1(1.8%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
薬物過敏症	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
多形紅斑	Any Grade	1(1.8%)
	Grade 1	1(1.8%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
「感染症」	Any Grade	19(34.5%)
	Grade 1	3(5.5%)
	Grade 2	13(23.6%)
	Grade 3	2(3.6%)
	Grade 4	0(0.0%)
	Grade 5	1(1.8%)
	>=Grade 3	3(5.5%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
上気道感染	Any Grade	4(7.3%)
	Grade 1	0(0.0%)
	Grade 2	4(7.3%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
咽頭炎	Any Grade	3(5.5%)
	Grade 1	0(0.0%)
	Grade 2	2(3.6%)
	Grade 3	1(1.8%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(1.8%)
気管支炎	Any Grade	2(3.6%)
	Grade 1	0(0.0%)
	Grade 2	2(3.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
結膜炎	Any Grade	2(3.6%)
	Grade 1	1(1.8%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
インフルエンザ	Any Grade	2(3.6%)
	Grade 1	0(0.0%)
	Grade 2	2(3.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
上咽頭炎	Any Grade	2(3.6%)
	Grade 1	1(1.8%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
膀胱炎	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
サイトメガロウイルス感染	Any Grade	1(1.8%)
	Grade 1	1(1.8%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
感染性小腸結腸炎	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(1.8%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(1.8%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
胃腸炎	Any Grade	1(1.8%)
	Grade 1	1(1.8%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
帯状疱疹	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
膿痂疹	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
ニューモシスチス・イロベチイ肺炎	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(1.8%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(1.8%)
肺炎	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	1(1.8%)
	>=Grade 3	1(1.8%)
鼻炎	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
ブドウ球菌皮膚感染	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(1.8%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(1.8%)
「間質性肺疾患」	Any Grade	5(9.1%)
	Grade 1	1(1.8%)
	Grade 2	1(1.8%)
	Grade 3	3(5.5%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	3(5.5%)
肺臓炎	Any Grade	4(7.3%)
	Grade 1	1(1.8%)
	Grade 2	1(1.8%)
	Grade 3	2(3.6%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	2(3.6%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
間質性肺疾患	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(1.8%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(1.8%)
「リンパ球減少症」	Any Grade	16(29.1%)
	Grade 1	1(1.8%)
	Grade 2	3(5.5%)
	Grade 3	10(18.2%)
	Grade 4	2(3.6%)
	Grade 5	0(0.0%)
	>=Grade 3	12(21.8%)
リンパ球減少症+リンパ球数減少	Any Grade	16(29.1%)
	Grade 1	1(1.8%)
	Grade 2	3(5.5%)
	Grade 3	10(18.2%)
	Grade 4	2(3.6%)
	Grade 5	0(0.0%)
	>=Grade 3	12(21.8%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
リンパ球数減少	Any Grade	11(20.0%)
	Grade 1	1(1.8%)
	Grade 2	2(3.6%)
	Grade 3	6(10.9%)
	Grade 4	2(3.6%)
	Grade 5	0(0.0%)
	>=Grade 3	8(14.5%)
リンパ球減少症	Any Grade	5(9.1%)
	Grade 1	0(0.0%)
	Grade 2	1(1.8%)
	Grade 3	4(7.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	4(7.3%)
「好中球減少症」	Any Grade	35(63.6%)
	Grade 1	0(0.0%)
	Grade 2	11(20.0%)
	Grade 3	19(34.5%)
	Grade 4	5(9.1%)
	Grade 5	0(0.0%)
	>=Grade 3	24(43.6%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
好中球减少症+好中球数减少+顆粒球减少症	Any Grade	31(56.4%)
	Grade 1	1(1.8%)
	Grade 2	10(18.2%)
	Grade 3	15(27.3%)
	Grade 4	5(9.1%)
	Grade 5	0(0.0%)
	>=Grade 3	20(36.4%)
白血球減少症+白血球数減少	Any Grade	24(43.6%)
	Grade 1	2(3.6%)
	Grade 2	11(20.0%)
	Grade 3	10(18.2%)
	Grade 4	1(1.8%)
	Grade 5	0(0.0%)
	>=Grade 3	11(20.0%)
好中球数減少	Any Grade	20(36.4%)
	Grade 1	1(1.8%)
	Grade 2	4(7.3%)
	Grade 3	12(21.8%)
	Grade 4	3(5.5%)
	Grade 5	0(0.0%)
	>=Grade 3	15(27.3%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
白血球数減少	Any Grade	18(32.7%)
	Grade 1	2(3.6%)
	Grade 2	7(12.7%)
	Grade 3	8(14.5%)
	Grade 4	1(1.8%)
	Grade 5	0(0.0%)
	>=Grade 3	9(16.4%)
好中球減少症	Any Grade	11(20.0%)
	Grade 1	0(0.0%)
	Grade 2	6(10.9%)
	Grade 3	3(5.5%)
	Grade 4	2(3.6%)
	Grade 5	0(0.0%)
	>=Grade 3	5(9.1%)
白血球減少症	Any Grade	6(10.9%)
	Grade 1	0(0.0%)
	Grade 2	4(7.3%)
	Grade 3	2(3.6%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	2(3.6%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
発熱性好中球減少症	Any Grade	3(5.5%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	3(5.5%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	3(5.5%)
顆粒球減少症	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(1.8%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(1.8%)
「血小板減少症」	Any Grade	46(83.6%)
	Grade 1	8(14.5%)
	Grade 2	10(18.2%)
	Grade 3	19(34.5%)
	Grade 4	9(16.4%)
	Grade 5	0(0.0%)
	>=Grade 3	28(50.9%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
血小板减少症+血小板数减少	Any Grade	46(83.6%)
	Grade 1	8(14.5%)
	Grade 2	10(18.2%)
	Grade 3	19(34.5%)
	Grade 4	9(16.4%)
	Grade 5	0(0.0%)
	>=Grade 3	28(50.9%)
血小板数减少	Any Grade	31(56.4%)
	Grade 1	7(12.7%)
	Grade 2	7(12.7%)
	Grade 3	11(20.0%)
	Grade 4	6(10.9%)
	Grade 5	0(0.0%)
	>=Grade 3	17(30.9%)
血小板减少症	Any Grade	15(27.3%)
	Grade 1	1(1.8%)
	Grade 2	3(5.5%)
	Grade 3	8(14.5%)
	Grade 4	3(5.5%)
	Grade 5	0(0.0%)
	>=Grade 3	11(20.0%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
「トルサード　ド　ポアント／QT 延長」	Any Grade	5(9.1%)
	Grade 1	4(7.3%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
心電図ＱＴ延長	Any Grade	5(9.1%)
	Grade 1	4(7.3%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
「ウイルス再活性化」	Any Grade	2(3.6%)
	Grade 1	1(1.8%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Grouped Term Preferred term	Severity	40 mg (N=55) n (%)
サイトメガロウイルス感染	Any Grade	1(1.8%)
	Grade 1	1(1.8%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
帯状疱疹	Any Grade	1(1.8%)
	Grade 1	0(0.0%)
	Grade 2	1(1.8%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

表 2.7.4.7-51　注目すべき有害事象：血液学的有害事象（201 試験）（安全性解析対象集団）

Grouped Term Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Number of patients with at least one Adverse Event of Special Interest		5 (71.4%)	7 (100.0%)	12 (85.7%)
白血球減少症（Grouped）	Any Grade	4 (57.1%)	1 (14.3%)	5 (35.7%)
	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 3	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade >= 3	1 (14.3%)	1 (14.3%)	2 (14.3%)
白血球減少症	Any Grade	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 1	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade >= 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
白血球数減少	Any Grade	3 (42.9%)	1 (14.3%)	4 (28.6%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 3	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade >= 3	1 (14.3%)	1 (14.3%)	2 (14.3%)

SOURCE: Listing 16.2.6 3

MedDRA Version 19.1 was used to code adverse events.

n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.

Grouped Term Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
好中球減少症（Grouped）	Any Grade	3 (42.9%)	2 (28.6%)	5 (35.7%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	3 (42.9%)	0 (0.0%)	3 (21.4%)
	Grade 4	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade >= 3	3 (42.9%)	2 (28.6%)	5 (35.7%)
好中球減少症	Any Grade	1 (14.3%)	2 (28.6%)	3 (21.4%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 4	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade >= 3	1 (14.3%)	2 (28.6%)	3 (21.4%)
好中球数減少	Any Grade	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade >= 3	2 (28.6%)	0 (0.0%)	2 (14.3%)

SOURCE: Listing 16.2.6 3s

MedDRA Version 19.1 was used to code adverse events.

n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.

Grouped Term Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
血小板减少症（Grouped）	Any Grade	5 (71.4%)	7 (100.0%)	12 (85.7%)
	Grade 1	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 2	5 (71.4%)	4 (57.1%)	9 (64.3%)
	Grade 3	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade >= 3	0 (0.0%)	2 (28.6%)	2 (14.3%)
血小板数减少	Any Grade	3 (42.9%)	3 (42.9%)	6 (42.9%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	3 (42.9%)	3 (42.9%)	6 (42.9%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade >= 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
血小板减少症	Any Grade	2 (28.6%)	4 (57.1%)	6 (42.9%)
	Grade 1	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 2	2 (28.6%)	1 (14.3%)	3 (21.4%)
	Grade 3	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade >= 3	0 (0.0%)	2 (28.6%)	2 (14.3%)

SOURCE: Listing 16.2.6 3

MedDRA Version 19.1 was used to code adverse events.

n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.

Grouped Term Preferred term	Severity	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
貧血（Grouped）	Any Grade	5 (71.4%)	0 (0.0%)	5 (35.7%)
	Grade 1	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 2	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 3	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade >= 3	1 (14.3%)	0 (0.0%)	1 (7.1%)
貧血	Any Grade	5 (71.4%)	0 (0.0%)	5 (35.7%)
	Grade 1	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 2	2 (28.6%)	0 (0.0%)	2 (14.3%)
	Grade 3	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade >= 3	1 (14.3%)	0 (0.0%)	1 (7.1%)
ヘモグロビン減少	Any Grade	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade >= 3	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.6 3

MedDRA Version 19.1 was used to code adverse events.

n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.

表 2.7.4.7-52　注目すべき有害事象（210 試験）（安全性解析対象集団）

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
Number of subjects with at least one Adverse Event of Special Interest		21(91.3%)
「貧血」	Any Grade	9(39.1%)
	Grade 1	1(4.3%)
	Grade 2	3(13.0%)
	Grade 3	5(21.7%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	5(21.7%)
貧血+ヘモグロビン減少	Any Grade	9(39.1%)
	Grade 1	1(4.3%)
	Grade 2	3(13.0%)
	Grade 3	5(21.7%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	5(21.7%)
貧血	Any Grade	8(34.8%)
	Grade 1	1(4.3%)
	Grade 2	3(13.0%)
	Grade 3	4(17.4%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	4(17.4%)

Source: Listing 16 2.6.5
MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
ヘモグロビン減少	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(4.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(4.3%)
「心臓障害」	Any Grade	2(8.7%)
	Grade 1	2(8.7%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
第一度房室ブロック	Any Grade	1(4.3%)
	Grade 1	1(4.3%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

Source: Listing 16 2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
動悸	Any Grade	1(4.3%)
	Grade 1	1(4.3%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
「ウイルス再活性化を除く肝障害」	Any Grade	3(13.0%)
	Grade 1	2(8.7%)
	Grade 2	0(0.0%)
	Grade 3	1(4.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(4.3%)
アスパラギン酸アミノトランスフェラーゼ増加	Any Grade	2(8.7%)
	Grade 1	2(8.7%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

Source: Listing 16.2.6 5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
γーグルタミルトランスフェラーゼ増加	Any Grade	2(8.7%)
	Grade 1	1(4.3%)
	Grade 2	0(0.0%)
	Grade 3	1(4.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(4.3%)
アラニンアミノトランスフェラーゼ増加	Any Grade	1(4.3%)
	Grade 1	1(4.3%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
「過敏症」	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	1(4.3%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

Source: Listing 16.2.6 5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
多形紅斑	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	1(4.3%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
「感染症」	Any Grade	7(30.4%)
	Grade 1	1(4.3%)
	Grade 2	3(13.0%)
	Grade 3	3(13.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	3(13.0%)
細菌感染	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	1(4.3%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

Source: Listing 16.2.6 5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
サイトメガロウイルス感染	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	1(4.3%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
医療機器関連感染	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(4.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(4.3%)
麦粒腫	Any Grade	1(4.3%)
	Grade 1	1(4.3%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

Source: Listing 16.2.6 5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
口腔カンジダ症	Any Grade	1(4.3%)
	Grade 1	1(4.3%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
ニューモシスチス・イロベチイ肺炎	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(4.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(4.3%)
皮膚感染	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	1(4.3%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

Source: Listing 16.2.6 5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
扁桃炎	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	1(4.3%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
上気道感染	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	1(4.3%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
尿路感染	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(4.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(4.3%)

Source: Listing 16 2.6.5

MedDRA Version 21.1 was used to code adverse events.

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
「間質性肺疾患」	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	1(4.3%)
	Grade 5	0(0.0%)
	>=Grade 3	1(4.3%)
間質性肺疾患	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	1(4.3%)
	Grade 5	0(0.0%)
	>=Grade 3	1(4.3%)
「リンパ球減少症」	Any Grade	2(8.7%)
	Grade 1	0(0.0%)
	Grade 2	1(4.3%)
	Grade 3	1(4.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(4.3%)

Source: Listing 16 2.6.5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
リンパ球数減少	Any Grade	2(8.7%)
	Grade 1	0(0.0%)
	Grade 2	1(4.3%)
	Grade 3	1(4.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(4.3%)
リンパ球減少症+リンパ球数減少	Any Grade	2(8.7%)
	Grade 1	0(0.0%)
	Grade 2	1(4.3%)
	Grade 3	1(4.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(4.3%)
「好中球減少症」	Any Grade	13(56.5%)
	Grade 1	1(4.3%)
	Grade 2	2(8.7%)
	Grade 3	7(30.4%)
	Grade 4	3(13.0%)
	Grade 5	0(0.0%)
	>=Grade 3	10(43.5%)

Source: Listing 16.2.6 5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
好中球减少症+好中球数减少	Any Grade	12(52.2%)
	Grade 1	0(0.0%)
	Grade 2	2(8.7%)
	Grade 3	7(30.4%)
	Grade 4	3(13.0%)
	Grade 5	0(0.0%)
	>=Grade 3	10(43.5%)
好中球数减少	Any Grade	11(47.8%)
	Grade 1	0(0.0%)
	Grade 2	2(8.7%)
	Grade 3	7(30.4%)
	Grade 4	2(8.7%)
	Grade 5	0(0.0%)
	>=Grade 3	9(39.1%)
白血球减少症+白血球数减少	Any Grade	10(43.5%)
	Grade 1	1(4.3%)
	Grade 2	2(8.7%)
	Grade 3	7(30.4%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	7(30.4%)

Source: Listing 16.2.6 5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
白血球数減少	Any Grade	9(39.1%)
	Grade 1	0(0.0%)
	Grade 2	2(8.7%)
	Grade 3	7(30.4%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	7(30.4%)
発熱性好中球減少症	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(4.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(4.3%)
白血球減少症	Any Grade	1(4.3%)
	Grade 1	1(4.3%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

Source: Listing 16.2.6 5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
好中球減少症	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	1(4.3%)
	Grade 5	0(0.0%)
	>=Grade 3	1(4.3%)
「血小板減少症」	Any Grade	18(78.3%)
	Grade 1	1(4.3%)
	Grade 2	5(21.7%)
	Grade 3	6(26.1%)
	Grade 4	6(26.1%)
	Grade 5	0(0.0%)
	>=Grade 3	12(52.2%)
血小板減少症+血小板数減少	Any Grade	18(78.3%)
	Grade 1	1(4.3%)
	Grade 2	5(21.7%)
	Grade 3	6(26.1%)
	Grade 4	6(26.1%)
	Grade 5	0(0.0%)
	>=Grade 3	12(52.2%)

Source: Listing 16.2.6 5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
血小板数減少	Any Grade	15(65.2%)
	Grade 1	1(4.3%)
	Grade 2	5(21.7%)
	Grade 3	4(17.4%)
	Grade 4	5(21.7%)
	Grade 5	0(0.0%)
	>=Grade 3	9(39.1%)
血小板減少症	Any Grade	3(13.0%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	2(8.7%)
	Grade 4	1(4.3%)
	Grade 5	0(0.0%)
	>=Grade 3	3(13.0%)
「ウイルス再活性化」	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	1(4.3%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

Source: Listing 16.2.6 5

MedDRA Version 21.1 was used to code adverse events.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

Grouped Term Preferred term	Severity	40 mg (N=23) n (%)
サイトメガロウイルス感染	Any Grade	1(4.3%)
	Grade 1	0(0.0%)
	Grade 2	1(4.3%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

Source: Listing 16.2.6 5

MedDRA Version 21.1 was used to code adverse events.

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.

表 2.7.4.7-53　人種別（日本人、韓国人）注目すべき有害事象（203 試験）（安全性解析対象集団）

Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
Number of subjects with at least one Adverse Event of Special Interest		39(100.0%)
「貧血」	Any Grade	14(35.9%)
	Grade 1	2(5.1%)
	Grade 2	5(12.8%)
	Grade 3	6(15.4%)
	Grade 4	1(2.6%)
	Grade 5	0(0.0%)
	>=Grade 3	7(17.9%)
貧血	Any Grade	14(35.9%)
	Grade 1	2(5.1%)
	Grade 2	5(12.8%)
	Grade 3	6(15.4%)
	Grade 4	1(2.6%)
	Grade 5	0(0.0%)
	>=Grade 3	7(17.9%)
貧血+ヘモグロビン減少	Any Grade	14(35.9%)
	Grade 1	2(5.1%)
	Grade 2	5(12.8%)
	Grade 3	6(15.4%)
	Grade 4	1(2.6%)
	Grade 5	0(0.0%)
	>=Grade 3	7(17.9%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1
MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
「心臓障害」	Any Grade	6(15.4%)
	Grade 1	3(7.7%)
	Grade 2	2(5.1%)
	Grade 3	1(2.6%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(2.6%)
動悸	Any Grade	3(7.7%)
	Grade 1	3(7.7%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
不安定狭心症	Any Grade	1(2.6%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(2.6%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(2.6%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
不整脈	Any Grade	1(2.6%)
	Grade 1	0(0.0%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
心房細動	Any Grade	1(2.6%)
	Grade 1	1(2.6%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
心嚢液貯留	Any Grade	1(2.6%)
	Grade 1	0(0.0%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
「ウイルス再活性化を除く肝障害」	Any Grade	10(25.6%)
	Grade 1	3(7.7%)
	Grade 2	4(10.3%)
	Grade 3	3(7.7%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	3(7.7%)
γーグルタミルトランスフェラーゼ増加	Any Grade	8(20.5%)
	Grade 1	2(5.1%)
	Grade 2	3(7.7%)
	Grade 3	3(7.7%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	3(7.7%)
アスパラギン酸アミノトランスフェラーゼ増加	Any Grade	7(17.9%)
	Grade 1	5(12.8%)
	Grade 2	2(5.1%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
アラニンアミノトランスフェラーゼ増加	Any Grade	5(12.8%)
	Grade 1	3(7.7%)
	Grade 2	2(5.1%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
「過敏症」	Any Grade	3(7.7%)
	Grade 1	2(5.1%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
全身性剥脱性皮膚炎	Any Grade	1(2.6%)
	Grade 1	1(2.6%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
薬物過敏症	Any Grade	1(2.6%)
	Grade 1	0(0.0%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
多形紅斑	Any Grade	1(2.6%)
	Grade 1	1(2.6%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
「感染症」	Any Grade	15(38.5%)
	Grade 1	2(5.1%)
	Grade 2	12(30.8%)
	Grade 3	1(2.6%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(2.6%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
咽頭炎	Any Grade	3(7.7%)
	Grade 1	0(0.0%)
	Grade 2	2(5.1%)
	Grade 3	1(2.6%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(2.6%)
気管支炎	Any Grade	2(5.1%)
	Grade 1	0(0.0%)
	Grade 2	2(5.1%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
結膜炎	Any Grade	2(5.1%)
	Grade 1	1(2.6%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
インフルエンザ	Any Grade	2(5.1%)
	Grade 1	0(0.0%)
	Grade 2	2(5.1%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
上咽頭炎	Any Grade	2(5.1%)
	Grade 1	1(2.6%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
上気道感染	Any Grade	2(5.1%)
	Grade 1	0(0.0%)
	Grade 2	2(5.1%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
膀胱炎	Any Grade	1(2.6%)
	Grade 1	0(0.0%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
サイトメガロウイルス感染	Any Grade	1(2.6%)
	Grade 1	1(2.6%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
帯状疱疹	Any Grade	1(2.6%)
	Grade 1	0(0.0%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
膿痂疹	Any Grade	1(2.6%)
	Grade 1	0(0.0%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
ニューモシスチス・イロベチイ肺炎	Any Grade	1(2.6%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(2.6%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(2.6%)
鼻炎	Any Grade	1(2.6%)
	Grade 1	0(0.0%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
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Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
「間質性肺疾患」	Any Grade	4(10.3%)
	Grade 1	1(2.6%)
	Grade 2	1(2.6%)
	Grade 3	2(5.1%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	2(5.1%)
肺臓炎	Any Grade	3(7.7%)
	Grade 1	1(2.6%)
	Grade 2	1(2.6%)
	Grade 3	1(2.6%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(2.6%)
間質性肺疾患	Any Grade	1(2.6%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(2.6%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(2.6%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
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Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
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Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
「リンパ球減少症」	Any Grade	16(41.0%)
	Grade 1	1(2.6%)
	Grade 2	3(7.7%)
	Grade 3	10(25.6%)
	Grade 4	2(5.1%)
	Grade 5	0(0.0%)
	>=Grade 3	12(30.8%)
リンパ球減少症+リンパ球数減少	Any Grade	16(41.0%)
	Grade 1	1(2.6%)
	Grade 2	3(7.7%)
	Grade 3	10(25.6%)
	Grade 4	2(5.1%)
	Grade 5	0(0.0%)
	>=Grade 3	12(30.8%)
リンパ球数減少	Any Grade	11(28.2%)
	Grade 1	1(2.6%)
	Grade 2	2(5.1%)
	Grade 3	6(15.4%)
	Grade 4	2(5.1%)
	Grade 5	0(0.0%)
	>=Grade 3	8(20.5%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
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Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
リンパ球減少症	Any Grade	5(12.8%)
	Grade 1	0(0.0%)
	Grade 2	1(2.6%)
	Grade 3	4(10.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	4(10.3%)
「好中球減少症」	Any Grade	32(82.1%)
	Grade 1	0(0.0%)
	Grade 2	11(28.2%)
	Grade 3	17(43.6%)
	Grade 4	4(10.3%)
	Grade 5	0(0.0%)
	>=Grade 3	21(53.8%)
好中球減少症+好中球数減少+顆粒球減少症	Any Grade	28(71.8%)
	Grade 1	1(2.6%)
	Grade 2	10(25.6%)
	Grade 3	13(33.3%)
	Grade 4	4(10.3%)
	Grade 5	0(0.0%)
	>=Grade 3	17(43.6%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
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Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
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Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
白血球減少症+白血球数減少	Any Grade	24(61.5%)
	Grade 1	2(5.1%)
	Grade 2	11(28.2%)
	Grade 3	10(25.6%)
	Grade 4	1(2.6%)
	Grade 5	0(0.0%)
	>=Grade 3	11(28.2%)
好中球数減少	Any Grade	18(46.2%)
	Grade 1	1(2.6%)
	Grade 2	4(10.3%)
	Grade 3	10(25.6%)
	Grade 4	3(7.7%)
	Grade 5	0(0.0%)
	>=Grade 3	13(33.3%)
白血球数減少	Any Grade	18(46.2%)
	Grade 1	2(5.1%)
	Grade 2	7(17.9%)
	Grade 3	8(20.5%)
	Grade 4	1(2.6%)
	Grade 5	0(0.0%)
	>=Grade 3	9(23.1%)

SOURCE: Listing 16.2.6.5 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
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Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
好中球減少症	Any Grade	9(23.1%)
	Grade 1	0(0.0%)
	Grade 2	6(15.4%)
	Grade 3	2(5.1%)
	Grade 4	1(2.6%)
	Grade 5	0(0.0%)
	>=Grade 3	3(7.7%)
白血球減少症	Any Grade	6(15.4%)
	Grade 1	0(0.0%)
	Grade 2	4(10.3%)
	Grade 3	2(5.1%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	2(5.1%)
発熱性好中球減少症	Any Grade	2(5.1%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	2(5.1%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	2(5.1%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
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Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
顆粒球減少症	Any Grade	1(2.6%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(2.6%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(2.6%)
「血小板減少症」	Any Grade	35(89.7%)
	Grade 1	6(15.4%)
	Grade 2	7(17.9%)
	Grade 3	14(35.9%)
	Grade 4	8(20.5%)
	Grade 5	0(0.0%)
	>=Grade 3	22(56.4%)
血小板減少症+血小板数減少	Any Grade	35(89.7%)
	Grade 1	6(15.4%)
	Grade 2	7(17.9%)
	Grade 3	14(35.9%)
	Grade 4	8(20.5%)
	Grade 5	0(0.0%)
	>=Grade 3	22(56.4%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
血小板数減少	Any Grade	26(66.7%)
	Grade 1	5(12.8%)
	Grade 2	6(15.4%)
	Grade 3	9(23.1%)
	Grade 4	6(15.4%)
	Grade 5	0(0.0%)
	>=Grade 3	15(38.5%)
血小板減少症	Any Grade	9(23.1%)
	Grade 1	1(2.6%)
	Grade 2	1(2.6%)
	Grade 3	5(12.8%)
	Grade 4	2(5.1%)
	Grade 5	0(0.0%)
	>=Grade 3	7(17.9%)
「トルサード　ド　ポアント／QT 延長」	Any Grade	5(12.8%)
	Grade 1	4(10.3%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
心電図ＱＴ延長	Any Grade	5(12.8%)
	Grade 1	4(10.3%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
「ウイルス再活性化」	Any Grade	2(5.1%)
	Grade 1	1(2.6%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
サイトメガロウイルス感染	Any Grade	1(2.6%)
	Grade 1	1(2.6%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
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Country: Japan

Grouped Term Preferred term	Severity	40 mg (N=39) n (%)
帯状疱疹	Any Grade	1(2.6%)
	Grade 1	0(0.0%)
	Grade 2	1(2.6%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Korea

Grouped Term Preferred term	Severity	40 mg (N=16) n (%)
Number of subjects with at least one Adverse Event of Special Interest		14(87.5%)
「貧血」	Any Grade	4(25.0%)
	Grade 1	0(0.0%)
	Grade 2	2(12.5%)
	Grade 3	2(12.5%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	2(12.5%)
貧血	Any Grade	4(25.0%)
	Grade 1	0(0.0%)
	Grade 2	2(12.5%)
	Grade 3	2(12.5%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	2(12.5%)
貧血+ヘモグロビン減少	Any Grade	4(25.0%)
	Grade 1	0(0.0%)
	Grade 2	2(12.5%)
	Grade 3	2(12.5%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	2(12.5%)

SOURCE: Listing 16.2.6.5 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Korea

Grouped Term Preferred term	Severity	40 mg (N=16) n (%)
「心臓障害」	Any Grade	1(6.3%)
	Grade 1	0(0.0%)
	Grade 2	1(6.3%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
心房細動	Any Grade	1(6.3%)
	Grade 1	0(0.0%)
	Grade 2	1(6.3%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
「感染症」	Any Grade	4(25.0%)
	Grade 1	1(6.3%)
	Grade 2	1(6.3%)
	Grade 3	1(6.3%)
	Grade 4	0(0.0%)
	Grade 5	1(6.3%)
	>=Grade 3	2(12.5%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
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Country: Korea

Grouped Term Preferred term	Severity	40 mg (N=16) n (%)
上気道感染	Any Grade	2(12.5%)
	Grade 1	0(0.0%)
	Grade 2	2(12.5%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)
感染性小腸結腸炎	Any Grade	1(6.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(6.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(6.3%)
胃腸炎	Any Grade	1(6.3%)
	Grade 1	1(6.3%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	0(0.0%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Korea

Grouped Term Preferred term	Severity	40 mg (N=16) n (%)
肺炎	Any Grade	1(6.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	0(0.0%)
	Grade 4	0(0.0%)
	Grade 5	1(6.3%)
	>=Grade 3	1(6.3%)
ブドウ球菌皮膚感染	Any Grade	1(6.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(6.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(6.3%)
「間質性肺疾患」	Any Grade	1(6.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(6.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(6.3%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Korea

Grouped Term Preferred term	Severity	40 mg (N=16) n (%)
肺臓炎	Any Grade	1(6.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(6.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(6.3%)
「好中球減少症」	Any Grade	3(18.8%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	2(12.5%)
	Grade 4	1(6.3%)
	Grade 5	0(0.0%)
	>=Grade 3	3(18.8%)
好中球減少症+好中球数減少+顆粒球減少症	Any Grade	3(18.8%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	2(12.5%)
	Grade 4	1(6.3%)
	Grade 5	0(0.0%)
	>=Grade 3	3(18.8%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Korea

Grouped Term Preferred term	Severity	40 mg (N=16) n (%)
好中球減少症	Any Grade	2(12.5%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(6.3%)
	Grade 4	1(6.3%)
	Grade 5	0(0.0%)
	>=Grade 3	2(12.5%)
好中球数減少	Any Grade	2(12.5%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	2(12.5%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	2(12.5%)
発熱性好中球減少症	Any Grade	1(6.3%)
	Grade 1	0(0.0%)
	Grade 2	0(0.0%)
	Grade 3	1(6.3%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	1(6.3%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Korea

Grouped Term Preferred term	Severity	40 mg (N=16) n (%)
「血小板減少症」	Any Grade	11(68.8%)
	Grade 1	2(12.5%)
	Grade 2	3(18.8%)
	Grade 3	5(31.3%)
	Grade 4	1(6.3%)
	Grade 5	0(0.0%)
	>=Grade 3	6(37.5%)
血小板減少症+血小板数減少	Any Grade	11(68.8%)
	Grade 1	2(12.5%)
	Grade 2	3(18.8%)
	Grade 3	5(31.3%)
	Grade 4	1(6.3%)
	Grade 5	0(0.0%)
	>=Grade 3	6(37.5%)
血小板減少症	Any Grade	6(37.5%)
	Grade 1	0(0.0%)
	Grade 2	2(12.5%)
	Grade 3	3(18.8%)
	Grade 4	1(6.3%)
	Grade 5	0(0.0%)
	>=Grade 3	4(25.0%)

SOURCE: Listing 16.2.6.5 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

Country: Korea

Grouped Term Preferred term	Severity	40 mg (N=16) n (%)
血小板数减少	Any Grade	5(31.3%)
	Grade 1	2(12.5%)
	Grade 2	1(6.3%)
	Grade 3	2(12.5%)
	Grade 4	0(0.0%)
	Grade 5	0(0.0%)
	>=Grade 3	2(12.5%)

SOURCE: Listing 16.2.6.5 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = Number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in a subgroup in the analysis set.
Subjects with more than one TEAE are counted once in the worst severity category within the same SOC and PT.

Program: HUYA¥HBI-8000¥RXA97790¥BIOSTATISTICS¥PRODUCTION¥TABLES¥ADHOC¥T14_05_12_03_ADHOC.SAS
07MAY2020 03:21

表 2.7.4.7-54　血液学的検査値異常のベースライン後の Grade の概要（203 試験）（安全性解析対象集団）

Parameter	Worst Post-Baseline Grade	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Anemia	Any Grade	36 (92.3)	15 (93.8)	51 (92.7)
	Grade 3, 4	9 (23.1)	2 (12.5)	11 (20.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
White blood cell decreased	Any Grade	33 (84.6)	8 (50.0)	41 (74.5)
	Grade 3, 4	14 (35.9)	3 (18.8)	17 (30.9)
	Grade 4	1 (2.6)	0 (0.0)	1 (1.8)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count decreased	Any Grade	35 (89.7)	11 (68.8)	46 (83.6)
	Grade 3, 4	20 (51.3)	7 (43.8)	27 (49.1)
	Grade 4	6 (15.4)	0 (0.0)	6 (10.9)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count increased	Any Grade	1 (2.6)	1 (6.3)	2 (3.6)
	Grade 3, 4	1 (2.6)	0 (0.0)	1 (1.8)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.7 1

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug up till the end of treatment assessment visit.

Parameter	Worst Post-Baseline Grade	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Neutrophil count decreased	Any Grade	33 (84.6)	10 (62.5)	43 (78.2)
	Grade 3, 4	19 (48.7)	4 (25.0)	23 (41.8)
	Grade 4	4 (10.3)	1 (6.3)	5 (9.1)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Platelet count decreased	Any Grade	38 (97.4)	16 (100.0)	54 (98.2)
	Grade 3, 4	22 (56.4)	5 (31.3)	27 (49.1)
	Grade 4	9 (23.1)	0 (0.0)	9 (16.4)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.7 1

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug up till the end of treatment assessment visit.

表 2.7.4.7-55　血液学的検査値異常のベースラインの Grade と投与後の Grade のシフトテーブル（203 試験）（安全性解析対象集団）

Country: Japan

		40 mg (N=39)						
		Worst Post-Baseline Grade						
Parameter	Baseline Grade	Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Anemia	Grade 0	3	6	0	1	0	0	10
	Grade 1	0	11	7	2	0	0	20
	Grade 2	0	0	3	5	0	0	8
	Grade 3	0	0	0	1	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	3	17	10	9	0	0	39
White blood cell decreased	Grade 0	6	5	11	8	0	0	30
	Grade 1	0	0	1	1	0	0	2
	Grade 2	0	1	1	3	1	0	6
	Grade 3	0	0	0	1	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	6	6	13	13	1	0	39

Source: Listing 16.2.7 1

Abnormalities are graded using NCI-CTCAE Version 4.03.

N = number of subjects in the Safety Analysis Set by country.

n = number of subjects.

Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.

Local reference ranges are used to set the margin for limits defined in CTCAE grading. For neutrophil count, lymphocyte count or leukocytes, the local reference ranges are set as the higher limits of Grade 0 in the CTCAE grading. However, at some investigational sites, the local reference ranges are lower than the upper limit of CTCAE Grade 1. In such cases, these are graded as 0 in ‘Neutrophil count decreased’, ‘Lymphocyte count decreased’ or ‘white blood cell decreased’, respectively.

Country: Japan

Parameter	Baseline Grade	40 mg (N=39) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Lymphocyte count decreased	Grade 0	4	2	5	4	0	0	15
	Grade 1	0	2	2	3	1	0	8
	Grade 2	0	1	1	7	0	0	9
	Grade 3	0	0	2	0	3	0	5
	Grade 4	0	0	0	0	2	0	2
	Missing	0	0	0	0	0	0	0
	Overall	4	5	10	14	6	0	39
Lymphocyte count increased	Grade 0	38	0	0	0	0	0	38
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	1	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	38	0	0	1	0	0	39

Source: Listing 16.2.7 1

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For neutrophil count, lymphocyte count or leukocytes, the local reference ranges are set as the higher limits of Grade 0 in the CTCAE grading. However, at some investigational sites, the local reference ranges are lower than the upper limit of CTCAE Grade 1. In such cases, these are graded as 0 in 'Neutrophil count decreased', 'Lymphocyte count decreased' or 'white blood cell decreased', respectively.

Country: Japan

Parameter	Baseline Grade	40 mg (N=39) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Neutrophil count decreased	Grade 0	6	2	9	11	4	0	32
	Grade 1	0	0	2	3	0	0	5
	Grade 2	0	0	0	1	0	0	1
	Grade 3	0	0	1	0	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	6	2	12	15	4	0	39
Platelet count decreased	Grade 0	1	8	6	7	6	0	28
	Grade 1	0	0	2	6	3	0	11
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	1	8	8	13	9	0	39

Source: Listing 16.2.7 1

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For neutrophil count, lymphocyte count or leukocytes, the local reference ranges are set as the higher limits of Grade 0 in the CTCAE grading. However, at some investigational sites, the local reference ranges are lower than the upper limit of CTCAE Grade 1. In such cases, these are graded as 0 in 'Neutrophil count decreased', 'Lymphocyte count decreased' or 'white blood cell decreased', respectively.

Country: Korea

Parameter	Baseline Grade	40 mg (N=16) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Anemia	Grade 0	1	3	1	0	0	0	5
	Grade 1	0	4	3	1	0	0	8
	Grade 2	0	0	2	1	0	0	3
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	1	7	6	2	0	0	16
White blood cell decreased	Grade 0	8	1	2	1	0	0	12
	Grade 1	0	0	2	1	0	0	3
	Grade 2	0	0	0	1	0	0	1
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	8	1	4	3	0	0	16

Source: Listing 16 2.7.1

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For neutrophil count, lymphocyte count or leukocytes, the local reference ranges are set as the higher limits of Grade 0 in the CTCAE grading. However, at some investigational sites, the local reference ranges are lower than the upper limit of CTCAE Grade 1. In such cases, these are graded as 0 in 'Neutrophil count decreased', 'Lymphocyte count decreased' or 'white blood cell decreased', respectively.

Country: Korea

Parameter	Baseline Grade	40 mg (N=16) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Lymphocyte count decreased	Grade 0	5	1	1	4	0	0	11
	Grade 1	0	0	0	1	0	0	1
	Grade 2	0	0	2	0	0	0	2
	Grade 3	0	0	0	2	0	0	2
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	5	1	3	7	0	0	16
Lymphocyte count increased	Grade 0	15	0	1	0	0	0	16
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	15	0	1	0	0	0	16

Source: Listing 16.2.7 1

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For neutrophil count, lymphocyte count or leukocytes, the local reference ranges are set as the higher limits of Grade 0 in the CTCAE grading. However, at some investigational sites, the local reference ranges are lower than the upper limit of CTCAE Grade 1. In such cases, these are graded as 0 in 'Neutrophil count decreased', 'Lymphocyte count decreased' or 'white blood cell decreased', respectively.

Country: Korea

Parameter	Baseline Grade	40 mg (N=16) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Neutrophil count decreased	Grade 0	6	2	4	1	1	0	14
	Grade 1	0	0	0	2	0	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	6	2	4	3	1	0	16
Platelet count decreased	Grade 0	0	4	3	1	0	0	8
	Grade 1	0	0	4	4	0	0	8
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	0	4	7	5	0	0	16

Source: Listing 16.2.7 1

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For neutrophil count, lymphocyte count or leukocytes, the local reference ranges are set as the higher limits of Grade 0 in the CTCAE grading. However, at some investigational sites, the local reference ranges are lower than the upper limit of CTCAE Grade 1. In such cases, these are graded as 0 in 'Neutrophil count decreased', 'Lymphocyte count decreased' or 'white blood cell decreased', respectively.

Country: Overall

Parameter	Baseline Grade	40 mg (N=55) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Anemia	Grade 0	4	9	1	1	0	0	15
	Grade 1	0	15	10	3	0	0	28
	Grade 2	0	0	5	6	0	0	11
	Grade 3	0	0	0	1	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	4	24	16	11	0	0	55
White blood cell decreased	Grade 0	14	6	13	9	0	0	42
	Grade 1	0	0	3	2	0	0	5
	Grade 2	0	1	1	4	1	0	7
	Grade 3	0	0	0	1	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	14	7	17	16	1	0	55

Source: Listing 16.2.7 1

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For neutrophil count, lymphocyte count or leukocytes, the local reference ranges are set as the higher limits of Grade 0 in the CTCAE grading. However, at some investigational sites, the local reference ranges are lower than the upper limit of CTCAE Grade 1. In such cases, these are graded as 0 in 'Neutrophil count decreased', 'Lymphocyte count decreased' or 'white blood cell decreased', respectively.

Country: Overall

Parameter	Baseline Grade	40 mg (N=55) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Lymphocyte count decreased	Grade 0	9	3	6	8	0	0	26
	Grade 1	0	2	2	4	1	0	9
	Grade 2	0	1	3	7	0	0	11
	Grade 3	0	0	2	2	3	0	7
	Grade 4	0	0	0	0	2	0	2
	Missing	0	0	0	0	0	0	0
	Overall	9	6	13	21	6	0	55
Lymphocyte count increased	Grade 0	53	0	1	0	0	0	54
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	1	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	53	0	1	1	0	0	55

Source: Listing 16.2.7 1

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For neutrophil count, lymphocyte count or leukocytes, the local reference ranges are set as the higher limits of Grade 0 in the CTCAE grading. However, at some investigational sites, the local reference ranges are lower than the upper limit of CTCAE Grade 1. In such cases, these are graded as 0 in 'Neutrophil count decreased', 'Lymphocyte count decreased' or 'white blood cell decreased', respectively.

Country: Overall

Parameter	Baseline Grade	40 mg (N=55) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Neutrophil count decreased	Grade 0	12	4	13	12	5	0	46
	Grade 1	0	0	2	5	0	0	7
	Grade 2	0	0	0	1	0	0	1
	Grade 3	0	0	1	0	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	12	4	16	18	5	0	55
Platelet count decreased	Grade 0	1	12	9	8	6	0	36
	Grade 1	0	0	6	10	3	0	19
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	1	12	15	18	9	0	55

Source: Listing 16.2.7 1

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For neutrophil count, lymphocyte count or leukocytes, the local reference ranges are set as the higher limits of Grade 0 in the CTCAE grading. However, at some investigational sites, the local reference ranges are lower than the upper limit of CTCAE Grade 1. In such cases, these are graded as 0 in 'Neutrophil count decreased', 'Lymphocyte count decreased' or 'white blood cell decreased', respectively.

表 2.7.4.7-56　血液学的検査値異常のベースライン後の Grade の概要（201 試験）（安全性解析対象集団）

Category	Worst Post-Baseline Grade	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Anemia	Any Grade	7 (100.0%)	5 (71.4%)	12 (85.7%)
	Grade 3, 4	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 4	-	-	-
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
White blood cell decreased	Any Grade	5 (71.4%)	5 (71.4%)	10 (71.4%)
	Grade 3, 4	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lymphocyte count decreased	Any Grade	5 (71.4%)	4 (57.1%)	9 (64.3%)
	Grade 3, 4	3 (42.9%)	3 (42.9%)	6 (42.9%)
	Grade 4	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lymphocyte count increased	Any Grade	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	-	-	-
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.7.1
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Worst Post-Baseline Grade	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Neutrophil count decreased	Any Grade	6 (85.7%)	5 (71.4%)	11 (78.6%)
	Grade 3, 4	3 (42.9%)	2 (28.6%)	5 (35.7%)
	Grade 4	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Platelet count decreased	Any Grade	7 (100.0%)	7 (100.0%)	14 (100.0%)
	Grade 3, 4	0 (0.0%)	3 (42.9%)	3 (21.4%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.7.1
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

表 2.7.4.7-57　血液学的検査値異常のベースラインの Grade と投与後の Grade のシフトテーブル（201 試験）（安全性解析対象集団）

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Anemia	Grade 0	0 (0.0%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	3 (42.9%)
	Grade 1	0 (0.0%)	1 (14.3%)	2 (28.6%)	1 (14.3%)	-	0 (0.0%)	4 (57.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Grade 4	-	-	-	-	-	-	-
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Overall	0 (0.0%)	4 (57.1%)	2 (28.6%)	1 (14.3%)	-	0 (0.0%)	7 (100.0%)
White blood cell decreased	Grade 0	2 (28.6%)	1 (14.3%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (71.4%)
	Grade 1	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	2 (28.6%)	1 (14.3%)	3 (42.9%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.1
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Lymphocyte count decreased	Grade 0	2 (28.6%)	2 (28.6%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	5 (71.4%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	2 (28.6%)	2 (28.6%)	0 (0.0%)	2 (28.6%)	1 (14.3%)	0 (0.0%)	7 (100.0%)
Lymphocyte count increased	Grade 0	7 (100.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	7 (100.0%)
	Grade 1	-	-	-	-	-	-	-
	Grade 2	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Grade 4	-	-	-	-	-	-	-
	Missing	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Overall	7 (100.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.1
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Neutrophil count decreased	Grade 0	1 (14.3%)	2 (28.6%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	5 (71.4%)
	Grade 1	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	1 (14.3%)	3 (42.9%)	0 (0.0%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Platelet count decreased	Grade 0	0 (0.0%)	2 (28.6%)	4 (57.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (85.7%)
	Grade 1	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	0 (0.0%)	2 (28.6%)	5 (71.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.1
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Anemia	Grade 0	2 (28.6%)	1 (14.3%)	1 (14.3%)	0 (0.0%)	-	0 (0.0%)	4 (57.1%)
	Grade 1	0 (0.0%)	1 (14.3%)	1 (14.3%)	0 (0.0%)	-	0 (0.0%)	2 (28.6%)
	Grade 2	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	-	0 (0.0%)	1 (14.3%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Grade 4	-	-	-	-	-	-	-
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Overall	2 (28.6%)	2 (28.6%)	3 (42.9%)	0 (0.0%)	-	0 (0.0%)	7 (100.0%)
White blood cell decreased	Grade 0	2 (28.6%)	1 (14.3%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (85.7%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	2 (28.6%)	1 (14.3%)	3 (42.9%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.1
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Lymphocyte count decreased	Grade 0	3 (42.9%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (57.1%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	3 (42.9%)	1 (14.3%)	0 (0.0%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Lymphocyte count increased	Grade 0	6 (85.7%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	6 (85.7%)
	Grade 1	-	-	-	-	-	-	-
	Grade 2	0 (0.0%)	-	1 (14.3%)	0 (0.0%)	-	0 (0.0%)	1 (14.3%)
	Grade 3	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Grade 4	-	-	-	-	-	-	-
	Missing	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Overall	6 (85.7%)	-	1 (14.3%)	0 (0.0%)	-	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.1
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Neutrophil count decreased	Grade 0	2 (28.6%)	1 (14.3%)	2 (28.6%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	6 (85.7%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	2 (28.6%)	1 (14.3%)	2 (28.6%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	7 (100.0%)
Platelet count decreased	Grade 0	0 (0.0%)	1 (14.3%)	3 (42.9%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	6 (85.7%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	0 (0.0%)	1 (14.3%)	3 (42.9%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.1
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Anemia	Grade 0	2 (14.3%)	4 (28.6%)	1 (7.1%)	0 (0.0%)	-	0 (0.0%)	7 (50.0%)
	Grade 1	0 (0.0%)	2 (14.3%)	3 (21.4%)	1 (7.1%)	-	0 (0.0%)	6 (42.9%)
	Grade 2	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	-	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Grade 4	-	-	-	-	-	-	-
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Overall	2 (14.3%)	6 (42.9%)	5 (35.7%)	1 (7.1%)	-	0 (0.0%)	14 (100.0%)
White blood cell decreased	Grade 0	4 (28.6%)	2 (14.3%)	5 (35.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (78.6%)
	Grade 1	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	4 (28.6%)	2 (14.3%)	6 (42.9%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.1
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Lymphocyte count decreased	Grade 0	5 (35.7%)	3 (21.4%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	9 (64.3%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.1%)	0 (0.0%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (21.4%)	0 (0.0%)	0 (0.0%)	3 (21.4%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	5 (35.7%)	3 (21.4%)	0 (0.0%)	5 (35.7%)	1 (7.1%)	0 (0.0%)	14 (100.0%)
Lymphocyte count increased	Grade 0	13 (92.9%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	13 (92.9%)
	Grade 1	-	-	-	-	-	-	-
	Grade 2	0 (0.0%)	-	1 (7.1%)	0 (0.0%)	-	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Grade 4	-	-	-	-	-	-	-
	Missing	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Overall	13 (92.9%)	-	1 (7.1%)	0 (0.0%)	-	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.1
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Neutrophil count decreased	Grade 0	3 (21.4%)	3 (21.4%)	2 (14.3%)	2 (14.3%)	1 (7.1%)	0 (0.0%)	11 (78.6%)
	Grade 1	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	3 (21.4%)	4 (28.6%)	2 (14.3%)	3 (21.4%)	2 (14.3%)	0 (0.0%)	14 (100.0%)
Platelet count decreased	Grade 0	0 (0.0%)	3 (21.4%)	7 (50.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	12 (85.7%)
	Grade 1	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	0 (0.0%)	3 (21.4%)	8 (57.1%)	3 (21.4%)	0 (0.0%)	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.1
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

表 2.7.4.7-58　血液学的検査値異常のベースライン後の Grade の概要（210 試験）（安全性解析対象集団）

Parameter	Worst Post-Baseline Grade	40 mg (N=23) n (%)
Anemia	Any Grade	20 (87.0%)
	Grade 3, 4	5 (21.7%)
	Grade 4	0 (0.0%)
	Missing	1 (4.3%)
White blood cell decreased	Any Grade	13 (56.5%)
	Grade 3, 4	7 (30.4%)
	Grade 4	0 (0.0%)
	Missing	1 (4.3%)
Lymphocyte count decreased	Any Grade	17 (73.9%)
	Grade 3, 4	11 (47.8%)
	Grade 4	2 (8.7%)
	Missing	1 (4.3%)
Lymphocyte count increased	Any Grade	2 (8.7%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	1 (4.3%)
Neutrophil count decreased	Any Grade	16 (69.6%)
	Grade 3, 4	9 (39.1%)
	Grade 4	3 (13.0%)
	Missing	1 (4.3%)
Platelet count decreased	Any Grade	22 (95.7%)
	Grade 3, 4	12 (52.2%)
	Grade 4	6 (26.1%)
	Missing	1 (4.3%)

Source: Listing 16.2.7 1

Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.

表 2.7.4.7-59　血液学的検査値異常のベースラインの Grade と投与後の Grade のシフトテーブル（210 試験）（安全性解析対象集団）

		40 mg (N=23)						
		Worst Post-Baseline Grade						
Parameter	Baseline Grade	Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Anemia	Grade 0	2	2	1	0	0	0	5
	Grade 1	0	6	4	2	0	0	12
	Grade 2	0	0	2	3	0	1	6
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	2	8	7	5	0	1	23
White blood cell decreased	Grade 0	9	1	5	2	0	1	18
	Grade 1	0	0	0	3	0	0	3
	Grade 2	0	0	0	2	0	0	2
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	9	1	5	7	0	1	23
Lymphocyte count decreased	Grade 0	4	0	2	3	0	0	9
	Grade 1	0	1	1	1	0	0	3
	Grade 2	0	1	1	2	0	0	4
	Grade 3	1	0	0	2	1	1	5
	Grade 4	0	0	0	1	1	0	2
	Missing	0	0	0	0	0	0	0
	Overall	5	2	4	9	2	1	23

Source: Listing 16.2.7 1

Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For neutrophil count or lymphocyte count, the local reference ranges are set as the higher limits of Grade 0 in the CTCAE grading. However, at some investigational sites, the local reference ranges are lower than the upper limit of CTCAE Grade 1. In such cases, these are graded as 0 in 'Neutrophil count decreased' or 'Lymphocyte count decreased', respectively.

Parameter	Baseline Grade	40 mg (N=23) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Lymphocyte count increased	Grade 0	20	0	1	0	0	1	22
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	1	0	0	0	1
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	20	0	2	0	0	1	23
Neutrophil count decreased	Grade 0	6	1	6	5	2	1	21
	Grade 1	0	0	0	1	1	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	6	1	6	6	3	1	23
Platelet count decreased	Grade 0	0	4	3	3	2	1	13
	Grade 1	0	1	2	3	4	0	10
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	0	5	5	6	6	1	23

Source: Listing 16.2.7 1

Abnormalities are graded using NCI-CTCAE Version 4.03.

n = number of subjects.

Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.

Local reference ranges are used to set the margin for limits defined in CTCAE grading. For neutrophil count or lymphocyte count, the local reference ranges are set as the higher limits of Grade 0 in the CTCAE grading. However, at some investigational sites, the local reference ranges are lower than the upper limit of CTCAE Grade 1. In such cases, these are graded as 0 in 'Neutrophil count decreased' or 'Lymphocyte count decreased', respectively.

表 2.7.4.7-60　血液生化学検査値異常のベースライン後の Grade の概要（203 試験）（安全性解析対象集団）

Parameter	Worst Post-Baseline Grade	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Hypoalbuminemia	Any Grade	38 (97.4)	6 (37.5)	44 (80.0)
	Grade 3, 4	2 (5.1)	0 (0.0)	2 (3.6)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Alkaline Phosphatase increased	Any Grade	22 (56.4)	5 (31.3)	27 (49.1)
	Grade 3, 4	1 (2.6)	0 (0.0)	1 (1.8)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
ALT increased	Any Grade	12 (30.8)	4 (25.0)	16 (29.1)
	Grade 3, 4	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Serum amylase increased	Any Grade	5 (12.8)	3 (18.8)	8 (14.5)
	Grade 3, 4	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug up till the end of treatment assessment visit.

Parameter	Worst Post-Baseline Grade	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
AST increased	Any Grade	21 (53.8)	2 (12.5)	23 (41.8)
	Grade 3, 4	1 (2.6)	0 (0.0)	1 (1.8)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	Any Grade	6 (15.4)	1 (6.3)	7 (12.7)
	Grade 3, 4	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Lipase increased	Any Grade	8 (20.5)	5 (31.3)	13 (23.6)
	Grade 3, 4	2 (5.1)	2 (12.5)	4 (7.3)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine increased	Any Grade	34 (87.2)	12 (75.0)	46 (83.6)
	Grade 3, 4	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug up till the end of treatment assessment visit.

Parameter	Worst Post-Baseline Grade	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Hypokalemia	Any Grade	14 (35.9)	4 (25.0)	18 (32.7)
	Grade 3, 4	1 (2.6)	1 (6.3)	2 (3.6)
	Grade 4	1 (2.6)	1 (6.3)	2 (3.6)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkalemia	Any Grade	8 (20.5)	1 (6.3)	9 (16.4)
	Grade 3, 4	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatremia	Any Grade	15 (38.5)	6 (37.5)	21 (38.2)
	Grade 3, 4	4 (10.3)	1 (6.3)	5 (9.1)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hypernatremia	Any Grade	6 (15.4)	1 (6.3)	7 (12.7)
	Grade 3, 4	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug up till the end of treatment assessment visit.

Parameter	Worst Post-Baseline Grade	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Hypomagnesemia	Any Grade	4 (10.3)	6 (37.5)	10 (18.2)
	Grade 3, 4	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hypermagnesemia	Any Grade	6 (15.4)	2 (12.5)	8 (14.5)
	Grade 3, 4	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hypocalcemia	Any Grade	34 (87.2)	13 (81.3)	47 (85.5)
	Grade 3, 4	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hypercalcemia	Any Grade	2 (5.1)	0 (0.0)	2 (3.6)
	Grade 3, 4	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug up till the end of treatment assessment visit.

Parameter	Worst Post-Baseline Grade	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Hypoglycemia	Any Grade	4 (10.3)	0 (0.0)	4 (7.3)
	Grade 3, 4	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hyperglycemia	Any Grade	34 (87.2)	16 (100.0)	50 (90.9)
	Grade 3, 4	0 (0.0)	0 (0.0)	0 (0.0)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)
GGT increased	Any Grade	18 (46.2)	6 (37.5)	24 (43.6)
	Grade 3, 4	4 (10.3)	0 (0.0)	4 (7.3)
	Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set;
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug up till the end of treatment assessment visit.

表 2.7.4.7-61　血液生化学検査値異常のベースラインの Grade と投与後の Grade のシフトテーブル（203 試験）（安全性解析対象集団）

Country: Japan

		40 mg (N=39)						
		Worst Post-Baseline Grade						
Parameter	Baseline Grade	Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypoalbuminemia	Grade 0	1	12	0	0	0	0	13
	Grade 1	0	10	11	1	0	0	22
	Grade 2	0	0	3	1	0	0	4
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	1	22	14	2	0	0	39
Alkaline Phosphatase increased	Grade 0	17	14	2	0	0	0	33
	Grade 1	0	3	2	1	0	0	6
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	17	17	4	1	0	0	39

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Japan

Parameter	Baseline Grade	40 mg (N=39) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
ALT increased	Grade 0	27	8	2	0	0	0	37
	Grade 1	0	2	0	0	0	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	27	10	2	0	0	0	39
Serum amylase increased	Grade 0	34	2	0	0	0	0	36
	Grade 1	0	2	0	0	0	0	2
	Grade 2	0	1	0	0	0	0	1
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	34	5	0	0	0	0	39

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Japan

Parameter	Baseline Grade	40 mg (N=39) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
AST increased	Grade 0	18	12	2	1	0	0	33
	Grade 1	0	5	1	0	0	0	6
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	18	17	3	1	0	0	39
Blood bilirubin increased	Grade 0	33	5	1	0	0	0	39
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	33	5	1	0	0	0	39

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Japan

Parameter	Baseline Grade	40 mg (N=39) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Lipase increased	Grade 0	31	3	1	1	0	0	36
	Grade 1	0	0	1	1	0	0	2
	Grade 2	0	0	1	0	0	0	1
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	31	3	3	2	0	0	39
Creatinine increased	Grade 0	5	22	4	0	0	0	31
	Grade 1	0	6	1	0	0	0	7
	Grade 2	0	0	1	0	0	0	1
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	5	28	6	0	0	0	39

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Japan

Parameter	Baseline Grade	40 mg (N=39) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypokalemia	Grade 0	25	12	0	0	0	0	37
	Grade 1	0	1	0	0	1	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	25	13	0	0	1	0	39
Hyperkalemia	Grade 0	29	7	1	0	0	0	37
	Grade 1	2	0	0	0	0	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	31	7	1	0	0	0	39

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Japan

Parameter	Baseline Grade	40 mg (N=39) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hyponatremia	Grade 0	23	10	0	2	0	0	35
	Grade 1	1	1	0	1	0	0	3
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	1	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	24	11	0	4	0	0	39
Hypernatremia	Grade 0	33	4	0	0	0	0	37
	Grade 1	0	2	0	0	0	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	33	6	0	0	0	0	39

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Japan

Parameter	Baseline Grade	40 mg (N=39) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypomagnesemia	Grade 0	35	3	0	0	0	0	38
	Grade 1	0	1	0	0	0	0	1
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	35	4	0	0	0	0	39
Hypermagnesemia	Grade 0	33	5	0	0	0	0	38
	Grade 1	0	1	0	0	0	0	1
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	33	6	0	0	0	0	39

Source: Listing 16 2.7.2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Japan

Parameter	Baseline Grade	40 mg (N=39) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypocalcemia	Grade 0	5	29	2	0	0	0	36
	Grade 1	0	3	0	0	0	0	3
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	5	32	2	0	0	0	39
Hypercalcemia	Grade 0	36	2	0	0	0	0	38
	Grade 1	1	0	0	0	0	0	1
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	37	2	0	0	0	0	39

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Japan

Parameter	Baseline Grade	40 mg (N=39) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypoglycemia	Grade 0	34	3	1	0	0	0	38
	Grade 1	1	0	0	0	0	0	1
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	35	3	1	0	0	0	39
Hyperglycemia	Grade 0	4	14	6	0	0	0	24
	Grade 1	1	8	4	0	0	0	13
	Grade 2	0	1	0	0	0	0	1
	Grade 3	0	1	0	0	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	5	24	10	0	0	0	39

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Japan

Parameter	Baseline Grade	40 mg (N=39) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
GGT increased	Grade 0	21	6	5	1	0	0	33
	Grade 1	0	1	1	3	0	0	5
	Grade 2	0	1	0	0	0	0	1
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	21	8	6	4	0	0	39

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for 'hypomagnesemia' and the local upper reference ranges are set as the lower limits of Grade 0 for 'hypermagnesemia'. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in 'hypomagnesemia' or 'hypermagnesemia', respectively.

Country: Korea

Parameter	Baseline Grade	40 mg (N=16) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypoalbuminemia	Grade 0	10	1	1	0	0	0	12
	Grade 1	0	1	1	0	0	0	2
	Grade 2	0	0	2	0	0	0	2
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	10	2	4	0	0	0	16
Alkaline Phosphatase increased	Grade 0	11	2	0	0	0	0	13
	Grade 1	0	3	0	0	0	0	3
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	11	5	0	0	0	0	16

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Korea

Parameter	Baseline Grade	40 mg (N=16) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
ALT increased	Grade 0	10	2	1	0	0	0	13
	Grade 1	2	1	0	0	0	0	3
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	12	3	1	0	0	0	16
Serum amylase increased	Grade 0	13	1	0	0	0	0	14
	Grade 1	0	1	1	0	0	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	13	2	1	0	0	0	16

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Korea

Parameter	Baseline Grade	40 mg (N=16) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
AST increased	Grade 0	12	2	0	0	0	0	14
	Grade 1	2	0	0	0	0	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	14	2	0	0	0	0	16
Blood bilirubin increased	Grade 0	15	1	0	0	0	0	16
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	15	1	0	0	0	0	16

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Korea

Parameter	Baseline Grade	40 mg (N=16) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Lipase increased	Grade 0	10	2	1	1	0	0	14
	Grade 1	1	0	0	0	0	0	1
	Grade 2	0	0	0	1	0	0	1
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	11	2	1	2	0	0	16
Creatinine increased	Grade 0	4	12	0	0	0	0	16
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	4	12	0	0	0	0	16

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Korea

Parameter	Baseline Grade	40 mg (N=16) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypokalemia	Grade 0	12	3	0	0	1	0	16
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	12	3	0	0	1	0	16
Hyperkalemia	Grade 0	15	0	1	0	0	0	16
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	15	0	1	0	0	0	16

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Korea

Parameter	Baseline Grade	40 mg (N=16) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hyponatremia	Grade 0	10	4	0	0	0	0	14
	Grade 1	0	1	0	1	0	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	10	5	0	1	0	0	16
Hypernatremia	Grade 0	14	0	0	0	0	0	14
	Grade 1	1	1	0	0	0	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	15	1	0	0	0	0	16

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Korea

Parameter	Baseline Grade	40 mg (N=16) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypomagnesemia	Grade 0	10	4	0	0	0	0	14
	Grade 1	0	1	0	0	0	0	1
	Grade 2	0	0	1	0	0	0	1
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	10	5	1	0	0	0	16
Hypermagnesemia	Grade 0	14	2	0	0	0	0	16
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	14	2	0	0	0	0	16

Source: Listing 16 2.7.2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Korea

Parameter	Baseline Grade	40 mg (N=16) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypocalcemia	Grade 0	3	10	0	0	0	0	13
	Grade 1	0	2	1	0	0	0	3
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	3	12	1	0	0	0	16
Hypercalcemia	Grade 0	16	0	0	0	0	0	16
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	16	0	0	0	0	0	16

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Korea

Parameter	Baseline Grade	40 mg (N=16) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypoglycemia	Grade 0	16	0	0	0	0	0	16
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	16	0	0	0	0	0	16
Hyperglycemia	Grade 0	0	7	1	0	0	0	8
	Grade 1	0	4	1	0	0	0	5
	Grade 2	0	0	2	0	0	0	2
	Grade 3	0	1	0	0	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	0	12	4	0	0	0	16

Source: Listing 16 2.7.2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Korea

		40 mg (N=16)						
		Worst Post-Baseline Grade						
Parameter	Baseline Grade	Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
GGT increased	Grade 0	10	2	0	0	0	0	12
	Grade 1	0	1	1	0	0	0	2
	Grade 2	0	0	1	0	0	0	1
	Grade 3	0	0	1	0	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	10	3	3	0	0	0	16

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Overall

Parameter	Baseline Grade	40 mg (N=55) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypoalbuminemia	Grade 0	11	13	1	0	0	0	25
	Grade 1	0	11	12	1	0	0	24
	Grade 2	0	0	5	1	0	0	6
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	11	24	18	2	0	0	55
Alkaline Phosphatase increased	Grade 0	28	16	2	0	0	0	46
	Grade 1	0	6	2	1	0	0	9
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	28	22	4	1	0	0	55

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Overall

Parameter	Baseline Grade	40 mg (N=55) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
ALT increased	Grade 0	37	10	3	0	0	0	50
	Grade 1	2	3	0	0	0	0	5
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	39	13	3	0	0	0	55
Serum amylase increased	Grade 0	47	3	0	0	0	0	50
	Grade 1	0	3	1	0	0	0	4
	Grade 2	0	1	0	0	0	0	1
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	47	7	1	0	0	0	55

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Overall

Parameter	Baseline Grade	40 mg (N=55) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
AST increased	Grade 0	30	14	2	1	0	0	47
	Grade 1	2	5	1	0	0	0	8
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	32	19	3	1	0	0	55
Blood bilirubin increased	Grade 0	48	6	1	0	0	0	55
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	48	6	1	0	0	0	55

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Overall

Parameter	Baseline Grade	40 mg (N=55) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Lipase increased	Grade 0	41	5	2	2	0	0	50
	Grade 1	1	0	1	1	0	0	3
	Grade 2	0	0	1	1	0	0	2
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	42	5	4	4	0	0	55
Creatinine increased	Grade 0	9	34	4	0	0	0	47
	Grade 1	0	6	1	0	0	0	7
	Grade 2	0	0	1	0	0	0	1
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	9	40	6	0	0	0	55

Source: Listing 16 2.7.2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Overall

Parameter	Baseline Grade	40 mg (N=55) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypokalemia	Grade 0	37	15	0	0	1	0	53
	Grade 1	0	1	0	0	1	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	37	16	0	0	2	0	55
Hyperkalemia	Grade 0	44	7	2	0	0	0	53
	Grade 1	2	0	0	0	0	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	46	7	2	0	0	0	55

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Overall

Parameter	Baseline Grade	40 mg (N=55) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hyponatremia	Grade 0	33	14	0	2	0	0	49
	Grade 1	1	2	0	2	0	0	5
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	1	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	34	16	0	5	0	0	55
Hypernatremia	Grade 0	47	4	0	0	0	0	51
	Grade 1	1	3	0	0	0	0	4
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	48	7	0	0	0	0	55

Source: Listing 16 2.7.2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Overall

Parameter	Baseline Grade	40 mg (N=55) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypomagnesemia	Grade 0	45	7	0	0	0	0	52
	Grade 1	0	2	0	0	0	0	2
	Grade 2	0	0	1	0	0	0	1
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	45	9	1	0	0	0	55
Hypermagnesemia	Grade 0	47	7	0	0	0	0	54
	Grade 1	0	1	0	0	0	0	1
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	47	8	0	0	0	0	55

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Overall

Parameter	Baseline Grade	40 mg (N=55) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypocalcemia	Grade 0	8	39	2	0	0	0	49
	Grade 1	0	5	1	0	0	0	6
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	8	44	3	0	0	0	55
Hypercalcemia	Grade 0	52	2	0	0	0	0	54
	Grade 1	1	0	0	0	0	0	1
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	53	2	0	0	0	0	55

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Overall

Parameter	Baseline Grade	40 mg (N=55) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypoglycemia	Grade 0	50	3	1	0	0	0	54
	Grade 1	1	0	0	0	0	0	1
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	51	3	1	0	0	0	55
Hyperglycemia	Grade 0	4	21	7	0	0	0	32
	Grade 1	1	12	5	0	0	0	18
	Grade 2	0	1	2	0	0	0	3
	Grade 3	0	2	0	0	0	0	2
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	5	36	14	0	0	0	55

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

Country: Overall

		40 mg (N=55)						
		Worst Post-Baseline Grade						
Parameter	Baseline Grade	Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
GGT increased	Grade 0	31	8	5	1	0	0	45
	Grade 1	0	2	2	3	0	0	7
	Grade 2	0	1	1	0	0	0	2
	Grade 3	0	0	1	0	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	31	11	9	4	0	0	55

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by country.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of Treatment assessment visit.
Local reference ranges are used to set the margin for limits defined in CTCAE grading. For magnesium, the local lower reference ranges are set as the higher limits of Grade 0 for ‘hypomagnesemia’ and the local upper reference ranges are set as the lower limits of Grade 0 for ‘hypermagnesemia’. However, at some investigational sites, the local reference ranges are either lower or higher than the limit defined for CTCAE Grade 1. In such cases, these are graded as 0 in ‘hypomagnesemia’ or ‘hypermagnesemia’, respectively.

表 2.7.4.7-62　血液生化学検査値異常のベースライン後の Grade の概要（201 試験）（安全性解析対象集団）

Category	Worst Post-Baseline Grade	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Hypoalbuminemia	Any Grade	7 (100.0%)	7 (100.0%)	14 (100.0%)
	Grade 3, 4	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 4	-	-	-
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Alkaline phosphatase increased	Any Grade	3 (42.9%)	6 (85.7%)	9 (64.3%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
ALT increased	Any Grade	2 (28.6%)	4 (57.1%)	6 (42.9%)
	Grade 3, 4	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serum amylase increased	Any Grade	1 (14.3%)	1 (14.3%)	2 (14.3%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Worst Post-Baseline Grade	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
AST increased	Any Grade	4 (57.1%)	6 (85.7%)	10 (71.4%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood bilirubin increased	Any Grade	3 (42.9%)	0 (0.0%)	3 (21.4%)
	Grade 3, 4	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cholesterol high	Any Grade	4 (57.1%)	4 (57.1%)	8 (57.1%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Creatinine increased	Any Grade	6 (85.7%)	6 (85.7%)	12 (85.7%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Worst Post-Baseline Grade	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Hypokalemia	Any Grade	3 (42.9%)	2 (28.6%)	5 (35.7%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyperkalemia	Any Grade	0 (0.0%)	3 (42.9%)	3 (21.4%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyponatremia	Any Grade	2 (28.6%)	3 (42.9%)	5 (35.7%)
	Grade 3, 4	1 (14.3%)	0 (0.0%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypernatremia	Any Grade	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Worst Post-Baseline Grade	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Hypomagnesemia	Any Grade	0 (0.0%)	3 (42.9%)	3 (21.4%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypermagnesemia	Any Grade	2 (28.6%)	3 (42.9%)	5 (35.7%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypocalcemia	Any Grade	5 (71.4%)	5 (71.4%)	10 (71.4%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypercalcemia	Any Grade	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Worst Post-Baseline Grade	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Hypoglycemia	Any Grade	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyperglycemia	Any Grade	5 (71.4%)	5 (71.4%)	10 (71.4%)
	Grade 3, 4	0 (0.0%)	2 (28.6%)	2 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
GGT increased	Any Grade	4 (57.1%)	3 (42.9%)	7 (50.0%)
	Grade 3, 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypophosphatemia	Any Grade	2 (28.6%)	4 (57.1%)	6 (42.9%)
	Grade 3, 4	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Worst Post-Baseline Grade	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Hypertriglyceridemia	Any Grade	4 (57.1%)	5 (71.4%)	9 (64.3%)
	Grade 3, 4	0 (0.0%)	1 (14.3%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

表 2.7.4.7-63　血液生化学検査値異常のベースラインの Grade と投与後の Grade のシフトテーブル（201 試験）（安全性解析対象集団）

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypoalbuminemia	Grade 0	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	2 (28.6%)
	Grade 1	0 (0.0%)	2 (28.6%)	2 (28.6%)	0 (0.0%)	-	0 (0.0%)	4 (57.1%)
	Grade 2	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	-	0 (0.0%)	1 (14.3%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Grade 4	-	-	-	-	-	-	-
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Overall	0 (0.0%)	4 (57.1%)	3 (42.9%)	0 (0.0%)	-	0 (0.0%)	7 (100.0%)
Alkaline phosphatase increased	Grade 0	4 (57.1%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (71.4%)
	Grade 1	0 (0.0%)	1 (14.3%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	4 (57.1%)	1 (14.3%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
ALT increased	Grade 0	5 (71.4%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	5 (71.4%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Serum amylase increased	Grade 0	6 (85.7%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	6 (85.7%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
AST increased	Grade 0	3 (42.9%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (85.7%)
	Grade 1	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	3 (42.9%)	4 (57.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Blood bilirubin increased	Grade 0	4 (57.1%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (85.7%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	4 (57.1%)	0 (0.0%)	2 (28.6%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Cholesterol high	Grade 0	3 (42.9%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (57.1%)
	Grade 1	0 (0.0%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (42.9%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	3 (42.9%)	4 (57.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Creatinine increased	Grade 0	1 (14.3%)	5 (71.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (85.7%)
	Grade 1	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	1 (14.3%)	6 (85.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypokalemia	Grade 0	4 (57.1%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	4 (57.1%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Hyperkalemia	Grade 0	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hyponatremia	Grade 0	5 (71.4%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	6 (85.7%)
	Grade 1	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	5 (71.4%)	1 (14.3%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Hypernatremia	Grade 0	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypomagnesemia	Grade 0	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Hypermagnesemia	Grade 0	5 (71.4%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	5 (71.4%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypocalcemia	Grade 0	2 (28.6%)	5 (71.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	2 (28.6%)	5 (71.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Hypercalcemia	Grade 0	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypoglycemia	Grade 0	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Hyperglycemia	Grade 0	2 (28.6%)	2 (28.6%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (71.4%)
	Grade 1	0 (0.0%)	1 (14.3%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	2 (28.6%)	3 (42.9%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
GGT increased	Grade 0	3 (42.9%)	1 (14.3%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (71.4%)
	Grade 1	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	3 (42.9%)	3 (42.9%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Hypophosphatemia	Grade 0	5 (71.4%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	5 (71.4%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	30 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypertriglyceridemia	Grade 0	3 (42.9%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (85.7%)
	Grade 1	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	3 (42.9%)	4 (57.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypoalbuminemia	Grade 0	0 (0.0%)	5 (71.4%)	1 (14.3%)	0 (0.0%)	-	0 (0.0%)	6 (85.7%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	-	0 (0.0%)	1 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Grade 4	-	-	-	-	-	-	-
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Overall	0 (0.0%)	5 (71.4%)	1 (14.3%)	1 (14.3%)	-	0 (0.0%)	7 (100.0%)
Alkaline phosphatase increased	Grade 0	1 (14.3%)	4 (57.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (71.4%)
	Grade 1	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	1 (14.3%)	6 (85.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
ALT increased	Grade 0	3 (42.9%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (57.1%)
	Grade 1	0 (0.0%)	1 (14.3%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	3 (42.9%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	3 (42.9%)	2 (28.6%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Serum amylase increased	Grade 0	6 (85.7%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	6 (85.7%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
AST increased	Grade 0	1 (14.3%)	3 (42.9%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (71.4%)
	Grade 1	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	1 (14.3%)	5 (71.4%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Blood bilirubin increased	Grade 0	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Cholesterol high	Grade 0	3 (42.9%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (57.1%)
	Grade 1	0 (0.0%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (42.9%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	3 (42.9%)	4 (57.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Creatinine increased	Grade 0	1 (14.3%)	5 (71.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (85.7%)
	Grade 1	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	1 (14.3%)	6 (85.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypokalemia	Grade 0	5 (71.4%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	5 (71.4%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Hyperkalemia	Grade 0	4 (57.1%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	4 (57.1%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hyponatremia	Grade 0	4 (57.1%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (85.7%)
	Grade 1	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	4 (57.1%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Hypernatremia	Grade 0	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypomagnesemia	Grade 0	4 (57.1%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	4 (57.1%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Hypermagnesemia	Grade 0	4 (57.1%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	4 (57.1%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypocalcemia	Grade 0	2 (28.6%)	5 (71.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	2 (28.6%)	5 (71.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Hypercalcemia	Grade 0	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypoglycemia	Grade 0	6 (85.7%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	6 (85.7%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Hyperglycemia	Grade 0	2 (28.6%)	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (71.4%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	2 (28.6%)	3 (42.9%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
GGT increased	Grade 0	4 (57.1%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (71.4%)
	Grade 1	0 (0.0%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	4 (57.1%)	1 (14.3%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
Hypophosphatemia	Grade 0	3 (42.9%)	0 (0.0%)	3 (42.9%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	3 (42.9%)	0 (0.0%)	3 (42.9%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	40 mg (N=7)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypertriglyceridemia	Grade 0	2 (28.6%)	3 (42.9%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	6 (85.7%)
	Grade 1	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	2 (28.6%)	4 (57.1%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	7 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypoalbuminemia	Grade 0	0 (0.0%)	7 (50.0%)	1 (7.1%)	0 (0.0%)	-	0 (0.0%)	8 (57.1%)
	Grade 1	0 (0.0%)	2 (14.3%)	2 (14.3%)	1 (7.1%)	-	0 (0.0%)	5 (35.7%)
	Grade 2	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	-	0 (0.0%)	1 (7.1%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Grade 4	-	-	-	-	-	-	-
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Overall	0 (0.0%)	9 (64.3%)	4 (28.6%)	1 (7.1%)	-	0 (0.0%)	14 (100.0%)
Alkaline phosphatase increased	Grade 0	5 (35.7%)	4 (28.6%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (71.4%)
	Grade 1	0 (0.0%)	3 (21.4%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (28.6%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	5 (35.7%)	7 (50.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
ALT increased	Grade 0	8 (57.1%)	3 (21.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (78.6%)
	Grade 1	0 (0.0%)	1 (7.1%)	0 (0.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	3 (21.4%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	8 (57.1%)	4 (28.6%)	0 (0.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
Serum amylase increased	Grade 0	12 (85.7%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	12 (85.7%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
AST increased	Grade 0	4 (28.6%)	6 (42.9%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (78.6%)
	Grade 1	0 (0.0%)	3 (21.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (21.4%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	4 (28.6%)	9 (64.3%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
Blood bilirubin increased	Grade 0	11 (78.6%)	0 (0.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (92.9%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	11 (78.6%)	0 (0.0%)	2 (14.3%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Cholesterol high	Grade 0	6 (42.9%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (57.1%)
	Grade 1	0 (0.0%)	6 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (42.9%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	6 (42.9%)	8 (57.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
Creatinine increased	Grade 0	2 (14.3%)	10 (71.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (85.7%)
	Grade 1	0 (0.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	2 (14.3%)	12 (85.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypokalemia	Grade 0	9 (64.3%)	5 (35.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	9 (64.3%)	5 (35.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
Hyperkalemia	Grade 0	11 (78.6%)	3 (21.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	11 (78.6%)	3 (21.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hyponatremia	Grade 0	9 (64.3%)	2 (14.3%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	12 (85.7%)
	Grade 1	0 (0.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	9 (64.3%)	4 (28.6%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
Hypernatremia	Grade 0	14 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	14 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypomagnesemia	Grade 0	11 (78.6%)	3 (21.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	11 (78.6%)	3 (21.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
Hypermagnesemia	Grade 0	9 (64.3%)	5 (35.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	9 (64.3%)	5 (35.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypocalcemia	Grade 0	4 (28.6%)	10 (71.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	4 (28.6%)	10 (71.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
Hypercalcemia	Grade 0	14 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	14 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypoglycemia	Grade 0	13 (92.9%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	13 (92.9%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
Hyperglycemia	Grade 0	4 (28.6%)	5 (35.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (71.4%)
	Grade 1	0 (0.0%)	1 (7.1%)	1 (7.1%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	4 (28.6%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	4 (28.6%)	6 (42.9%)	2 (14.3%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
GGT increased	Grade 0	7 (50.0%)	2 (14.3%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (71.4%)
	Grade 1	0 (0.0%)	2 (14.3%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (28.6%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	7 (50.0%)	4 (28.6%)	3 (21.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
Hypophosphatemia	Grade 0	8 (57.1%)	0 (0.0%)	5 (35.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
	Grade 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	8 (57.1%)	0 (0.0%)	5 (35.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

Category	Baseline Grade	Total (N=14)						
		Worst Post-Baseline Grade						
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)	Overall n (%)
Hypertriglyceridemia	Grade 0	5 (35.7%)	6 (42.9%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	12 (85.7%)
	Grade 1	0 (0.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
	Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	5 (35.7%)	8 (57.1%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	14 (100.0%)

SOURCE: Listing 16.2.7.2
Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set.
Baseline is defined as pre-dose of Day 1 of Cycle 1.
Only on-treatment toxicity grades are presented.
On-treatment period is defined as date of first study drug administration and end date of study.
JCOG common reference range is used as reference range where normal range lower limit/ normal range upper limit are not available in the site.

表 2.7.4.7-64　血液生化学検査値異常のベースライン後の Grade の概要（210 試験）（安全性解析対象集団）

Parameter	Worst Post-Baseline Grade	40 mg (N=23) n (%)
Hypoalbuminemia	Any Grade	23 (100.0%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	0 (0.0%)
Alkaline phosphatase increased	Any Grade	10 (43.5%)
	Grade 3, 4	1 (4.3%)
	Grade 4	0 (0.0%)
	Missing	0 (0.0%)
ALT increased	Any Grade	6 (26.1%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	0 (0.0%)
Serum amylase increased	Any Grade	3 (13.0%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	0 (0.0%)
AST increased	Any Grade	10 (43.5%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	0 (0.0%)
Blood bilirubin increased	Any Grade	1 (4.3%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	0 (0.0%)

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.

Parameter	Worst Post-Baseline Grade	40 mg (N=23) n (%)
Lipase increased	Any Grade	9 (39.1%)
	Grade 3, 4	2 (8.7%)
	Grade 4	1 (4.3%)
	Missing	1 (4.3%)
Creatinine increased	Any Grade	21 (91.3%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	0 (0.0%)
Hypokalemia	Any Grade	11 (47.8%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	0 (0.0%)
Hyperkalemia	Any Grade	4 (17.4%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	0 (0.0%)
Hyponatremia	Any Grade	14 (60.9%)
	Grade 3, 4	3 (13.0%)
	Grade 4	1 (4.3%)
	Missing	0 (0.0%)
Hypernatremia	Any Grade	0 (0.0%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	0 (0.0%)

Source: Listing 16 2.7.2

Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.

Parameter	Worst Post-Baseline Grade	40 mg (N=23) n (%)
Hypomagnesemia	Any Grade	10 (43.5%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	1 (4.3%)
Hypermagnesemia	Any Grade	4 (17.4%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	1 (4.3%)
Hypocalcemia	Any Grade	10 (43.5%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	0 (0.0%)
Hypercalcemia	Any Grade	8 (34.8%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	0 (0.0%)
Hypoglycemia	Any Grade	1 (4.3%)
	Grade 3, 4	0 (0.0%)
	Grade 4	0 (0.0%)
	Missing	1 (4.3%)
Hyperglycemia	Any Grade	17 (73.9%)
	Grade 3, 4	1 (4.3%)
	Grade 4	0 (0.0%)
	Missing	1 (4.3%)

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.

Parameter	Worst Post-Baseline Grade	40 mg (N=23) n (%)
GGT increased	Any Grade	8 (34.8%)
	Grade 3, 4	1 (4.3%)
	Grade 4	0 (0.0%)
	Missing	0 (0.0%)

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set.
Only on-treatment abnormalities (toxicity grade >= 1) are presented.
On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.

表 2.7.4.7-65　血液生化学検査値異常のベースラインの Grade と投与後の Grade のシフトテーブル（210 試験）（安全性解析対象集団）

		40 mg (N=23)						
		Worst Post-Baseline Grade						
Parameter	Baseline Grade	Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypoalbuminemia	Grade 0	0	5	1	0	0	0	6
	Grade 1	0	8	6	0	0	0	14
	Grade 2	0	0	3	0	0	0	3
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	0	13	10	0	0	0	23
Alkaline phosphatase increased	Grade 0	12	5	0	0	0	0	17
	Grade 1	1	4	0	1	0	0	6
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	13	9	0	1	0	0	23
ALT increased	Grade 0	16	4	1	0	0	0	21
	Grade 1	1	1	0	0	0	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	17	5	1	0	0	0	23

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.

Parameter	Baseline Grade	40 mg (N=23) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Serum amylase increased	Grade 0	19	2	1	0	0	0	22
	Grade 1	1	0	0	0	0	0	1
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	20	2	1	0	0	0	23
AST increased	Grade 0	12	7	1	0	0	0	20
	Grade 1	1	2	0	0	0	0	3
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	13	9	1	0	0	0	23
Blood bilirubin increased	Grade 0	22	0	1	0	0	0	23
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	22	0	1	0	0	0	23

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.

Parameter	Baseline Grade	40 mg (N=23) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Lipase increased	Grade 0	13	3	0	0	0	0	16
	Grade 1	0	3	1	1	0	1	6
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	1	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	13	6	1	1	1	1	23
Creatinine increased	Grade 0	2	14	0	0	0	0	16
	Grade 1	0	7	0	0	0	0	7
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	2	21	0	0	0	0	23
Hypokalemia	Grade 0	12	10	0	0	0	0	22
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	1	0	0	0	0	1
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	12	11	0	0	0	0	23

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.

		40 mg (N=23)						
		Worst Post-Baseline Grade						
Parameter	Baseline Grade	Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hyperkalemia	Grade 0	17	2	1	0	0	0	20
	Grade 1	2	1	0	0	0	0	3
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	19	3	1	0	0	0	23
Hyponatremia	Grade 0	9	8	0	0	0	0	17
	Grade 1	0	3	0	2	1	0	6
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	9	11	0	2	1	0	23
Hypernatremia	Grade 0	23	0	0	0	0	0	23
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	23	0	0	0	0	0	23

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.

Parameter	Baseline Grade	40 mg (N=23) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypomagnesemia	Grade 0	12	6	0	0	0	1	19
	Grade 1	0	4	0	0	0	0	4
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	12	10	0	0	0	1	23
Hypermagnesemia	Grade 0	18	3	0	0	0	1	22
	Grade 1	0	1	0	0	0	0	1
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	18	4	0	0	0	1	23
Hypocalcemia	Grade 0	13	8	0	0	0	0	21
	Grade 1	0	1	1	0	0	0	2
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	13	9	1	0	0	0	23

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.

Parameter	Baseline Grade	40 mg (N=23) Worst Post-Baseline Grade Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
Hypercalcemia	Grade 0	14	5	0	0	0	0	19
	Grade 1	1	1	1	0	0	0	3
	Grade 2	0	0	1	0	0	0	1
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	15	6	2	0	0	0	23
Hypoglycemia	Grade 0	21	1	0	0	0	1	23
	Grade 1	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	21	1	0	0	0	1	23
Hyperglycemia	Grade 0	5	6	1	0	0	1	13
	Grade 1	0	3	3	1	0	0	7
	Grade 2	0	2	1	0	0	0	3
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	5	11	5	1	0	1	23

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.

		40 mg (N=23)						
		Worst Post-Baseline Grade						
Parameter	Baseline Grade	Grade 0 n	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Missing n	Overall n
GGT increased	Grade 0	15	3	0	0	0	0	18
	Grade 1	0	3	0	1	0	0	4
	Grade 2	0	0	1	0	0	0	1
	Grade 3	0	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0
	Overall	15	6	1	1	0	0	23

Source: Listing 16.2.7 2

Abnormalities are graded using NCI-CTCAE Version 4.03.
n = number of subjects.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
On-treatment period is defined as date of first study drug up till the End of treatment assessment visit.

表 2.7.4.7-66　臨床的に重大なバイタルサインの異常（203 試験）（安全性解析対象集団）

		Japan		Korea		Total	
Parameter	Criteria	N	n (%)	N	n (%)	N	n (%)
SBP	<= 90 mmHg AND change from baseline <= -20 mmHg	39	3 (7.7)	16	1 (6.3)	55	4 (7.3)
	>= 180 mmHg AND change from baseline >= 20 mmHg	39	0 (0.0)	16	0 (0.0)	55	0 (0.0)
DBP	<= 50 mmHg AND change from baseline <= -15 mmHg	39	4 (10.3)	16	0 (0.0)	55	4 (7.3)
	>= 105 mmHg AND change from baseline >= 15 mmHg	39	0 (0.0)	16	0 (0.0)	55	0 (0.0)
Pulse Rate	<= 50 bpm AND change from baseline <= -15 bpm	39	0 (0.0)	16	0 (0.0)	55	0 (0.0)
	>= 120 bpm AND change from baseline >= 15 bpm	39	2 (5.1)	16	2 (12.5)	55	4 (7.3)
Weight	>= 7% weight loss from baseline	39	11 (28.2)	16	2 (12.5)	55	13 (23.6)
	>= 7% weight gained from baseline	39	4 (10.3)	16	1 (6.3)	55	5 (9.1)

Source: Listing 16.2.9

N = number of subjects in a country who have at least one post-baseline assessment with baseline;
n = number of subjects who meet the category; % = percentages of subjects are calculated relative to the total number of subjects in a country with data;
DBP = diastolic blood pressure; SBP = systolic blood pressure; bpm = beats per minute.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

表 2.7.4.7-67　臨床的に重大なバイタルサインの異常（201 試験）（安全性解析対象集団）

Parameter	Criteria	30 mg		40 mg		Total	
		N	n (%)	N	n (%)	N	n (%)
SBP	<= 90 mmHg AND change from baseline <= -20 mmHg	7	3 (42.9%)	7	1 (14.3%)	14	4 (28.6%)
	>= 180 mmHg AND change from baseline >= 20 mmHg	7	0 (0.0%)	7	0 (0.0%)	14	0 (0.0%)
DBP	<= 50 mmHg AND change from baseline <= -15 mmHg	7	2 (28.6%)	7	1 (14.3%)	14	3 (21.4%)
	>= 105 mmHg AND change from baseline >= 15 mmHg	7	0 (0.0%)	7	0 (0.0%)	14	0 (0.0%)
Pulse Rate	<= 50 bpm AND change from baseline <= -15 bpm	7	0 (0.0%)	7	0 (0.0%)	14	0 (0.0%)
	>= 120 bpm AND change from baseline >= 15 bpm	7	0 (0.0%)	7	0 (0.0%)	14	0 (0.0%)
Temperature	>= 38.3 °C AND change from baseline >= 1.1 °C	7	0 (0.0%)	7	1 (14.3%)	14	1 (7.1%)
Weight	percentage change from baseline <= -7.0 %	6	1 (16.7%)	7	1 (14.3%)	13	2 (15.4%)
	percentage change from baseline >= 7.0 %	6	1 (16.7%)	7	0 (0.0%)	13	1 (7.7%)

SOURCE: Listing 16.2.9.1
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort with data.
DBP = diastolic blood pressure; SBP = systolic blood pressure; bpm = beats per minute.
Baseline is defined as pre-dose of Day 1 of Cycle 1.

表 2.7.4.7-68　臨床的に重大なバイタルサインの異常（210 試験）（安全性解析対象集団）

Parameter	Criteria	40 mg N	40 mg n (%)
SBP	<= 90 mmHg AND change from baseline <= -20 mmHg	22	3 (13.6%)
	>= 180 mmHg AND change from baseline >= 20 mmHg	22	0 (0.0%)
DBP	<= 50 mmHg AND change from baseline <= -15 mmHg	22	5 (22.7%)
	>= 105 mmHg AND change from baseline >= 15 mmHg	22	0 (0.0%)
Pulse Rate	<= 50 bpm AND change from baseline <= -15 bpm	22	0 (0.0%)
	>= 120 bpm AND change from baseline >= 15 bpm	22	3 (13.6%)
Weight	>= 7% weight loss from baseline	22	8 (36.4%)
	>= 7% weight gained from baseline	22	1 (4.5%)

Source: Listing 16.2.9

N = number of subjects who have at least one post-baseline assessment with baseline;
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set with data;
DBP = diastolic blood pressure; SBP = systolic blood pressure; bpm = beats per minute.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

表 2.7.4.7-69　心電図パラメータの要約（203 試験）（安全性解析対象集団）

Parameter (unit)	Visit	Statistic	40 mg (N=55)
PR Interval (msec)	Baseline	n	54
		Mean	164.64
		SD	22.53
		Median	165.50
		Minimum	123.0
		Maximum	216.0
	Cycle1 Day1, 3.5hrs Post-dose	n	54
		Mean	167.27
		SD	22.84
		Median	167.00
		Minimum	124.7
		Maximum	226.7
	Change from Baseline at Cycle1 Day1, 3.5hrs Post-dose	n	54
		Mean	2.63
		SD	8.13
		Median	1.67
		Minimum	-26.3
		Maximum	27.3
	Cycle2 Day1, Pre-dose	n	44
		Mean	163.90
		SD	20.22
		Median	165.33
		Minimum	124.3
		Maximum	205.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
PR Interval (msec)	Change from Baseline at Cycle2 Day1, Pre-dose	Mean	44
		SD	-3.12
		Median	10.92
		Minimum	-4.17
		Maximum	-29.3
		Mean	18.7
	Cycle2 Day1, 3.5hrs Post-dose	Mean	40
		SD	164.99
		Median	21.05
		Minimum	163.50
		Maximum	124.3
		Mean	211.3
	Change from Baseline at Cycle2 Day1, 3.5hrs Post-dose	Mean	40
		SD	-1.64
		Median	11.12
		Minimum	-0.83
		Maximum	-27.0
		Mean	29.7
	Cycle3 Day1	Mean	33
		SD	164.27
		Median	22.58
		Minimum	163.00
		Maximum	128.0
		Mean	207.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
PR Interval (msec)	Change from Baseline at Cycle3 Day1	n	33
		Mean	-3.12
		SD	10.73
		Median	-4.33
		Minimum	-28.7
		Maximum	16.3
	Cycle4 Day1	n	26
		Mean	161.88
		SD	27.33
		Median	164.50
		Minimum	115.0
		Maximum	226.0
	Change from Baseline at Cycle4 Day1	n	26
		Mean	-3.97
		SD	11.78
		Median	-5.50
		Minimum	-30.7
		Maximum	23.7
	Cycle5 Day1	n	20
		Mean	164.80
		SD	20.90
		Median	162.50
		Minimum	136.0
		Maximum	211.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
PR Interval (msec)	Change from Baseline at Cycle5 Day1	n	20
		Mean	-5.13
		SD	10.89
		Median	-5.33
		Minimum	-21.7
		Maximum	15.3
	Cycle6 Day1	n	14
		Mean	164.93
		SD	23.41
		Median	161.50
		Minimum	131.0
		Maximum	212.0
	Change from Baseline at Cycle6 Day1	n	14
		Mean	-3.17
		SD	8.04
		Median	-3.50
		Minimum	-20.3
		Maximum	8.7
	Cycle7 Day1	n	14
		Mean	163.36
		SD	19.04
		Median	167.50
		Minimum	124.0
		Maximum	193.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
PR Interval (msec)	Change from Baseline at Cycle7 Day1	n	14
		Mean	-2.52
		SD	12.87
		Median	-2.17
		Minimum	-21.7
		Maximum	15.3
	Cycle8 Day1	n	12
		Mean	158.75
		SD	16.77
		Median	159.50
		Minimum	135.0
		Maximum	181.0
	Change from Baseline at Cycle8 Day1	n	12
		Mean	-7.08
		SD	15.02
		Median	-9.50
		Minimum	-30.3
		Maximum	29.7
	Cycle9 Day1	n	11
		Mean	158.82
		SD	23.20
		Median	163.00
		Minimum	108.0
		Maximum	193.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
PR Interval (msec)	Change from Baseline at Cycle9 Day1	n	11
		Mean	-5.00
		SD	15.90
		Median	-1.00
		Minimum	-33.7
		Maximum	24.7
	Cycle10 Day1	n	7
		Mean	159.00
		SD	23.35
		Median	153.00
		Minimum	132.0
		Maximum	194.0
	Change from Baseline at Cycle10 Day1	n	7
		Mean	-0.33
		SD	10.24
		Median	-3.00
		Minimum	-12.3
		Maximum	14.3
	Cycle11 Day1	n	7
		Mean	156.00
		SD	25.37
		Median	168.00
		Minimum	116.0
		Maximum	179.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
PR Interval (msec)	Change from Baseline at Cycle11 Day1	n	7
		Mean	-3.33
		SD	16.02
		Median	-8.33
		Minimum	-27.3
		Maximum	15.7
	Cycle12 Day1	n	5
		Mean	174.40
		SD	18.50
		Median	167.00
		Minimum	152.0
		Maximum	196.0
	Change from Baseline at Cycle12 Day1	n	5
		Mean	4.53
		SD	8.41
		Median	8.00
		Minimum	-10.3
		Maximum	10.3
	Cycle13 Day1	n	3
		Mean	171.00
		SD	27.87
		Median	158.00
		Minimum	152.0
		Maximum	203.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
PR Interval (msec)	Change from Baseline at Cycle13 Day1	n	3
		Mean	1.11
		SD	6.05
		Median	-1.33
		Minimum	-3.3
		Maximum	8.0
	Cycle14 Day1	n	3
		Mean	169.00
		SD	25.16
		Median	156.00
		Minimum	153.0
		Maximum	198.0
	Change from Baseline at Cycle14 Day1	n	3
		Mean	-0.89
		SD	8.92
		Median	-3.33
		Minimum	-8.3
		Maximum	9.0
	Cycle15 Day1	n	3
		Mean	161.67
		SD	16.50
		Median	162.00
		Minimum	145.0
		Maximum	178.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
PR Interval (msec)	Change from Baseline at Cycle15 Day1	n	3
		Mean	-8.22
		SD	17.44
		Median	1.00
		Minimum	-28.3
		Maximum	2.7
	Cycle16 Day1	n	3
		Mean	165.33
		SD	27.23
		Median	156.00
		Minimum	144.0
		Maximum	196.0
	Change from Baseline at Cycle16 Day1	n	3
		Mean	-4.56
		SD	5.27
		Median	-3.33
		Minimum	-10.3
		Maximum	0.0
	Cycle17 Day1	n	3
		Mean	167.00
		SD	11.53
		Median	163.00
		Minimum	158.0
		Maximum	180.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
PR Interval (msec)	Change from Baseline at Cycle17 Day1	n	3
		Mean	-2.89
		SD	22.71
		Median	-1.33
		Minimum	-26.3
		Maximum	19.0
	Cycle18 Day1	n	2
		Mean	182.00
		SD	21.21
		Median	182.00
		Minimum	167.0
		Maximum	197.0
	Change from Baseline at Cycle18 Day1	n	2
		Mean	-0.83
		SD	12.02
		Median	-0.83
		Minimum	-9.3
		Maximum	7.7
	Cycle19 Day1	n	2
		Mean	184.00
		SD	28.28
		Median	184.00
		Minimum	164.0
		Maximum	204.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
PR Interval (msec)	Change from Baseline at Cycle19 Day1	n	2
		Mean	1.17
		SD	4.95
		Median	1.17
		Minimum	-2.3
		Maximum	4.7
	Cycle20 Day1	n	1
		Mean	155.00
		SD	-
		Median	155.00
		Minimum	155.0
		Maximum	155.0
	Change from Baseline at Cycle20 Day1	n	1
		Mean	-4.33
		SD	-
		Median	-4.33
		Minimum	-4.3
		Maximum	-4.3
	Cycle21 Day1	n	1
		Mean	155.00
		SD	-
		Median	155.00
		Minimum	155.0
		Maximum	155.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
PR Interval (msec)	Change from Baseline at Cycle21 Day1	n	1
		Mean	-4.33
		SD	-
		Median	-4.33
		Minimum	-4.3
		Maximum	-4.3
	End of Treatment	n	33
		Mean	159.52
		SD	25.61
		Median	163.00
		Minimum	122.0
		Maximum	225.0
	Change from Baseline at End of Treatment	n	33
		Mean	-4.47
		SD	15.12
		Median	-3.00
		Minimum	-48.3
		Maximum	28.7
QRS Duration (msec)	Baseline	n	55
		Mean	92.13
		SD	16.81
		Median	89.67
		Minimum	73.3
		Maximum	186.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QRS Duration (msec)	Cycle1 Day1, 3.5hrs Post-dose	n	55
		Mean	91.44
		SD	14.82
		Median	89.33
		Minimum	73.7
		Maximum	164.7
	Change from Baseline at Cycle1 Day1, 3.5hrs Post-dose	n	55
		Mean	-0.68
		SD	4.66
		Median	-0.33
		Minimum	-22.0
		Maximum	7.0
	Cycle2 Day1, Pre-dose	n	45
		Mean	90.50
		SD	11.67
		Median	88.67
		Minimum	78.7
		Maximum	155.3
	Change from Baseline at Cycle2 Day1, Pre-dose	n	45
		Mean	-0.56
		SD	7.65
		Median	-1.67
		Minimum	-31.3
		Maximum	23.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QRS Duration (msec)	Cycle2 Day1, 3.5hrs Post-dose	n	41
		Mean	89.89
		SD	6.13
		Median	89.67
		Minimum	77.0
		Maximum	104.0
	Change from Baseline at Cycle2 Day1, 3.5hrs Post-dose	n	41
		Mean	1.00
		SD	5.51
		Median	0.67
		Minimum	-9.0
		Maximum	16.7
	Cycle3 Day1	n	34
		Mean	89.94
		SD	7.93
		Median	90.00
		Minimum	73.0
		Maximum	106.0
	Change from Baseline at Cycle3 Day1	n	34
		Mean	1.13
		SD	5.36
		Median	2.50
		Minimum	-14.0
		Maximum	10.3

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QRS Duration (msec)	Cycle4 Day1	n	26
		Mean	89.73
		SD	8.67
		Median	88.00
		Minimum	69.0
		Maximum	106.0
	Change from Baseline at Cycle4 Day1	n	26
		Mean	-0.23
		SD	7.27
		Median	-0.17
		Minimum	-14.3
		Maximum	14.3
	Cycle5 Day1	n	20
		Mean	90.40
		SD	9.41
		Median	90.00
		Minimum	73.0
		Maximum	107.0
	Change from Baseline at Cycle5 Day1	n	20
		Mean	0.03
		SD	8.42
		Median	-0.83
		Minimum	-15.0
		Maximum	17.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QRS Duration (msec)	Cycle6 Day1	n	15
		Mean	89.67
		SD	7.44
		Median	90.00
		Minimum	72.0
		Maximum	102.0
	Change from Baseline at Cycle6 Day1	n	15
		Mean	-2.78
		SD	5.13
		Median	-3.00
		Minimum	-13.7
		Maximum	5.7
	Cycle7 Day1	n	14
		Mean	90.07
		SD	8.04
		Median	88.00
		Minimum	74.0
		Maximum	104.0
	Change from Baseline at Cycle7 Day1	n	14
		Mean	-1.71
		SD	5.55
		Median	-1.17
		Minimum	-11.3
		Maximum	6.3

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QRS Duration (msec)	Cycle8 Day1	n	12
		Mean	89.25
		SD	10.23
		Median	89.50
		Minimum	70.0
		Maximum	105.0
	Change from Baseline at Cycle8 Day1	n	12
		Mean	-2.11
		SD	4.68
		Median	-1.33
		Minimum	-9.0
		Maximum	6.3
	Cycle9 Day1	n	11
		Mean	91.27
		SD	7.14
		Median	94.00
		Minimum	77.0
		Maximum	103.0
	Change from Baseline at Cycle9 Day1	n	11
		Mean	1.03
		SD	5.50
		Median	-0.67
		Minimum	-5.7
		Maximum	13.3

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QRS Duration (msec)	Cycle10 Day1	n	7
		Mean	88.29
		SD	8.75
		Median	85.00
		Minimum	79.0
		Maximum	101.0
	Change from Baseline at Cycle10 Day1	n	7
		Mean	-2.95
		SD	5.57
		Median	-3.67
		Minimum	-8.0
		Maximum	8.7
	Cycle11 Day1	n	7
		Mean	91.00
		SD	8.35
		Median	91.00
		Minimum	79.0
		Maximum	105.0
	Change from Baseline at Cycle11 Day1	n	7
		Mean	-0.24
		SD	3.02
		Median	-1.67
		Minimum	-3.0
		Maximum	5.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QRS Duration (msec)	Cycle12 Day1	n	5
		Mean	93.20
		SD	7.89
		Median	91.00
		Minimum	87.0
		Maximum	106.0
	Change from Baseline at Cycle12 Day1	n	5
		Mean	-1.00
		SD	3.95
		Median	-1.67
		Minimum	-4.7
		Maximum	5.7
	Cycle13 Day1	n	3
		Mean	84.67
		SD	6.66
		Median	83.00
		Minimum	79.0
		Maximum	92.0
	Change from Baseline at Cycle13 Day1	n	3
		Mean	-6.67
		SD	3.84
		Median	-5.33
		Minimum	-11.0
		Maximum	-3.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QRS Duration (msec)	Cycle14 Day1	n	3
		Mean	89.00
		SD	5.29
		Median	91.00
		Minimum	83.0
		Maximum	93.0
	Change from Baseline at Cycle14 Day1	n	3
		Mean	-2.33
		SD	4.84
		Median	-2.67
		Minimum	-7.0
		Maximum	2.7
	Cycle15 Day1	n	3
		Mean	85.67
		SD	5.51
		Median	86.00
		Minimum	80.0
		Maximum	91.0
	Change from Baseline at Cycle15 Day1	n	3
		Mean	-5.67
		SD	2.33
		Median	-4.67
		Minimum	-8.3
		Maximum	-4.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QRS Duration (msec)	Cycle16 Day1	n	3
		Mean	88.67
		SD	3.06
		Median	88.00
		Minimum	86.0
		Maximum	92.0
	Change from Baseline at Cycle16 Day1	n	3
		Mean	-2.67
		SD	5.78
		Median	-4.00
		Minimum	-7.7
		Maximum	3.7
	Cycle17 Day1	n	3
		Mean	86.67
		SD	2.08
		Median	86.00
		Minimum	85.0
		Maximum	89.0
	Change from Baseline at Cycle17 Day1	n	3
		Mean	-4.67
		SD	1.76
		Median	-4.00
		Minimum	-6.7
		Maximum	-3.3

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QRS Duration (msec)	Cycle18 Day1	n	2
		Mean	87.00
		SD	8.49
		Median	87.00
		Minimum	81.0
		Maximum	93.0
	Change from Baseline at Cycle18 Day1	n	2
		Mean	-5.00
		SD	3.30
		Median	-5.00
		Minimum	-7.3
		Maximum	-2.7
	Cycle19 Day1	n	2
		Mean	91.00
		SD	4.24
		Median	91.00
		Minimum	88.0
		Maximum	94.0
	Change from Baseline at Cycle19 Day1	n	2
		Mean	-1.00
		SD	9.43
		Median	-1.00
		Minimum	-7.7
		Maximum	5.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QRS Duration (msec)	Cycle20 Day1	n	1
		Mean	96.00
		SD	-
		Median	96.00
		Minimum	96.0
		Maximum	96.0
	Change from Baseline at Cycle20 Day1	n	1
		Mean	0.33
		SD	-
		Median	0.33
		Minimum	0.3
		Maximum	0.3
	Cycle21 Day1	n	1
		Mean	95.00
		SD	-
		Median	95.00
		Minimum	95.0
		Maximum	95.0
	Change from Baseline at Cycle21 Day1	n	1
		Mean	-0.67
		SD	-
		Median	-0.67
		Minimum	-0.7
		Maximum	-0.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QRS Duration (msec)	End of Treatment	n	34
		Mean	94.03
		SD	16.45
		Median	90.50
		Minimum	73.0
		Maximum	166.0
	Change from Baseline at End of Treatment	n	34
		Mean	-0.53
		SD	7.54
		Median	-0.50
		Minimum	-20.7
		Maximum	12.0
QT Interval (msec)	Baseline	n	55
		Mean	380.10
		SD	32.38
		Median	379.00
		Minimum	317.0
		Maximum	459.7
	Cycle1 Day1, 3.5hrs Post-dose	n	55
		Mean	381.13
		SD	33.40
		Median	379.33
		Minimum	306.0
		Maximum	464.3

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QT Interval (msec)	Change from Baseline at Cycle1 Day1, 3.5hrs Post-dose	n	55
		Mean	1.04
		SD	13.49
		Median	2.00
		Minimum	-24.7
		Maximum	43.7
	Cycle2 Day1, Pre-dose	n	45
		Mean	380.24
		SD	32.57
		Median	381.33
		Minimum	302.7
		Maximum	461.7
	Change from Baseline at Cycle2 Day1, Pre-dose	n	45
		Mean	-4.07
		SD	22.64
		Median	0.00
		Minimum	-76.0
		Maximum	52.0
	Cycle2 Day1, 3.5hrs Post-dose	n	40
		Mean	372.70
		SD	30.75
		Median	369.33
		Minimum	293.7
		Maximum	443.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QT Interval (msec)	Change from Baseline at Cycle2 Day1, 3.5hrs Post-dose	n	40
		Mean	-12.09
		SD	29.60
		Median	-13.50
		Minimum	-88.0
		Maximum	45.3
	Cycle3 Day1	n	34
		Mean	386.59
		SD	30.36
		Median	390.00
		Minimum	316.0
		Maximum	444.0
	Change from Baseline at Cycle3 Day1	n	34
		Mean	-2.02
		SD	24.42
		Median	-2.83
		Minimum	-60.7
		Maximum	44.7
	Cycle4 Day1	n	26
		Mean	386.42
		SD	32.77
		Median	384.00
		Minimum	304.0
		Maximum	460.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QT Interval (msec)	Change from Baseline at Cycle4 Day1	n	26
		Mean	-1.81
		SD	17.40
		Median	-3.00
		Minimum	-36.7
		Maximum	41.7
	Cycle5 Day1	n	20
		Mean	391.60
		SD	28.50
		Median	386.00
		Minimum	359.0
		Maximum	457.0
	Change from Baseline at Cycle5 Day1	n	20
		Mean	1.17
		SD	21.41
		Median	10.17
		Minimum	-32.3
		Maximum	34.3
	Cycle6 Day1	n	15
		Mean	381.67
		SD	25.98
		Median	381.00
		Minimum	357.0
		Maximum	465.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QT Interval (msec)	Change from Baseline at Cycle6 Day1	n	15
		Mean	-4.40
		SD	33.13
		Median	-5.67
		Minimum	-96.7
		Maximum	44.3
	Cycle7 Day1	n	14
		Mean	388.43
		SD	41.35
		Median	381.50
		Minimum	323.0
		Maximum	494.0
	Change from Baseline at Cycle7 Day1	n	14
		Mean	-0.17
		SD	29.98
		Median	9.83
		Minimum	-47.7
		Maximum	54.0
	Cycle8 Day1	n	12
		Mean	399.00
		SD	32.99
		Median	389.00
		Minimum	360.0
		Maximum	488.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QT Interval (msec)	Change from Baseline at Cycle8 Day1	n	12
		Mean	8.22
		SD	28.65
		Median	15.33
		Minimum	-44.7
		Maximum	52.0
	Cycle9 Day1	n	11
		Mean	393.09
		SD	29.70
		Median	387.00
		Minimum	354.0
		Maximum	449.0
	Change from Baseline at Cycle9 Day1	n	11
		Mean	6.79
		SD	23.90
		Median	2.67
		Minimum	-26.7
		Maximum	45.0
	Cycle10 Day1	n	7
		Mean	393.29
		SD	11.76
		Median	393.00
		Minimum	379.0
		Maximum	410.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QT Interval (msec)	Change from Baseline at Cycle10 Day1	n	7
		Mean	14.33
		SD	22.33
		Median	19.00
		Minimum	-16.3
		Maximum	43.0
	Cycle11 Day1	n	7
		Mean	407.86
		SD	11.28
		Median	405.00
		Minimum	396.0
		Maximum	424.0
	Change from Baseline at Cycle11 Day1	n	7
		Mean	28.90
		SD	14.33
		Median	30.33
		Minimum	6.3
		Maximum	50.0
	Cycle12 Day1	n	5
		Mean	394.60
		SD	25.84
		Median	397.00
		Minimum	356.0
		Maximum	424.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QT Interval (msec)	Change from Baseline at Cycle12 Day1	n	5
		Mean	16.80
		SD	35.77
		Median	31.67
		Minimum	-30.7
		Maximum	57.0
	Cycle13 Day1	n	3
		Mean	406.67
		SD	26.39
		Median	394.00
		Minimum	389.0
		Maximum	437.0
	Change from Baseline at Cycle13 Day1	n	3
		Mean	33.67
		SD	32.51
		Median	23.67
		Minimum	7.3
		Maximum	70.0
	Cycle14 Day1	n	3
		Mean	395.33
		SD	7.64
		Median	397.00
		Minimum	387.0
		Maximum	402.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QT Interval (msec)	Change from Baseline at Cycle14 Day1	n	3
		Mean	22.33
		SD	12.35
		Median	21.67
		Minimum	10.3
		Maximum	35.0
	Cycle15 Day1	n	3
		Mean	400.33
		SD	15.01
		Median	401.00
		Minimum	385.0
		Maximum	415.0
	Change from Baseline at Cycle15 Day1	n	3
		Mean	27.33
		SD	18.10
		Median	19.67
		Minimum	14.3
		Maximum	48.0
	Cycle16 Day1	n	3
		Mean	376.00
		SD	25.51
		Median	366.00
		Minimum	357.0
		Maximum	405.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QT Interval (msec)	Change from Baseline at Cycle16 Day1	n	3
		Mean	3.00
		SD	30.93
		Median	-8.33
		Minimum	-20.7
		Maximum	38.0
	Cycle17 Day1	n	3
		Mean	396.67
		SD	27.61
		Median	390.00
		Minimum	373.0
		Maximum	427.0
	Change from Baseline at Cycle17 Day1	n	3
		Mean	23.67
		SD	31.54
		Median	7.67
		Minimum	3.3
		Maximum	60.0
	Cycle18 Day1	n	2
		Mean	380.00
		SD	11.31
		Median	380.00
		Minimum	372.0
		Maximum	388.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QT Interval (msec)	Change from Baseline at Cycle18 Day1	n	2
		Mean	4.00
		SD	3.77
		Median	4.00
		Minimum	1.3
		Maximum	6.7
	Cycle19 Day1	n	2
		Mean	393.00
		SD	8.49
		Median	393.00
		Minimum	387.0
		Maximum	399.0
	Change from Baseline at Cycle19 Day1	n	2
		Mean	17.00
		SD	6.60
		Median	17.00
		Minimum	12.3
		Maximum	21.7
	Cycle20 Day1	n	1
		Mean	382.00
		SD	-
		Median	382.00
		Minimum	382.0
		Maximum	382.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QT Interval (msec)	Change from Baseline at Cycle20 Day1	n	1
		Mean	-4.67
		SD	-
		Median	-4.67
		Minimum	-4.7
		Maximum	-4.7
	Cycle21 Day1	n	1
		Mean	405.00
		SD	-
		Median	405.00
		Minimum	405.0
		Maximum	405.0
	Change from Baseline at Cycle21 Day1	n	1
		Mean	18.33
		SD	-
		Median	18.33
		Minimum	18.3
		Maximum	18.3
	End of Treatment	n	34
		Mean	384.21
		SD	41.35
		Median	376.50
		Minimum	306.0
		Maximum	472.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QT Interval (msec)	Change from Baseline at End of Treatment	n	34
		Mean	-1.30
		SD	32.15
		Median	-1.33
		Minimum	-72.0
		Maximum	62.7
QTcB Interval (msec)	Baseline	n	55
		Mean	424.58
		SD	23.67
		Median	423.00
		Minimum	369.3
		Maximum	490.0
	Cycle1 Day1, 3.5hrs Post-dose	n	55
		Mean	423.40
		SD	22.34
		Median	420.67
		Minimum	378.0
		Maximum	468.7
	Change from Baseline at Cycle1 Day1, 3.5hrs Post-dose	n	55
		Mean	-1.18
		SD	12.77
		Median	1.00
		Minimum	-39.3
		Maximum	26.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcB Interval (msec)	Cycle2 Day1, Pre-dose	n	45
		Mean	431.01
		SD	25.56
		Median	432.33
		Minimum	384.3
		Maximum	492.0
	Change from Baseline at Cycle2 Day1, Pre-dose	n	45
		Mean	7.01
		SD	22.55
		Median	10.00
		Minimum	-54.3
		Maximum	63.0
	Cycle2 Day1, 3.5hrs Post-dose	n	40
		Mean	426.97
		SD	22.36
		Median	427.83
		Minimum	378.3
		Maximum	465.3
	Change from Baseline at Cycle2 Day1, 3.5hrs Post-dose	n	40
		Mean	4.63
		SD	23.45
		Median	6.00
		Minimum	-61.0
		Maximum	53.3

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcB Interval (msec)	Cycle3 Day1	n	34
		Mean	433.71
		SD	24.17
		Median	430.50
		Minimum	385.0
		Maximum	486.0
	Change from Baseline at Cycle3 Day1	n	34
		Mean	11.91
		SD	14.89
		Median	10.83
		Minimum	-11.7
		Maximum	41.7
	Cycle4 Day1	n	26
		Mean	430.88
		SD	23.03
		Median	428.50
		Minimum	378.0
		Maximum	469.0
	Change from Baseline at Cycle4 Day1	n	26
		Mean	12.94
		SD	15.77
		Median	12.17
		Minimum	-27.7
		Maximum	41.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcB Interval (msec)	Cycle5 Day1	n	20
		Mean	431.35
		SD	22.77
		Median	430.00
		Minimum	398.0
		Maximum	479.0
	Change from Baseline at Cycle5 Day1	n	20
		Mean	16.50
		SD	17.46
		Median	14.33
		Minimum	-7.7
		Maximum	72.0
	Cycle6 Day1	n	15
		Mean	431.00
		SD	18.58
		Median	427.00
		Minimum	412.0
		Maximum	476.0
	Change from Baseline at Cycle6 Day1	n	15
		Mean	11.29
		SD	12.81
		Median	10.67
		Minimum	-14.0
		Maximum	31.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcB Interval (msec)	Cycle7 Day1	n	14
		Mean	437.36
		SD	24.53
		Median	436.50
		Minimum	404.0
		Maximum	496.0
	Change from Baseline at Cycle7 Day1	n	14
		Mean	16.64
		SD	18.48
		Median	14.83
		Minimum	-7.0
		Maximum	56.7
	Cycle8 Day1	n	12
		Mean	440.25
		SD	21.19
		Median	435.50
		Minimum	407.0
		Maximum	480.0
	Change from Baseline at Cycle8 Day1	n	12
		Mean	16.86
		SD	21.01
		Median	17.33
		Minimum	-9.0
		Maximum	49.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcB Interval (msec)	Cycle9 Day1	n	11
		Mean	442.00
		SD	22.84
		Median	436.00
		Minimum	416.0
		Maximum	495.0
	Change from Baseline at Cycle9 Day1	n	11
		Mean	20.06
		SD	17.14
		Median	16.00
		Minimum	-11.0
		Maximum	54.0
	Cycle10 Day1	n	7
		Mean	436.14
		SD	14.09
		Median	431.00
		Minimum	424.0
		Maximum	460.0
	Change from Baseline at Cycle10 Day1	n	7
		Mean	12.57
		SD	19.24
		Median	6.67
		Minimum	-12.0
		Maximum	44.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcB Interval (msec)	Cycle11 Day1	n	7
		Mean	435.29
		SD	17.53
		Median	433.00
		Minimum	410.0
		Maximum	458.0
	Change from Baseline at Cycle11 Day1	n	7
		Mean	11.71
		SD	16.24
		Median	13.67
		Minimum	-18.0
		Maximum	34.7
	Cycle12 Day1	n	5
		Mean	435.20
		SD	12.50
		Median	433.00
		Minimum	423.0
		Maximum	456.0
	Change from Baseline at Cycle12 Day1	n	5
		Mean	16.80
		SD	6.43
		Median	13.67
		Minimum	10.0
		Maximum	26.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcB Interval (msec)	Cycle13 Day1	n	3
		Mean	439.33
		SD	12.86
		Median	434.00
		Minimum	430.0
		Maximum	454.0
	Change from Baseline at Cycle13 Day1	n	3
		Mean	24.78
		SD	17.51
		Median	14.67
		Minimum	14.7
		Maximum	45.0
	Cycle14 Day1	n	3
		Mean	429.67
		SD	10.97
		Median	426.00
		Minimum	421.0
		Maximum	442.0
	Change from Baseline at Cycle14 Day1	n	3
		Mean	15.11
		SD	10.36
		Median	12.00
		Minimum	6.7
		Maximum	26.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcB Interval (msec)	Cycle15 Day1	n	3
		Mean	437.33
		SD	15.01
		Median	438.00
		Minimum	422.0
		Maximum	452.0
	Change from Baseline at Cycle15 Day1	n	3
		Mean	22.78
		SD	17.83
		Median	29.00
		Minimum	2.7
		Maximum	36.7
	Cycle16 Day1	n	3
		Mean	415.33
		SD	8.33
		Median	418.00
		Minimum	406.0
		Maximum	422.0
	Change from Baseline at Cycle16 Day1	n	3
		Mean	0.78
		SD	9.31
		Median	2.67
		Minimum	-9.3
		Maximum	9.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcB Interval (msec)	Cycle17 Day1	n	3
		Mean	430.67
		SD	21.36
		Median	422.00
		Minimum	415.0
		Maximum	455.0
	Change from Baseline at Cycle17 Day1	n	3
		Mean	16.11
		SD	26.46
		Median	6.67
		Minimum	-4.3
		Maximum	46.0
	Cycle18 Day1	n	2
		Mean	427.50
		SD	2.12
		Median	427.50
		Minimum	426.0
		Maximum	429.0
	Change from Baseline at Cycle18 Day1	n	2
		Mean	10.17
		SD	0.71
		Median	10.17
		Minimum	9.7
		Maximum	10.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcB Interval (msec)	Cycle19 Day1	n	2
		Mean	428.50
		SD	10.61
		Median	428.50
		Minimum	421.0
		Maximum	436.0
	Change from Baseline at Cycle19 Day1	n	2
		Mean	11.17
		SD	13.44
		Median	11.17
		Minimum	1.7
		Maximum	20.7
	Cycle20 Day1	n	1
		Mean	398.00
		SD	-
		Median	398.00
		Minimum	398.0
		Maximum	398.0
	Change from Baseline at Cycle20 Day1	n	1
		Mean	-17.33
		SD	-
		Median	-17.33
		Minimum	-17.3
		Maximum	-17.3

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcB Interval (msec)	Cycle21 Day1	n	1
		Mean	443.00
		SD	-
		Median	443.00
		Minimum	443.0
		Maximum	443.0
	Change from Baseline at Cycle21 Day1	n	1
		Mean	27.67
		SD	-
		Median	27.67
		Minimum	27.7
		Maximum	27.7
	End of Treatment	n	34
		Mean	432.03
		SD	21.67
		Median	428.50
		Minimum	383.0
		Maximum	478.0
	Change from Baseline at End of Treatment	n	34
		Mean	3.75
		SD	19.79
		Median	6.17
		Minimum	-36.0
		Maximum	43.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcF Interval (msec)	Baseline	n	55
		Mean	408.77
		SD	20.23
		Median	407.33
		Minimum	374.0
		Maximum	446.7
	Cycle1 Day1, 3.5hrs Post-dose	n	55
		Mean	408.33
		SD	19.93
		Median	408.67
		Minimum	358.3
		Maximum	448.3
	Change from Baseline at Cycle1 Day1, 3.5hrs Post-dose	n	55
		Mean	-0.44
		SD	9.49
		Median	-0.33
		Minimum	-22.7
		Maximum	23.7
	Cycle2 Day1, Pre-dose	n	45
		Mean	412.95
		SD	20.88
		Median	413.33
		Minimum	370.7
		Maximum	456.3

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcF Interval (msec)	Change from Baseline at Cycle2 Day1, Pre-dose	n	45
		Mean	3.05
		SD	19.18
		Median	3.33
		Minimum	-54.0
		Maximum	48.0
	Cycle2 Day1, 3.5hrs Post-dose	n	40
		Mean	407.73
		SD	20.03
		Median	410.33
		Minimum	366.3
		Maximum	439.3
	Change from Baseline at Cycle2 Day1, 3.5hrs Post-dose	n	40
		Mean	-1.29
		SD	22.71
		Median	1.67
		Minimum	-70.0
		Maximum	47.7
	Cycle3 Day1	n	34
		Mean	417.09
		SD	21.89
		Median	415.50
		Minimum	371.0
		Maximum	471.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcF Interval (msec)	Change from Baseline at Cycle3 Day1	n	34
		Mean	6.95
		SD	11.44
		Median	5.17
		Minimum	-22.3
		Maximum	29.3
	Cycle4 Day1	n	26
		Mean	415.27
		SD	21.75
		Median	412.00
		Minimum	371.0
		Maximum	466.0
	Change from Baseline at Cycle4 Day1	n	26
		Mean	7.78
		SD	12.28
		Median	10.33
		Minimum	-15.3
		Maximum	28.3
	Cycle5 Day1	n	20
		Mean	417.45
		SD	20.39
		Median	411.50
		Minimum	391.0
		Maximum	460.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcF Interval (msec)	Change from Baseline at Cycle5 Day1	n	20
		Mean	11.25
		SD	13.24
		Median	11.33
		Minimum	-11.3
		Maximum	52.7
	Cycle6 Day1	n	15
		Mean	413.67
		SD	18.77
		Median	410.00
		Minimum	395.0
		Maximum	465.0
	Change from Baseline at Cycle6 Day1	n	15
		Mean	5.71
		SD	16.23
		Median	9.00
		Minimum	-33.3
		Maximum	25.7
	Cycle7 Day1	n	14
		Mean	420.14
		SD	28.38
		Median	417.00
		Minimum	375.0
		Maximum	495.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcF Interval (msec)	Change from Baseline at Cycle7 Day1	n	14
		Mean	10.64
		SD	15.72
		Median	7.83
		Minimum	-11.7
		Maximum	55.7
	Cycle8 Day1	n	12
		Mean	425.83
		SD	19.81
		Median	423.00
		Minimum	391.0
		Maximum	470.0
	Change from Baseline at Cycle8 Day1	n	12
		Mean	13.83
		SD	18.83
		Median	20.00
		Minimum	-18.3
		Maximum	39.3
	Cycle9 Day1	n	11
		Mean	424.91
		SD	22.13
		Median	415.00
		Minimum	401.0
		Maximum	479.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcF Interval (msec)	Change from Baseline at Cycle9 Day1	n	11
		Mean	15.39
		SD	15.92
		Median	13.67
		Minimum	-15.0
		Maximum	46.0
	Cycle10 Day1	n	7
		Mean	421.00
		SD	7.12
		Median	420.00
		Minimum	413.0
		Maximum	433.0
	Change from Baseline at Cycle10 Day1	n	7
		Mean	12.90
		SD	16.06
		Median	14.67
		Minimum	-10.0
		Maximum	29.7
	Cycle11 Day1	n	7
		Mean	425.86
		SD	11.51
		Median	421.00
		Minimum	414.0
		Maximum	446.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcF Interval (msec)	Change from Baseline at Cycle11 Day1	n	7
		Mean	17.76
		SD	9.49
		Median	20.67
		Minimum	4.0
		Maximum	28.3
	Cycle12 Day1	n	5
		Mean	421.00
		SD	11.49
		Median	421.00
		Minimum	403.0
		Maximum	431.0
	Change from Baseline at Cycle12 Day1	n	5
		Mean	16.67
		SD	16.50
		Median	20.67
		Minimum	-2.7
		Maximum	36.7
	Cycle13 Day1	n	3
		Mean	427.67
		SD	17.62
		Median	418.00
		Minimum	417.0
		Maximum	448.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcF Interval (msec)	Change from Baseline at Cycle13 Day1	n	3
		Mean	27.56
		SD	22.83
		Median	17.67
		Minimum	11.3
		Maximum	53.7
	Cycle14 Day1	n	3
		Mean	418.00
		SD	7.00
		Median	415.00
		Minimum	413.0
		Maximum	426.0
	Change from Baseline at Cycle14 Day1	n	3
		Mean	17.89
		SD	4.53
		Median	20.33
		Minimum	12.7
		Maximum	20.7
	Cycle15 Day1	n	3
		Mean	424.67
		SD	12.86
		Median	430.00
		Minimum	410.0
		Maximum	434.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcF Interval (msec)	Change from Baseline at Cycle15 Day1	n	3
		Mean	24.56
		SD	13.41
		Median	28.33
		Minimum	9.7
		Maximum	35.7
	Cycle16 Day1	n	3
		Mean	401.33
		SD	10.69
		Median	399.00
		Minimum	392.0
		Maximum	413.0
	Change from Baseline at Cycle16 Day1	n	3
		Mean	1.22
		SD	16.32
		Median	-1.33
		Minimum	-13.7
		Maximum	18.7
	Cycle17 Day1	n	3
		Mean	419.33
		SD	23.63
		Median	411.00
		Minimum	401.0
		Maximum	446.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcF Interval (msec)	Change from Baseline at Cycle17 Day1	n	3
		Mean	19.22
		SD	28.19
		Median	5.33
		Minimum	0.7
		Maximum	51.7
	Cycle18 Day1	n	2
		Mean	411.00
		SD	2.83
		Median	411.00
		Minimum	409.0
		Maximum	413.0
	Change from Baseline at Cycle18 Day1	n	2
		Mean	8.00
		SD	0.94
		Median	8.00
		Minimum	7.3
		Maximum	8.7
	Cycle19 Day1	n	2
		Mean	417.00
		SD	9.90
		Median	417.00
		Minimum	410.0
		Maximum	424.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcF Interval (msec)	Change from Baseline at Cycle19 Day1	n	2
		Mean	14.00
		SD	6.13
		Median	14.00
		Minimum	9.7
		Maximum	18.3
	Cycle20 Day1	n	1
		Mean	393.00
		SD	-
		Median	393.00
		Minimum	393.0
		Maximum	393.0
	Change from Baseline at Cycle20 Day1	n	1
		Mean	-12.67
		SD	-
		Median	-12.67
		Minimum	-12.7
		Maximum	-12.7
	Cycle21 Day1	n	1
		Mean	430.00
		SD	-
		Median	430.00
		Minimum	430.0
		Maximum	430.0

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=55)
QTcF Interval (msec)	Change from Baseline at Cycle21 Day1	n	1
		Mean	24.33
		SD	-
		Median	24.33
		Minimum	24.3
		Maximum	24.3
	End of Treatment	n	34
		Mean	414.97
		SD	24.28
		Median	411.50
		Minimum	368.0
		Maximum	460.0
	Change from Baseline at End of Treatment	n	34
		Mean	1.95
		SD	16.51
		Median	2.83
		Minimum	-49.7
		Maximum	27.7

SOURCE: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett’s correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

表 2.7.4.7-70　臨床的に重大な心電図の異常（203 試験）（安全性解析対象集団）

Description	Category	Japan (N=39) n (%)	Korea (N=16) n (%)	Total (N=55) n (%)
Number of patients with baseline and at least one post-baseline result of QTcF		39	16	55
Absolute QTcF (msec)	> 450 msec	5 (12.8)	0 (0.0)	5 (9.1)
	> 480 msec	1 (2.6)	0 (0.0)	1 (1.8)
	> 500 msec	0 (0.0)	0 (0.0)	0 (0.0)
Change from Baseline for QTcF	> 30 msec increase from baseline	5 (12.8)	3 (18.8)	8 (14.5)
	> 60 msec increase from baseline	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.8

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECG = electrocardiogram; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
Abnormal ECG results of average triplicate measurements are included in this analysis.
Absolute QTcF measurements only included post baseline measurements.

表 2.7.4.7-71　臨床的に重大な心電図の異常（201 試験）（安全性解析対象集団）

Description	Category	30 mg (N=7) n (%)	40 mg (N=7) n (%)	Total (N=14) n (%)
Number of patients with at least one post-baseline result of QTcF		7	7	14
Absolute QTcF (msec)	> 450 msec	3 (42.9%)	2 (28.6%)	5 (35.7%)
	> 480 msec	0 (0.0%)	1 (14.3%)	1 (7.1%)
	> 500 msec	0 (0.0%)	0 (0.0%)	0 (0.0%)
Change from Baseline for QTcF	> 30 msec increase from baseline	1 (14.3%)	3 (42.9%)	4 (28.6%)
	> 60 msec increase from baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.8.1
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort of the analysis set with data.
ECG = electrocardiogram; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as pre-dose of Day 1 of Cycle 1.

表 2.7.4.7-72　心電図パラメータの要約（210 試験）（安全性解析対象集団）

Parameter (unit)	Visit	Statistic	40 mg (N=23)
PR Interval (msec)	Baseline	n	23
		Mean	170.36
		SD	27.53
		Median	167.33
		Minimum	110.7
		Maximum	223.7
	Cycle1 Day1, 3.5hrs Post-dose	n	23
		Mean	175.81
		SD	24.61
		Median	178.33
		Minimum	124.7
		Maximum	226.0
	Change from Baseline at Cycle1 Day1, 3.5hrs Post-dose	n	23
		Mean	5.45
		SD	12.14
		Median	5.67
		Minimum	-21.0
		Maximum	38.0
	Cycle2 Day1, Pre-dose	n	14
		Mean	177.17
		SD	24.87
		Median	177.33
		Minimum	137.3
		Maximum	236.3

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
PR Interval (msec)	Change from Baseline at Cycle2 Day1, Pre-dose	n	14
		Mean	-6.45
		SD	9.04
		Median	-8.00
		Minimum	-19.3
		Maximum	12.7
	Cycle2 Day1, 3.5hrs Post-dose	n	12
		Mean	182.33
		SD	26.84
		Median	178.17
		Minimum	143.3
		Maximum	252.3
	Change from Baseline at Cycle2 Day1, 3.5hrs Post-dose	n	12
		Mean	-3.61
		SD	12.38
		Median	-7.00
		Minimum	-16.7
		Maximum	28.7
	Cycle3 Day1	n	7
		Mean	175.57
		SD	35.92
		Median	175.00
		Minimum	132.0
		Maximum	244.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
PR Interval (msec)	Change from Baseline at Cycle3 Day1	n	7
		Mean	-8.10
		SD	15.13
		Median	-14.00
		Minimum	-20.7
		Maximum	20.3
	Cycle4 Day1	n	5
		Mean	167.00
		SD	35.65
		Median	164.00
		Minimum	131.0
		Maximum	210.0
	Change from Baseline at Cycle4 Day1	n	5
		Mean	-15.13
		SD	14.07
		Median	-17.67
		Minimum	-31.7
		Maximum	7.0
	Cycle5 Day1	n	3
		Mean	187.33
		SD	15.04
		Median	186.00
		Minimum	173.0
		Maximum	203.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
PR Interval (msec)	Change from Baseline at Cycle5 Day1	n	3
		Mean	-10.78
		SD	9.02
		Median	-8.67
		Minimum	-20.7
		Maximum	-3.0
	Cycle6 Day1	n	3
		Mean	185.00
		SD	16.52
		Median	177.00
		Minimum	174.0
		Maximum	204.0
	Change from Baseline at Cycle6 Day1	n	3
		Mean	-13.11
		SD	6.08
		Median	-12.00
		Minimum	-19.7
		Maximum	-7.7
	Cycle7 Day1	n	3
		Mean	193.67
		SD	16.74
		Median	184.00
		Minimum	184.0
		Maximum	213.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
PR Interval (msec)	Change from Baseline at Cycle7 Day1	n	3
		Mean	-4.44
		SD	6.52
		Median	-5.00
		Minimum	-10.7
		Maximum	2.3
	Cycle8 Day1	n	3
		Mean	179.33
		SD	15.82
		Median	183.00
		Minimum	162.0
		Maximum	193.0
	Change from Baseline at Cycle8 Day1	n	3
		Mean	-18.78
		SD	12.36
		Median	-19.67
		Minimum	-30.7
		Maximum	-6.0
	Cycle9 Day1	n	3
		Mean	177.00
		SD	15.39
		Median	173.00
		Minimum	164.0
		Maximum	194.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
PR Interval (msec)	Change from Baseline at Cycle9 Day1	n	3
		Mean	-21.11
		SD	7.46
		Median	-17.67
		Minimum	-29.7
		Maximum	-16.0
	Cycle10 Day1	n	2
		Mean	180.00
		SD	21.21
		Median	180.00
		Minimum	165.0
		Maximum	195.0
	Change from Baseline at Cycle10 Day1	n	2
		Mean	-22.67
		SD	8.49
		Median	-22.67
		Minimum	-28.7
		Maximum	-16.7
	Cycle11 Day1	n	1
		Mean	163.00
		SD	-
		Median	163.00
		Minimum	163.0
		Maximum	163.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
PR Interval (msec)	Change from Baseline at Cycle11 Day1	n	1
		Mean	-18.67
		SD	-
		Median	-18.67
		Minimum	-18.7
		Maximum	-18.7
	Cycle12 Day1	n	1
		Mean	155.00
		SD	-
		Median	155.00
		Minimum	155.0
		Maximum	155.0
	Change from Baseline at Cycle12 Day1	n	1
		Mean	-26.67
		SD	-
		Median	-26.67
		Minimum	-26.7
		Maximum	-26.7
	Cycle13 Day1	n	1
		Mean	167.00
		SD	-
		Median	167.00
		Minimum	167.0
		Maximum	167.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
PR Interval (msec)	Change from Baseline at Cycle13 Day1	n	1
		Mean	-14.67
		SD	-
		Median	-14.67
		Minimum	-14.7
		Maximum	-14.7
	Cycle14 Day1	n	1
		Mean	152.00
		SD	-
		Median	152.00
		Minimum	152.0
		Maximum	152.0
	Change from Baseline at Cycle14 Day1	n	1
		Mean	-29.67
		SD	-
		Median	-29.67
		Minimum	-29.7
		Maximum	-29.7
	End of Treatment	n	18
		Mean	168.50
		SD	23.56
		Median	169.50
		Minimum	122.0
		Maximum	213.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
PR Interval (msec)	Change from Baseline at End of Treatment	n	18
		Mean	-8.57
		SD	13.58
		Median	-9.33
		Minimum	-43.0
		Maximum	14.0
QRS Duration (msec)	Baseline	n	23
		Mean	87.39
		SD	6.97
		Median	87.33
		Minimum	78.7
		Maximum	105.3
	Cycle1 Day1, 3.5hrs Post-dose	n	23
		Mean	88.74
		SD	6.79
		Median	91.33
		Minimum	73.7
		Maximum	100.7
	Change from Baseline at Cycle1 Day1, 3.5hrs Post-dose	n	23
		Mean	1.35
		SD	4.31
		Median	0.67
		Minimum	-5.0
		Maximum	9.3

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QRS Duration (msec)	Cycle2 Day1, Pre-dose	n	14
		Mean	87.10
		SD	5.30
		Median	87.00
		Minimum	79.3
		Maximum	96.3
	Change from Baseline at Cycle2 Day1, Pre-dose	n	14
		Mean	-1.33
		SD	6.26
		Median	-1.67
		Minimum	-10.3
		Maximum	10.3
	Cycle2 Day1, 3.5hrs Post-dose	n	12
		Mean	88.08
		SD	6.23
		Median	88.83
		Minimum	79.7
		Maximum	98.7
	Change from Baseline at Cycle2 Day1, 3.5hrs Post-dose	n	12
		Mean	-0.50
		SD	6.99
		Median	-3.00
		Minimum	-13.0
		Maximum	12.7

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QRS Duration (msec)	Cycle3 Day1	n	7
		Mean	87.71
		SD	6.63
		Median	89.00
		Minimum	78.0
		Maximum	98.0
	Change from Baseline at Cycle3 Day1	n	7
		Mean	-0.38
		SD	6.46
		Median	-4.00
		Minimum	-7.7
		Maximum	7.7
	Cycle4 Day1	n	5
		Mean	89.20
		SD	6.02
		Median	89.00
		Minimum	82.0
		Maximum	97.0
	Change from Baseline at Cycle4 Day1	n	5
		Mean	-1.20
		SD	6.17
		Median	-1.67
		Minimum	-10.0
		Maximum	7.3

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QRS Duration (msec)	Cycle5 Day1	n	3
		Mean	94.00
		SD	5.29
		Median	92.00
		Minimum	90.0
		Maximum	100.0
	Change from Baseline at Cycle5 Day1	n	3
		Mean	4.67
		SD	6.66
		Median	6.33
		Minimum	-2.7
		Maximum	10.3
	Cycle6 Day1	n	3
		Mean	90.67
		SD	1.15
		Median	90.00
		Minimum	90.0
		Maximum	92.0
	Change from Baseline at Cycle6 Day1	n	3
		Mean	1.33
		SD	4.58
		Median	0.33
		Minimum	-2.7
		Maximum	6.3

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QRS Duration (msec)	Cycle7 Day1	n	3
		Mean	86.33
		SD	3.51
		Median	86.00
		Minimum	83.0
		Maximum	90.0
	Change from Baseline at Cycle7 Day1	n	3
		Mean	-3.00
		SD	4.73
		Median	-4.67
		Minimum	-6.7
		Maximum	2.3
	Cycle8 Day1	n	3
		Mean	89.00
		SD	6.24
		Median	87.00
		Minimum	84.0
		Maximum	96.0
	Change from Baseline at Cycle8 Day1	n	3
		Mean	-0.33
		SD	4.73
		Median	1.33
		Minimum	-5.7
		Maximum	3.3

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QRS Duration (msec)	Cycle9 Day1	n	3
		Mean	89.00
		SD	3.00
		Median	89.00
		Minimum	86.0
		Maximum	92.0
	Change from Baseline at Cycle9 Day1	n	3
		Mean	-0.33
		SD	2.52
		Median	-0.67
		Minimum	-2.7
		Maximum	2.3
	Cycle10 Day1	n	2
		Mean	86.50
		SD	9.19
		Median	86.50
		Minimum	80.0
		Maximum	93.0
	Change from Baseline at Cycle10 Day1	n	2
		Mean	-2.67
		SD	1.41
		Median	-2.67
		Minimum	-3.7
		Maximum	-1.7

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QRS Duration (msec)	Cycle11 Day1	n	1
		Mean	85.00
		SD	-
		Median	85.00
		Minimum	85.0
		Maximum	85.0
	Change from Baseline at Cycle11 Day1	n	1
		Mean	1.33
		SD	-
		Median	1.33
		Minimum	1.3
		Maximum	1.3
	Cycle12 Day1	n	1
		Mean	94.00
		SD	-
		Median	94.00
		Minimum	94.0
		Maximum	94.0
	Change from Baseline at Cycle12 Day1	n	1
		Mean	10.33
		SD	-
		Median	10.33
		Minimum	10.3
		Maximum	10.3

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QRS Duration (msec)	Cycle13 Day1	n	1
		Mean	87.00
		SD	-
		Median	87.00
		Minimum	87.0
		Maximum	87.0
	Change from Baseline at Cycle13 Day1	n	1
		Mean	3.33
		SD	-
		Median	3.33
		Minimum	3.3
		Maximum	3.3
	Cycle14 Day1	n	1
		Mean	88.00
		SD	-
		Median	88.00
		Minimum	88.0
		Maximum	88.0
	Change from Baseline at Cycle14 Day1	n	1
		Mean	4.33
		SD	-
		Median	4.33
		Minimum	4.3
		Maximum	4.3

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QRS Duration (msec)	End of Treatment	n	18
		Mean	86.00
		SD	6.96
		Median	87.00
		Minimum	74.0
		Maximum	102.0
	Change from Baseline at End of Treatment	n	18
		Mean	-1.20
		SD	6.14
		Median	-3.00
		Minimum	-8.7
		Maximum	12.3
QT Interval (msec)	Baseline	n	23
		Mean	381.54
		SD	44.65
		Median	382.67
		Minimum	312.3
		Maximum	484.7
	Cycle1 Day1, 3.5hrs Post-dose	n	23
		Mean	380.87
		SD	42.75
		Median	392.67
		Minimum	317.0
		Maximum	487.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QT Interval (msec)	Change from Baseline at Cycle1 Day1, 3.5hrs Post-dose	n	23
		Mean	-0.67
		SD	13.67
		Median	3.00
		Minimum	-31.3
		Maximum	16.0
	Cycle2 Day1, Pre-dose	n	14
		Mean	392.81
		SD	49.42
		Median	384.00
		Minimum	290.0
		Maximum	471.3
	Change from Baseline at Cycle2 Day1, Pre-dose	n	14
		Mean	-5.52
		SD	28.21
		Median	-2.00
		Minimum	-58.0
		Maximum	42.3
	Cycle2 Day1, 3.5hrs Post-dose	n	12
		Mean	386.78
		SD	53.21
		Median	382.67
		Minimum	289.0
		Maximum	473.3

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QT Interval (msec)	Change from Baseline at Cycle2 Day1, 3.5hrs Post-dose	n	12
		Mean	-17.75
		SD	30.23
		Median	-14.00
		Minimum	-64.7
		Maximum	27.0
	Cycle3 Day1	n	7
		Mean	399.29
		SD	54.02
		Median	384.00
		Minimum	335.0
		Maximum	484.0
	Change from Baseline at Cycle3 Day1	n	7
		Mean	-6.00
		SD	30.87
		Median	1.33
		Minimum	-53.0
		Maximum	39.3
	Cycle4 Day1	n	5
		Mean	407.60
		SD	63.86
		Median	375.00
		Minimum	342.0
		Maximum	488.0

Source: Listing 16 2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QT Interval (msec)	Change from Baseline at Cycle4 Day1	n	5
		Mean	0.53
		SD	32.87
		Median	7.00
		Minimum	-46.0
		Maximum	43.3
	Cycle5 Day1	n	3
		Mean	431.33
		SD	46.20
		Median	457.00
		Minimum	378.0
		Maximum	459.0
	Change from Baseline at Cycle5 Day1	n	3
		Mean	9.78
		SD	5.93
		Median	12.33
		Minimum	3.0
		Maximum	14.0
	Cycle6 Day1	n	3
		Mean	421.67
		SD	54.60
		Median	431.00
		Minimum	363.0
		Maximum	471.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QT Interval (msec)	Change from Baseline at Cycle6 Day1	n	3
		Mean	0.11
		SD	14.37
		Median	-1.00
		Minimum	-13.7
		Maximum	15.0
	Cycle7 Day1	n	3
		Mean	443.33
		SD	30.55
		Median	450.00
		Minimum	410.0
		Maximum	470.0
	Change from Baseline at Cycle7 Day1	n	3
		Mean	21.78
		SD	21.42
		Median	14.00
		Minimum	5.3
		Maximum	46.0
	Cycle8 Day1	n	3
		Mean	420.67
		SD	41.88
		Median	433.00
		Minimum	374.0
		Maximum	455.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QT Interval (msec)	Change from Baseline at Cycle8 Day1	n	3
		Mean	-0.89
		SD	10.83
		Median	-1.00
		Minimum	-11.7
		Maximum	10.0
	Cycle9 Day1	n	3
		Mean	427.67
		SD	46.49
		Median	445.00
		Minimum	375.0
		Maximum	463.0
	Change from Baseline at Cycle9 Day1	n	3
		Mean	6.11
		SD	5.39
		Median	7.00
		Minimum	0.3
		Maximum	11.0
	Cycle10 Day1	n	2
		Mean	405.50
		SD	67.18
		Median	405.50
		Minimum	358.0
		Maximum	453.0

Source: Listing 16 2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QT Interval (msec)	Change from Baseline at Cycle10 Day1	n	2
		Mean	-4.50
		SD	2.12
		Median	-4.50
		Minimum	-6.0
		Maximum	-3.0
	Cycle11 Day1	n	1
		Mean	368.00
		SD	-
		Median	368.00
		Minimum	368.0
		Maximum	368.0
	Change from Baseline at Cycle11 Day1	n	1
		Mean	4.00
		SD	-
		Median	4.00
		Minimum	4.0
		Maximum	4.0
	Cycle12 Day1	n	1
		Mean	382.00
		SD	-
		Median	382.00
		Minimum	382.0
		Maximum	382.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QT Interval (msec)	Change from Baseline at Cycle12 Day1	n	1
		Mean	18.00
		SD	-
		Median	18.00
		Minimum	18.0
		Maximum	18.0
	Cycle13 Day1	n	1
		Mean	405.00
		SD	-
		Median	405.00
		Minimum	405.0
		Maximum	405.0
	Change from Baseline at Cycle13 Day1	n	1
		Mean	41.00
		SD	-
		Median	41.00
		Minimum	41.0
		Maximum	41.0
	Cycle14 Day1	n	1
		Mean	391.00
		SD	-
		Median	391.00
		Minimum	391.0
		Maximum	391.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QT Interval (msec)	Change from Baseline at Cycle14 Day1	n	1
		Mean	27.00
		SD	-
		Median	27.00
		Minimum	27.0
		Maximum	27.0
	End of Treatment	n	18
		Mean	369.89
		SD	46.54
		Median	362.50
		Minimum	294.0
		Maximum	453.0
	Change from Baseline at End of Treatment	n	18
		Mean	-18.48
		SD	25.32
		Median	-16.83
		Minimum	-71.0
		Maximum	36.3
QTcB Interval (msec)	Baseline	n	23
		Mean	424.74
		SD	22.12
		Median	425.33
		Minimum	384.3
		Maximum	464.7

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcB Interval (msec)	Cycle1 Day1, 3.5hrs Post-dose	n	23
		Mean	423.36
		SD	23.48
		Median	427.00
		Minimum	378.3
		Maximum	481.0
	Change from Baseline at Cycle1 Day1, 3.5hrs Post-dose	n	23
		Mean	-1.38
		SD	16.14
		Median	-4.67
		Minimum	-34.7
		Maximum	35.7
	Cycle2 Day1, Pre-dose	n	14
		Mean	416.95
		SD	23.07
		Median	418.83
		Minimum	365.0
		Maximum	452.0
	Change from Baseline at Cycle2 Day1, Pre-dose	n	14
		Mean	-5.43
		SD	16.44
		Median	-7.33
		Minimum	-27.7
		Maximum	29.7

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcB Interval (msec)	Cycle2 Day1, 3.5hrs Post-dose	n	12
		Mean	413.42
		SD	25.89
		Median	410.17
		Minimum	362.3
		Maximum	456.3
	Change from Baseline at Cycle2 Day1, 3.5hrs Post-dose	n	12
		Mean	-5.56
		SD	20.05
		Median	-14.17
		Minimum	-26.0
		Maximum	34.7
	Cycle3 Day1	n	7
		Mean	420.86
		SD	16.46
		Median	426.00
		Minimum	397.0
		Maximum	446.0
	Change from Baseline at Cycle3 Day1	n	7
		Mean	4.24
		SD	21.13
		Median	9.00
		Minimum	-20.7
		Maximum	26.7

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcB Interval (msec)	Cycle4 Day1	n	5
		Mean	416.40
		SD	19.62
		Median	411.00
		Minimum	393.0
		Maximum	445.0
	Change from Baseline at Cycle4 Day1	n	5
		Mean	0.80
		SD	16.33
		Median	-1.67
		Minimum	-14.7
		Maximum	24.7
	Cycle5 Day1	n	3
		Mean	410.00
		SD	24.88
		Median	415.00
		Minimum	383.0
		Maximum	432.0
	Change from Baseline at Cycle5 Day1	n	3
		Mean	6.56
		SD	19.41
		Median	-1.33
		Minimum	-7.7
		Maximum	28.7

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcB Interval (msec)	Cycle6 Day1	n	3
		Mean	392.33
		SD	37.21
		Median	384.00
		Minimum	360.0
		Maximum	433.0
	Change from Baseline at Cycle6 Day1	n	3
		Mean	-11.11
		SD	11.65
		Median	-6.67
		Minimum	-24.3
		Maximum	-2.3
	Cycle7 Day1	n	3
		Mean	428.67
		SD	43.09
		Median	451.00
		Minimum	379.0
		Maximum	456.0
	Change from Baseline at Cycle7 Day1	n	3
		Mean	25.22
		SD	35.84
		Median	16.33
		Minimum	-5.3
		Maximum	64.7

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcB Interval (msec)	Cycle8 Day1	n	3
		Mean	416.67
		SD	10.02
		Median	416.00
		Minimum	407.0
		Maximum	427.0
	Change from Baseline at Cycle8 Day1	n	3
		Mean	13.22
		SD	22.69
		Median	22.67
		Minimum	-12.7
		Maximum	29.7
	Cycle9 Day1	n	3
		Mean	418.33
		SD	17.04
		Median	417.00
		Minimum	402.0
		Maximum	436.0
	Change from Baseline at Cycle9 Day1	n	3
		Mean	14.89
		SD	18.18
		Median	15.67
		Minimum	-3.7
		Maximum	32.7

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcB Interval (msec)	Cycle10 Day1	n	2
		Mean	419.50
		SD	26.16
		Median	419.50
		Minimum	401.0
		Maximum	438.0
	Change from Baseline at Cycle10 Day1	n	2
		Mean	6.50
		SD	11.55
		Median	6.50
		Minimum	-1.7
		Maximum	14.7
	Cycle11 Day1	n	1
		Mean	399.00
		SD	-
		Median	399.00
		Minimum	399.0
		Maximum	399.0
	Change from Baseline at Cycle11 Day1	n	1
		Mean	12.67
		SD	-
		Median	12.67
		Minimum	12.7
		Maximum	12.7

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcB Interval (msec)	Cycle12 Day1	n	1
		Mean	420.00
		SD	-
		Median	420.00
		Minimum	420.0
		Maximum	420.0
	Change from Baseline at Cycle12 Day1	n	1
		Mean	33.67
		SD	-
		Median	33.67
		Minimum	33.7
		Maximum	33.7
	Cycle13 Day1	n	1
		Mean	434.00
		SD	-
		Median	434.00
		Minimum	434.0
		Maximum	434.0
	Change from Baseline at Cycle13 Day1	n	1
		Mean	47.67
		SD	-
		Median	47.67
		Minimum	47.7
		Maximum	47.7

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcB Interval (msec)	Cycle14 Day1	n	1
		Mean	459.00
		SD	-
		Median	459.00
		Minimum	459.0
		Maximum	459.0
	Change from Baseline at Cycle14 Day1	n	1
		Mean	72.67
		SD	-
		Median	72.67
		Minimum	72.7
		Maximum	72.7
	End of Treatment	n	18
		Mean	422.22
		SD	20.10
		Median	421.50
		Minimum	383.0
		Maximum	454.0
	Change from Baseline at End of Treatment	n	18
		Mean	-3.91
		SD	27.23
		Median	-11.83
		Minimum	-35.3
		Maximum	67.7

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcF Interval (msec)	Baseline	n	23
		Mean	409.09
		SD	21.69
		Median	409.67
		Minimum	366.0
		Maximum	458.0
	Cycle1 Day1, 3.5hrs Post-dose	n	23
		Mean	408.03
		SD	23.70
		Median	410.00
		Minimum	359.0
		Maximum	483.0
	Change from Baseline at Cycle1 Day1, 3.5hrs Post-dose	n	23
		Mean	-1.06
		SD	12.21
		Median	-2.00
		Minimum	-31.0
		Maximum	25.0
	Cycle2 Day1, Pre-dose	n	14
		Mean	408.12
		SD	25.34
		Median	413.17
		Minimum	338.3
		Maximum	436.3

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcF Interval (msec)	Change from Baseline at Cycle2 Day1, Pre-dose	n	14
		Mean	-5.52
		SD	18.49
		Median	-6.50
		Minimum	-35.0
		Maximum	27.7
	Cycle2 Day1, 3.5hrs Post-dose	n	12
		Mean	403.64
		SD	29.02
		Median	410.50
		Minimum	335.7
		Maximum	435.3
	Change from Baseline at Cycle2 Day1, 3.5hrs Post-dose	n	12
		Mean	-10.00
		SD	19.45
		Median	-13.50
		Minimum	-37.0
		Maximum	23.0
	Cycle3 Day1	n	7
		Mean	413.00
		SD	20.49
		Median	412.00
		Minimum	388.0
		Maximum	440.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcF Interval (msec)	Change from Baseline at Cycle3 Day1	n	7
		Mean	0.67
		SD	20.06
		Median	-5.00
		Minimum	-25.3
		Maximum	30.7
	Cycle4 Day1	n	5
		Mean	412.40
		SD	20.44
		Median	419.00
		Minimum	385.0
		Maximum	437.0
	Change from Baseline at Cycle4 Day1	n	5
		Mean	0.27
		SD	19.21
		Median	-5.33
		Minimum	-24.7
		Maximum	20.7
	Cycle5 Day1	n	3
		Mean	416.33
		SD	21.46
		Median	406.00
		Minimum	402.0
		Maximum	441.0

Source: Listing 16 2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcF Interval (msec)	Change from Baseline at Cycle5 Day1	n	3
		Mean	7.44
		SD	14.44
		Median	2.67
		Minimum	-4.0
		Maximum	23.7
	Cycle6 Day1	n	3
		Mean	401.33
		SD	37.90
		Median	382.00
		Minimum	377.0
		Maximum	445.0
	Change from Baseline at Cycle6 Day1	n	3
		Mean	-7.56
		SD	11.95
		Median	-1.33
		Minimum	-21.3
		Maximum	0.0
	Cycle7 Day1	n	3
		Mean	433.00
		SD	30.20
		Median	437.00
		Minimum	401.0
		Maximum	461.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcF Interval (msec)	Change from Baseline at Cycle7 Day1	n	3
		Mean	24.11
		SD	31.30
		Median	16.00
		Minimum	-2.3
		Maximum	58.7
	Cycle8 Day1	n	3
		Mean	418.00
		SD	17.09
		Median	416.00
		Minimum	402.0
		Maximum	436.0
	Change from Baseline at Cycle8 Day1	n	3
		Mean	9.11
		SD	16.62
		Median	12.67
		Minimum	-9.0
		Maximum	23.7
	Cycle9 Day1	n	3
		Mean	421.33
		SD	26.31
		Median	426.00
		Minimum	393.0
		Maximum	445.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcF Interval (msec)	Change from Baseline at Cycle9 Day1	n	3
		Mean	12.44
		SD	11.50
		Median	14.67
		Minimum	0.0
		Maximum	22.7
	Cycle10 Day1	n	2
		Mean	414.50
		SD	40.31
		Median	414.50
		Minimum	386.0
		Maximum	443.0
	Change from Baseline at Cycle10 Day1	n	2
		Mean	2.83
		SD	6.84
		Median	2.83
		Minimum	-2.0
		Maximum	7.7
	Cycle11 Day1	n	1
		Mean	389.00
		SD	-
		Median	389.00
		Minimum	389.0
		Maximum	389.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcF Interval (msec)	Change from Baseline at Cycle11 Day1	n	1
		Mean	10.67
		SD	-
		Median	10.67
		Minimum	10.7
		Maximum	10.7
	Cycle12 Day1	n	1
		Mean	407.00
		SD	-
		Median	407.00
		Minimum	407.0
		Maximum	407.0
	Change from Baseline at Cycle12 Day1	n	1
		Mean	28.67
		SD	-
		Median	28.67
		Minimum	28.7
		Maximum	28.7
	Cycle13 Day1	n	1
		Mean	424.00
		SD	-
		Median	424.00
		Minimum	424.0
		Maximum	424.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcF Interval (msec)	Change from Baseline at Cycle13 Day1	n	1
		Mean	45.67
		SD	-
		Median	45.67
		Minimum	45.7
		Maximum	45.7
	Cycle14 Day1	n	1
		Mean	435.00
		SD	-
		Median	435.00
		Minimum	435.0
		Maximum	435.0
	Change from Baseline at Cycle14 Day1	n	1
		Mean	56.67
		SD	-
		Median	56.67
		Minimum	56.7
		Maximum	56.7
	End of Treatment	n	18
		Mean	403.28
		SD	24.45
		Median	404.00
		Minimum	351.0
		Maximum	448.0

Source: Listing 16.2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Parameter (unit)	Visit	Statistic	40 mg (N=23)
QTcF Interval (msec)	Change from Baseline at End of Treatment	n	18
		Mean	-9.15
		SD	19.84
		Median	-13.67
		Minimum	-33.3
		Maximum	47.7

Source: Listing 16 2.8

ECG = electrocardiogram; QTcB = QT interval using Bazett's correction formula; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

表 2.7.4.7-73　臨床的に重大な心電図の異常（210 試験）（安全性解析対象集団）

Description	Category	40 mg (N=23) n (%)
Number of patients with baseline and at least one post-baseline result of QTcF		23
Absolute QTcF (msec)	> 450 msec	3 (13.0%)
	> 480 msec	1 (4.3%)
	> 500 msec	0 (0.0%)
Change from Baseline for QTcF	> 30 msec increase from baseline	2 (8.7%)
	> 60 msec increase from baseline	0 (0.0%)

Source: Listing 16.2.8

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set with data;
ECG = electrocardiogram; QTcF = QT interval using Fridericia's correction formula.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).
Abnormal ECG results of average triplicate measurements are included in this analysis.
Absolute QTcF measurements only included post baseline measurements.

表 2.7.4.7-74　ECOG PS の評価（203 試験）（安全性解析対象集団）

Country: Japan (N=39)

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle2 Day1	Total	22 (64.7)	12 (35.3)	0 (0.0)	0 (0.0)	0 (0.0)	34 (100.0)
	0	22 (64.7)	2 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	24 (70.6)
	1	0 (0.0)	8 (23.5)	0 (0.0)	0 (0.0)	0 (0.0)	8 (23.5)
	2	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
	3	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle3 Day1	Total	17 (65.4)	9 (34.6)	0 (0.0)	0 (0.0)	0 (0.0)	26 (100.0)
	0	16 (61.5)	4 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	20 (76.9)
	1	1 (3.8)	5 (19.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (23.1)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle4 Day1	Total	16 (76.2)	5 (23.8)	0 (0.0)	0 (0.0)	0 (0.0)	21 (100.0)
	0	15 (71.4)	3 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	18 (85.7)
	1	1 (4.8)	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (14.3)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle5 Day1	Total	14 (82.4)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	17 (100.0)
	0	14 (82.4)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	15 (88.2)
	1	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2 11.1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Japan (N=39)

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle6 Day1	Total	10 (83.3)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	12 (100.0)
	0	10 (83.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (83.3)
	1	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle7 Day1	Total	9 (81.8)	2 (18.2)	0 (0.0)	0 (0.0)	0 (0.0)	11 (100.0)
	0	8 (72.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (72.7)
	1	1 (9.1)	2 (18.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (27.3)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle8 Day1	Total	7 (77.8)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100.0)
	0	6 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)
	1	1 (11.1)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle9 Day1	Total	6 (75.0)	2 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (100.0)
	0	5 (62.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (62.5)
	1	1 (12.5)	2 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (37.5)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16 2 11.1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Japan (N=39)

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle10 Day1	Total	4 (80.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100.0)
	0	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)
	1	1 (20.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle11 Day1	Total	4 (80.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100.0)
	0	4 (80.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (80.0)
	1	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle12 Day1	Total	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	0	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle13 Day1	Total	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	0	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Japan (N=39)

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle14 Day1	Total	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	0	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle15 Day1	Total	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	0	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle16 Day1	Total	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	0	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle17 Day1	Total	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	0	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Japan (N=39)

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle18 Day1	Total	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	0	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle19 Day1	Total	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	0	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle20 Day1	Total	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	0	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle21 Day1	Total	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	0	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Japan (N=39)

Visit		ECOG Performance Status Assessment at Baseline n (%) 0	1	2	3	4	Total
End of Treatment	Total	19 (65.5)	10 (34.5)	0 (0.0)	0 (0.0)	0 (0.0)	29 (100.0)
	0	14 (48.3)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	16 (55.2)
	1	4 (13.8)	4 (13.8)	0 (0.0)	0 (0.0)	0 (0.0)	8 (27.6)
	2	1 (3.4)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.9)
	3	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.9)
	4	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Korea (N=16)

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle2 Day1	Total	2 (16.7)	9 (75.0)	1 (8.3)	0 (0.0)	0 (0.0)	12 (100.0)
	0	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
	1	2 (16.7)	8 (66.7)	1 (8.3)	0 (0.0)	0 (0.0)	11 (91.7)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle3 Day1	Total	1 (12.5)	7 (87.5)	0 (0.0)	0 (0.0)	0 (0.0)	8 (100.0)
	0	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
	1	1 (12.5)	6 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (87.5)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle4 Day1	Total	1 (20.0)	4 (80.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100.0)
	0	0 (0.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)
	1	1 (20.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle5 Day1	Total	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	0	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
	1	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Korea (N=16)

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle6 Day1	Total	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	0	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
	1	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle7 Day1	Total	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	0	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
	1	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle8 Day1	Total	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	0	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
	1	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle9 Day1	Total	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	0	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
	1	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Korea (N=16)

Visit		ECOG Performance Status Assessment at Baseline n (%) 0	1	2	3	4	Total
Cycle10 Day1	Total	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	0	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
	1	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle11 Day1	Total	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	0	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
	1	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle12 Day1	Total	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	0	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
	1	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle13 Day1	Total	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	0	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Korea (N=16)

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle14 Day1	Total	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	0	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle15 Day1	Total	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	0	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle16 Day1	Total	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	0	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle17 Day1	Total	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	0	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Korea (N=16)

Visit		ECOG Performance Status Assessment at Baseline n (%) 0	1	2	3	4	Total
End of Treatment	Total	1 (12.5)	6 (75.0)	1 (12.5)	0 (0.0)	0 (0.0)	8 (100.0)
	0	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
	1	1 (12.5)	5 (62.5)	1 (12.5)	0 (0.0)	0 (0.0)	7 (87.5)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Overall (N=55)

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle2 Day1	Total	24 (52.2)	21 (45.7)	1 (2.2)	0 (0.0)	0 (0.0)	46 (100.0)
	0	22 (47.8)	3 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	25 (54.3)
	1	2 (4.3)	16 (34.8)	1 (2.2)	0 (0.0)	0 (0.0)	19 (41.3)
	2	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
	3	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle3 Day1	Total	18 (52.9)	16 (47.1)	0 (0.0)	0 (0.0)	0 (0.0)	34 (100.0)
	0	16 (47.1)	5 (14.7)	0 (0.0)	0 (0.0)	0 (0.0)	21 (61.8)
	1	2 (5.9)	11 (32.4)	0 (0.0)	0 (0.0)	0 (0.0)	13 (38.2)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle4 Day1	Total	17 (65.4)	9 (34.6)	0 (0.0)	0 (0.0)	0 (0.0)	26 (100.0)
	0	15 (57.7)	5 (19.2)	0 (0.0)	0 (0.0)	0 (0.0)	20 (76.9)
	1	2 (7.7)	4 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	6 (23.1)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle5 Day1	Total	15 (75.0)	5 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	20 (100.0)
	0	14 (70.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (80.0)
	1	1 (5.0)	3 (15.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (20.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Overall (N=55)

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle6 Day1	Total	11 (73.3)	4 (26.7)	0 (0.0)	0 (0.0)	0 (0.0)	15 (100.0)
	0	10 (66.7)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	11 (73.3)
	1	1 (6.7)	3 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (26.7)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle7 Day1	Total	10 (71.4)	4 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	14 (100.0)
	0	8 (57.1)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	9 (64.3)
	1	2 (14.3)	3 (21.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (35.7)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle8 Day1	Total	8 (66.7)	4 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	12 (100.0)
	0	6 (50.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	7 (58.3)
	1	2 (16.7)	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (41.7)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle9 Day1	Total	7 (63.6)	4 (36.4)	0 (0.0)	0 (0.0)	0 (0.0)	11 (100.0)
	0	5 (45.5)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	6 (54.5)
	1	2 (18.2)	3 (27.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (45.5)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Overall (N=55)

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle10 Day1	Total	5 (71.4)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	7 (100.0)
	0	3 (42.9)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (57.1)
	1	2 (28.6)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (42.9)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle11 Day1	Total	5 (71.4)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	7 (100.0)
	0	4 (57.1)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (71.4)
	1	1 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle12 Day1	Total	4 (80.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100.0)
	0	3 (60.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (80.0)
	1	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle13 Day1	Total	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	0	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Overall (N=55)

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle14 Day1	Total	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	0	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle15 Day1	Total	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	0	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle16 Day1	Total	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	0	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle17 Day1	Total	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	0	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Overall (N=55)

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle18 Day1	Total	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	0	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle19 Day1	Total	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	0	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle20 Day1	Total	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	0	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle21 Day1	Total	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	0	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Country: Overall (N=55)

Visit		ECOG Performance Status Assessment at Baseline n (%) 0	1	2	3	4	Total
End of Treatment	Total	20 (54.1)	16 (43.2)	1 (2.7)	0 (0.0)	0 (0.0)	37 (100.0)
	0	14 (37.8)	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)	17 (45.9)
	1	5 (13.5)	9 (24.3)	1 (2.7)	0 (0.0)	0 (0.0)	15 (40.5)
	2	1 (2.7)	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.4)
	3	0 (0.0)	2 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.4)
	4	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)

Source: Listing 16.2.11 1

N = number of subjects in the Safety Analysis Set by country.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a country in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

表 2.7.4.7-75　ECOG PS の評価（201 試験）（安全性解析対象集団）

Visit	ECOG Performance Status Assessment	30 mg	40 mg	Total
		n (%)	n (%)	n (%)
Screening	N	7	7	14
	0	4 (57.1%)	4 (57.1%)	8 (57.1%)
	1	3 (42.9%)	3 (42.9%)	6 (42.9%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)
Baseline	N	7	7	14
	0	4 (57.1%)	5 (71.4%)	9 (64.3%)
	1	3 (42.9%)	2 (28.6%)	5 (35.7%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle2 Day1 Pre-dose	N	4	6	10
	0	2 (50.0%)	5 (83.3%)	7 (70.0%)
	1	2 (50.0%)	1 (16.7%)	3 (30.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.13.1
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort with data.
ECOG = Eastern Cooperative Oncology Group
Baseline is defined as pre-dose of Day 1 of Cycle 1.

Visit	ECOG Performance Status Assessment	30 mg	40 mg	Total
		n (%)	n (%)	n (%)
Cycle3 Day1 Pre-dose	N	2	3	5
	0	1 (50.0%)	2 (66.7%)	3 (60.0%)
	1	1 (50.0%)	1 (33.3%)	2 (40.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle4 Day1 Pre-dose	N	2	3	5
	0	1 (50.0%)	2 (66.7%)	3 (60.0%)
	1	1 (50.0%)	1 (33.3%)	2 (40.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle5 Day1 Pre-dose	N	1	2	3
	0	1 (100.0%)	1 (50.0%)	2 (66.7%)
	1	0 (0.0%)	1 (50.0%)	1 (33.3%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.13.1
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort with data.
ECOG = Eastern Cooperative Oncology Group
Baseline is defined as pre-dose of Day 1 of Cycle 1.

Visit	ECOG Performance Status Assessment	30 mg	40 mg	Total
		n (%)	n (%)	n (%)
Cycle6 Day1 Pre-dose	N	0	2	2
	0	-	2 (100.0%)	2 (100.0%)
	1	-	0 (0.0%)	0 (0.0%)
	2	-	0 (0.0%)	0 (0.0%)
	3	-	0 (0.0%)	0 (0.0%)
	4	-	0 (0.0%)	0 (0.0%)
Cycle7 Day1 Pre-dose	N	0	1	1
	0	-	0 (0.0%)	0 (0.0%)
	1	-	1 (100.0%)	1 (100.0%)
	2	-	0 (0.0%)	0 (0.0%)
	3	-	0 (0.0%)	0 (0.0%)
	4	-	0 (0.0%)	0 (0.0%)
End-of-Study	N	4	6	10
	0	3 (75.0%)	4 (66.7%)	7 (70.0%)
	1	0 (0.0%)	2 (33.3%)	2 (20.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	1 (25.0%)	0 (0.0%)	1 (10.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)

SOURCE: Listing 16.2.13.1
n = number of patients; % = percentage of patients calculated relative to the total number of patients in each cohort with data.
ECOG = Eastern Cooperative Oncology Group
Baseline is defined as pre-dose of Day 1 of Cycle 1.

表 2.7.4.7-76　ECOG PS の評価（210 試験）（安全性解析対象集団）

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle2 Day1	Total	10 (71.4%)	3 (21.4%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	14 (100.0%)
	0	7 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (50.0%)
	1	3 (21.4%)	3 (21.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (42.9%)
	2	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle3 Day1	Total	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100.0%)
	0	3 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (42.9%)
	1	4 (57.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (57.1%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle4 Day1	Total	5 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (100.0%)
	0	2 (40.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)
	1	2 (40.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)
	2	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle5 Day1	Total	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (100.0%)
	0	2 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (66.7%)
	1	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.11 1

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle6 Day1	Total	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (100.0%)
	0	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
	1	2 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (66.7%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle7 Day1	Total	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (100.0%)
	0	2 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (66.7%)
	1	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle8 Day1	Total	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (100.0%)
	0	2 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (66.7%)
	1	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle9 Day1	Total	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (100.0%)
	0	2 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (66.7%)
	1	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.11 1

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle10 Day1	Total	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)
	0	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
	1	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle11 Day1	Total	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle12 Day1	Total	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle13 Day1	Total	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Listing 16.2.11 1

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

Visit		ECOG Performance Status Assessment at Baseline n (%)					
		0	1	2	3	4	Total
Cycle14 Day1	Total	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
End of Treatment	Total	11 (52.4%)	9 (42.9%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	21 (100.0%)
	0	4 (19.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (19.0%)
	1	4 (19.0%)	3 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (33.3%)
	2	3 (14.3%)	3 (14.3%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	7 (33.3%)
	3	0 (0.0%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
	4	0 (0.0%)	2 (9.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.5%)

Source: Listing 16.2.11 1

n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in the analysis set with data;
ECOG = Eastern Cooperative Oncology Group.
Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

表 2.7.4.7-77　性別（男性、女性）の有害事象の概要（203 試験）（安全性解析対象集団）

Sex: Male

Description	40 mg (N=35) n (%)
Number of subjects with	
At least one TEAE	35 (100.0)
At least one TEAE related to the study drug	33 (94.3)
At least one serious TEAE	12 (34.3)
At least one serious TEAE related to the study drug	9 (25.7)
At least one TEAE leading to dose reduction or interruption	27 (77.1)
At least one TEAE leading to study drug discontinuation	11 (31.4)
At least one TEAE leading to death	1 (2.9)
At least one TEAE with grade 3 or higher	28 (80.0)
At least one TEAE with grade 3 or higher and related to the study drug	26 (74.3)

Source: Listing 16.2.6 1 and 16 2.4.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE.　For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

Sex: Female

Description	40 mg (N=20) n (%)
Number of subjects with	
At least one TEAE	20 (100.0)
At least one TEAE related to the study drug	18 (90.0)
At least one serious TEAE	2 (10.0)
At least one serious TEAE related to the study drug	1 (5.0)
At least one TEAE leading to dose reduction or interruption	13 (65.0)
At least one TEAE leading to study drug discontinuation	7 (35.0)
At least one TEAE leading to death	0 (0.0)
At least one TEAE with grade 3 or higher	18 (90.0)
At least one TEAE with grade 3 or higher and related to the study drug	16 (80.0)

Source: Listing 16.2.6 1 and 16 2.4.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

表 2.7.4.7-78　性別（男性、女性）の有害事象の発現割合（203 試験）（安全性解析対象集団）

System organ class Preferred term	Male (N=35) n (%)	Female (N=20) n (%)
Number of subjects with at least one TEAE	35(100.0)	20(100.0)
血液およびリンパ系障害	33(94.3)	19(95.0)
貧血*	8(22.9)	10(50.0)
再生不良性貧血	0	1(5.0)
好酸球増加症	1(2.9)	0
発熱性好中球減少症	3(8.6)	0
白血球減少症*	13(37.1)	11(55.0)
リンパ球減少症*	10(28.6)	6(30.0)
好中球減少症*	19(54.3)	12(60.0)
血小板減少症*	30(85.7)	16(80.0)
心臓障害	5(14.3)	2(10.0)
不安定狭心症	1(2.9)	0
不整脈	1(2.9)	0
心房細動	2(5.7)	0
動悸	2(5.7)	1(5.0)
心嚢液貯留	0	1(5.0)
耳および迷路障害	2(5.7)	0
耳痛	1(2.9)	0
回転性めまい	1(2.9)	0

Source: Listing 16 2.6.1 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Male (N=35) n (%)	Female (N=20) n (%)
眼障害	3(8.6)	2(10.0)
白内障	1(2.9)	0
結膜出血	0	1(5.0)
ドライアイ	1(2.9)	0
角膜炎	1(2.9)	0
霧視	0	1(5.0)

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Male (N=35) n (%)	Female (N=20) n (%)
胃腸障害	21(60.0)	11(55.0)
腹部不快感	1(2.9)	0
腹痛	3(8.6)	0
上腹部痛	1(2.9)	1(5.0)
肛門出血	0	1(5.0)
便秘	1(2.9)	0
齲歯	2(5.7)	0
下痢	12(34.3)	5(25.0)
消化不良	1(2.9)	0
心窩部不快感	1(2.9)	0
胃潰瘍	1(2.9)	0
胃炎	0	1(5.0)
痔出血	1(2.9)	0
悪心	7(20.0)	5(25.0)
口腔粘膜血腫	1(2.9)	0
口内炎	1(2.9)	1(5.0)
歯痛	0	1(5.0)
嘔吐	1(2.9)	2(10.0)

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Male (N=35) n (%)	Female (N=20) n (%)
一般・全身障害および投与部位の状態	16(45.7)	11(55.0)
無力症	1(2.9)	1(5.0)
カテーテル留置部位腫脹	0	1(5.0)
胸部不快感	0	1(5.0)
胸痛	1(2.9)	0
溢出	1(2.9)	0
疲労	3(8.6)	3(15.0)
歩行障害	0	1(5.0)
インフルエンザ様疾患	0	2(10.0)
倦怠感	6(17.1)	2(10.0)
末梢性浮腫	3(8.6)	1(5.0)
発熱	7(20.0)	4(20.0)
口渇	0	1(5.0)
免疫系障害	1(2.9)	0
薬物過敏症	1(2.9)	0

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Male (N=35) n (%)	Female (N=20) n (%)
感染症および寄生虫症	15(42.9)	4(20.0)
気管支炎	2(5.7)	0
結膜炎	1(2.9)	1(5.0)
膀胱炎	0	1(5.0)
サイトメガロウイルス感染	1(2.9)	0
感染性小腸結腸炎	1(2.9)	0
胃腸炎	1(2.9)	0
帯状疱疹	1(2.9)	0
膿痂疹	1(2.9)	0
インフルエンザ	2(5.7)	0
上咽頭炎	2(5.7)	0
咽頭炎	2(5.7)	1(5.0)
ニューモシスチス・イロベチイ肺炎	1(2.9)	0
肺炎	1(2.9)	0
鼻炎	0	1(5.0)
ブドウ球菌皮膚感染	1(2.9)	0
上気道感染	3(8.6)	1(5.0)

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Male (N=35) n (%)	Female (N=20) n (%)
傷害、中毒および処置合併症	2(5.7)	1(5.0)
胃瘻管部合併症	1(2.9)	0
爪損傷	1(2.9)	0
処置による疼痛	0	1(5.0)

Source: Listing 16 2.6.1 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Male (N=35) n (%)	Female (N=20) n (%)
臨床検査	18(51.4)	7(35.0)
アラニンアミノトランスフェラーゼ増加	4(11.4)	1(5.0)
アスパラギン酸アミノトランスフェラーゼ増加	6(17.1)	1(5.0)
血中アルカリホスファターゼ増加	7(20.0)	1(5.0)
血中コレステロール増加	0	1(5.0)
血中クレアチンホスホキナーゼＭＢ増加	1(2.9)	0
血中クレアチンホスホキナーゼ増加	0	1(5.0)
血中クレアチニン増加	1(2.9)	1(5.0)
血中免疫グロブリンＡ減少	1(2.9)	0
尿中血陽性	1(2.9)	0
脳性ナトリウム利尿ペプチド増加	2(5.7)	0
Ｃ－反応性蛋白増加	3(8.6)	0
心胸郭比増加	1(2.9)	0
心電図ＱＴ延長	3(8.6)	2(10.0)
心電図Ｔ波逆転	1(2.9)	0
好酸球数増加	2(5.7)	0
γ－グルタミルトランスフェラーゼ増加	6(17.1)	2(10.0)
リパーゼ増加	1(2.9)	0
体重減少	4(11.4)	2(10.0)
体重増加	0	1(5.0)

Source: Listing 16 2.6.1 and 16 2.4.1
MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Male (N=35) n (%)	Female (N=20) n (%)
代謝および栄養障害	15(42.9)	10(50.0)
食欲減退	7(20.0)	6(30.0)
糖尿病	1(2.9)	0
高カリウム血症	1(2.9)	0
高マグネシウム血症	1(2.9)	0
高トリグリセリド血症	0	1(5.0)
低アルブミン血症	5(14.3)	0
低カルシウム血症	2(5.7)	1(5.0)
低カリウム血症	3(8.6)	2(10.0)
低ナトリウム血症	1(2.9)	1(5.0)
低蛋白血症	1(2.9)	0

Source: Listing 16.2.6 1 and 16.2.4 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Male (N=35) n (%)	Female (N=20) n (%)
筋骨格系および結合組織障害	13(37.1)	6(30.0)
関節痛	1(2.9)	0
関節炎	0	1(5.0)
背部痛	2(5.7)	3(15.0)
出血性関節症	1(2.9)	0
関節腫脹	1(2.9)	0
筋肉疲労	1(2.9)	1(5.0)
筋痙縮	3(8.6)	2(10.0)
筋力低下	1(2.9)	0
筋骨格硬直	1(2.9)	0
筋肉痛	2(5.7)	0
頚部痛	1(2.9)	0
四肢痛	0	1(5.0)
肩回旋筋腱板症候群	0	1(5.0)
腱炎	1(2.9)	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	3(8.6)	1(5.0)
末梢性Ｔ細胞性リンパ腫、組織型不明	1(2.9)	0
皮膚乳頭腫	0	1(5.0)
腫瘍疼痛	2(5.7)	0

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Male (N=35) n (%)	Female (N=20) n (%)
神経系障害	7(20.0)	2(10.0)
浮動性めまい	1(2.9)	0
味覚異常	1(2.9)	1(5.0)
頭痛	5(14.3)	1(5.0)
感覚鈍麻	1(2.9)	0
末梢性感覚ニューロパチー	1(2.9)	0
失神寸前の状態	1(2.9)	0
精神障害	3(8.6)	2(10.0)
譫妄	1(2.9)	1(5.0)
不眠症	3(8.6)	1(5.0)

Source: Listing 16.2.6 1 and 16.2.4 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Male (N=35) n (%)	Female (N=20) n (%)
腎および尿路障害	2(5.7)	0
急性腎障害	1(2.9)	0
血尿	1(2.9)	0
蛋白尿	1(2.9)	0
生殖系および乳房障害	1(2.9)	0
陰嚢浮腫	1(2.9)	0
呼吸器、胸郭および縦隔障害	9(25.7)	12(60.0)
咳嗽	3(8.6)	3(15.0)
咽頭知覚不全	0	1(5.0)
発声障害	0	1(5.0)
呼吸困難	0	4(20.0)
労作性呼吸困難	0	1(5.0)
鼻出血	1(2.9)	1(5.0)
しゃっくり	1(2.9)	0
間質性肺疾患	1(2.9)	0
口腔咽頭痛	0	3(15.0)
胸水	1(2.9)	1(5.0)
肺臓炎	2(5.7)	2(10.0)
湿性咳嗽	1(2.9)	0
アレルギー性鼻炎	0	1(5.0)
鼻漏	0	1(5.0)
上気道の炎症	0	1(5.0)

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Male (N=35) n (%)	Female (N=20) n (%)
皮膚および皮下組織障害	14(40.0)	9(45.0)
褥瘡性潰瘍	0	1(5.0)
ざ瘡様皮膚炎	1(2.9)	0
全身性剥脱性皮膚炎	1(2.9)	0
皮膚乾燥	1(2.9)	0
皮脂欠乏性湿疹	0	1(5.0)
紅斑	2(5.7)	0
多形紅斑	1(2.9)	0
全身紅斑	1(2.9)	0
皮膚疼痛	1(2.9)	0
点状出血	1(2.9)	0
色素沈着障害	0	1(5.0)
全身性そう痒症	1(2.9)	1(5.0)
紫斑	0	2(10.0)
発疹	3(8.6)	2(10.0)
斑状丘疹状皮疹	2(5.7)	0
そう痒性皮疹	1(2.9)	0
蕁麻疹	2(5.7)	3(15.0)
血管障害	2(5.7)	1(5.0)
深部静脈血栓症	0	1(5.0)
低血圧	1(2.9)	0
末梢動脈閉塞性疾患	1(2.9)	0

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-79　性別（男性、女性）の有害事象の概要（210 試験）（安全性解析対象集団）

Sex: Female

Description	40 mg (N=8) n (%)
Number of subjects with	
At least one TEAE	8 (100.0%)
At least one TEAE related to the study drug	8 (100.0%)
At least one serious TEAE	6 (75.0%)
At least one serious TEAE related to the study drug	5 (62.5%)
At least one TEAE leading to dose reduction or interruption	7 (87.5%)
At least one TEAE leading to study drug discontinuation	5 (62.5%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	8 (100.0%)
At least one TEAE with grade 3 or higher and related to the study drug	8 (100.0%)

Source: Listing 16.2.6 1 and 16 2.4.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

Sex: Male

Description	40 mg (N=15) n (%)
Number of subjects with	
At least one TEAE	15 (100.0%)
At least one TEAE related to the study drug	15 (100.0%)
At least one serious TEAE	1 (6.7%)
At least one serious TEAE related to the study drug	1 (6.7%)
At least one TEAE leading to dose reduction or interruption	9 (60.0%)
At least one TEAE leading to study drug discontinuation	4 (26.7%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	10 (66.7%)
At least one TEAE with grade 3 or higher and related to the study drug	10 (66.7%)

Source: Listing 16.2.6 1 and 16 2.4.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

表 2.7.4.7-80　性別（男性、女性）の有害事象の発現割合（210 試験）（安全性解析対象集団）

System organ class Preferred term	Female (N=8) n (%)	Male (N=15) n (%)
Number of subjects with at least one TEAE	8(100.0%)	15(100.0%)
血液およびリンパ系障害	7(87.5%)	12(80.0%)
貧血*	3(37.5%)	6(40.0%)
好酸球増加症	1(12.5%)	0
発熱性好中球減少症	0	1(6.7%)
白血球減少症*	3(37.5%)	7(46.7%)
リンパ球減少症*	1(12.5%)	1(6.7%)
好中球減少症*	5(62.5%)	7(46.7%)
血小板減少症*	6(75.0%)	12(80.0%)
心臓障害	2(25.0%)	0
第一度房室ブロック	1(12.5%)	0
動悸	1(12.5%)	0
眼障害	1(12.5%)	0
ドライアイ	1(12.5%)	0
胃腸障害	4(50.0%)	5(33.3%)
腹痛	0	3(20.0%)
下痢	3(37.5%)	3(20.0%)
悪心	2(25.0%)	1(6.7%)
口内炎	1(12.5%)	0

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Female (N=8) n (%)	Male (N=15) n (%)
一般・全身障害および投与部位の状態	6(75.0%)	7(46.7%)
悪寒	0	1(6.7%)
疲労	2(25.0%)	1(6.7%)
倦怠感	3(37.5%)	4(26.7%)
非心臓性胸痛	0	1(6.7%)
末梢性浮腫	1(12.5%)	0
発熱	2(25.0%)	1(6.7%)
感染症および寄生虫症	3(37.5%)	4(26.7%)
細菌感染	0	1(6.7%)
サイトメガロウイルス感染	0	1(6.7%)
医療機器関連感染	0	1(6.7%)
麦粒腫	1(12.5%)	0
口腔カンジダ症	1(12.5%)	0
ニューモシスチス・イロベチイ肺炎	1(12.5%)	0
皮膚感染	0	1(6.7%)
扁桃炎	0	1(6.7%)
上気道感染	1(12.5%)	0
尿路感染	1(12.5%)	0
傷害、中毒および処置合併症	1(12.5%)	0
挫傷	1(12.5%)	0

Source: Listing 16 2.6.1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Female (N=8) n (%)	Male (N=15) n (%)
臨床検査	4(50.0%)	6(40.0%)
アラニンアミノトランスフェラーゼ増加	0	1(6.7%)
アスパラギン酸アミノトランスフェラーゼ増加	0	2(13.3%)
血中アルカリホスファターゼ増加	1(12.5%)	0
血中乳酸脱水素酵素増加	0	1(6.7%)
脳性ナトリウム利尿ペプチド増加	1(12.5%)	0
好酸球数増加	1(12.5%)	0
γ－グルタミルトランスフェラーゼ増加	1(12.5%)	1(6.7%)
リパーゼ増加	0	1(6.7%)
体重減少	1(12.5%)	3(20.0%)
代謝および栄養障害	5(62.5%)	8(53.3%)
食欲減退	4(50.0%)	4(26.7%)
高カルシウム血症	0	1(6.7%)
低アルブミン血症	0	3(20.0%)
低カリウム血症	1(12.5%)	0
低ナトリウム血症	0	2(13.3%)
低リン酸血症	1(12.5%)	0
筋骨格系および結合組織障害	5(62.5%)	2(13.3%)
関節痛	0	1(6.7%)
背部痛	3(37.5%)	1(6.7%)
脊椎すべり症	1(12.5%)	0
尺骨突き上げ症候群	1(12.5%)	0

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Female (N=8) n (%)	Male (N=15) n (%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	0	1(6.7%)
腫瘍疼痛	0	1(6.7%)
神経系障害	4(50.0%)	5(33.3%)
味覚消失	0	1(6.7%)
認知障害	0	1(6.7%)
浮動性めまい	1(12.5%)	0
味覚異常	2(25.0%)	2(13.3%)
頭痛	1(12.5%)	1(6.7%)
傾眠	1(12.5%)	0
腎および尿路障害	0	1(6.7%)
尿瘻	0	1(6.7%)

Source: Listing 16.2.6.1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Female (N=8) n (%)	Male (N=15) n (%)
呼吸器、胸郭および縦隔障害	3(37.5%)	1(6.7%)
急性呼吸不全	1(12.5%)	0
鼻出血	1(12.5%)	0
間質性肺疾患	0	1(6.7%)
口腔咽頭痛	1(12.5%)	0
皮膚および皮下組織障害	5(62.5%)	3(20.0%)
接触皮膚炎	0	1(6.7%)
湿疹	1(12.5%)	0
紅斑	1(12.5%)	0
多形紅斑	1(12.5%)	0
光線過敏性反応	1(12.5%)	0
そう痒症	1(12.5%)	0
発疹	1(12.5%)	0
皮膚剥脱	0	1(6.7%)
皮膚潰瘍	0	1(6.7%)
血管障害	0	1(6.7%)
高血圧	0	1(6.7%)

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by sex.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-81　年齢別（65 歳未満、65 歳以上 75 歳未満、75 歳以上）の有害事象の概要（203 試験）（安全性解析対象集団）

Age group: <65

Description	40 mg (N=15)
	n (%)
Number of subjects with	
At least one TEAE	15 (100.0)
At least one TEAE related to the study drug	13 (86.7)
At least one serious TEAE	1 (6.7)
At least one serious TEAE related to the study drug	0 (0.0)
At least one TEAE leading to dose reduction or interruption	10 (66.7)
At least one TEAE leading to study drug discontinuation	6 (40.0)
At least one TEAE leading to death	0 (0.0)
At least one TEAE with grade 3 or higher	11 (73.3)
At least one TEAE with grade 3 or higher and related to the study drug	10 (66.7)

Source: Listing 16.2.6 1 and 16 2.4.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE.　For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

Age group: >=65 to <75

Description	40 mg (N=23) n (%)
Number of subjects with	
At least one TEAE	23 (100.0)
At least one TEAE related to the study drug	21 (91.3)
At least one serious TEAE	7 (30.4)
At least one serious TEAE related to the study drug	6 (26.1)
At least one TEAE leading to dose reduction or interruption	15 (65.2)
At least one TEAE leading to study drug discontinuation	8 (34.8)
At least one TEAE leading to death	0 (0.0)
At least one TEAE with grade 3 or higher	19 (82.6)
At least one TEAE with grade 3 or higher and related to the study drug	16 (69.6)

Source: Listing 16 2.6.1 and 16 2.4.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

Age group: >=75

Description	40 mg (N=17) n (%)
Number of subjects with	
At least one TEAE	17 (100.0)
At least one TEAE related to the study drug	17 (100.0)
At least one serious TEAE	6 (35.3)
At least one serious TEAE related to the study drug	4 (23.5)
At least one TEAE leading to dose reduction or interruption	15 (88.2)
At least one TEAE leading to study drug discontinuation	4 (23.5)
At least one TEAE leading to death	1 (5.9)
At least one TEAE with grade 3 or higher	16 (94.1)
At least one TEAE with grade 3 or higher and related to the study drug	16 (94.1)

Source: Listing 16.2.6 1 and 16 2.4.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

表 2.7.4.7-82　年齢別（65 歳未満、65 歳以上 75 歳未満、75 歳以上）の有害事象の発現割合（203 試験）（安全性解析対象集団）

System organ class Preferred term	<65 (N=15) n (%)	>=65 to <75 (N=23) n (%)	>=75 (N=17) n (%)
Number of subjects with at least one TEAE	15(100.0)	23(100.0)	17 (100.0)
血液およびリンパ系障害	14(93.3)	21(91.3)	17 (100.0)
貧血*	3(20.0)	10(43.5)	5 (29.4)
再生不良性貧血	0	1(4.3)	0
好酸球増加症	0	1(4.3)	0
発熱性好中球減少症	0	2(8.7)	1 (5.9)
白血球減少症*	5(33.3)	11(47.8)	8 (47.1)
リンパ球減少症*	5(33.3)	9(39.1)	2 (11.8)
好中球減少症*	8(53.3)	14(60.9)	9 (52.9)
血小板減少症*	14(93.3)	16(69.6)	16 (94.1)
心臓障害	1(6.7)	3(13.0)	3 (17.6)
不安定狭心症	0	1(4.3)	0
不整脈	0	0	1 (5.9)
心房細動	0	0	2 (11.8)
動悸	1(6.7)	2(8.7)	0
心嚢液貯留	0	0	1 (5.9)
耳および迷路障害	0	1(4.3)	1 (5.9)
耳痛	0	1(4.3)	0
回転性めまい	0	0	1 (5.9)

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=15) n (%)	>=65 to <75 (N=23) n (%)	>=75 (N=17) n (%)
眼障害	1(6.7)	3(13.0)	1 (5.9)
白内障	0	1(4.3)	0
結膜出血	0	1(4.3)	0
ドライアイ	0	0	1 (5.9)
角膜炎	1(6.7)	0	0
霧視	0	1(4.3)	0

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=15) n (%)	>=65 to <75 (N=23) n (%)	>=75 (N=17) n (%)
胃腸障害	11(73.3)	11(47.8)	10 (58.8)
腹部不快感	0	0	1 (5.9)
腹痛	2(13.3)	0	1 (5.9)
上腹部痛	1(6.7)	1(4.3)	0
肛門出血	0	1(4.3)	0
便秘	1(6.7)	0	0
齲歯	2(13.3)	0	0
下痢	6(40.0)	4(17.4)	7 (41.2)
消化不良	0	1(4.3)	0
心窩部不快感	0	1(4.3)	0
胃潰瘍	1(6.7)	0	0
胃炎	1(6.7)	0	0
痔出血	1(6.7)	0	0
悪心	3(20.0)	4(17.4)	5 (29.4)
口腔粘膜血腫	0	1(4.3)	0
口内炎	0	1(4.3)	1 (5.9)
歯痛	0	1(4.3)	0
嘔吐	1(6.7)	1(4.3)	1 (5.9)

Source: Listing 16.2.6 1 and 16 2.4.1
MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=15) n (%)	>=65 to <75 (N=23) n (%)	>=75 (N=17) n (%)
一般・全身障害および投与部位の状態	6(40.0)	11(47.8)	10 (58.8)
無力症	1(6.7)	1(4.3)	0
カテーテル留置部位腫脹	0	1(4.3)	0
胸部不快感	0	1(4.3)	0
胸痛	0	1(4.3)	0
溢出	1(6.7)	0	0
疲労	0	4(17.4)	2 (11.8)
歩行障害	0	1(4.3)	0
インフルエンザ様疾患	0	2(8.7)	0
倦怠感	2(13.3)	1(4.3)	5 (29.4)
末梢性浮腫	1(6.7)	2(8.7)	1 (5.9)
発熱	2(13.3)	4(17.4)	5 (29.4)
口渇	0	1(4.3)	0
免疫系障害	0	1(4.3)	0
薬物過敏症	0	1(4.3)	0

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=15) n (%)	>=65 to <75 (N=23) n (%)	>=75 (N=17) n (%)
感染症および寄生虫症	7(46.7)	8(34.8)	4 (23.5)
気管支炎	0	2(8.7)	0
結膜炎	1(6.7)	1(4.3)	0
膀胱炎	1(6.7)	0	0
サイトメガロウイルス感染	0	1(4.3)	0
感染性小腸結腸炎	1(6.7)	0	0
胃腸炎	1(6.7)	0	0
帯状疱疹	0	0	1 (5.9)
膿痂疹	0	0	1 (5.9)
インフルエンザ	1(6.7)	1(4.3)	0
上咽頭炎	1(6.7)	1(4.3)	0
咽頭炎	1(6.7)	2(8.7)	0
ニューモシスチス・イロベチイ肺炎	0	1(4.3)	0
肺炎	0	0	1 (5.9)
鼻炎	0	1(4.3)	0
ブドウ球菌皮膚感染	1(6.7)	0	0
上気道感染	1(6.7)	1(4.3)	2 (11.8)

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=15) n (%)	>=65 to <75 (N=23) n (%)	>=75 (N=17) n (%)
傷害、中毒および処置合併症	2(13.3)	0	1 (5.9)
胃瘻管部合併症	1(6.7)	0	0
爪損傷	1(6.7)	0	0
処置による疼痛	0	0	1 (5.9)

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=15) n (%)	>=65 to <75 (N=23) n (%)	>=75 (N=17) n (%)
臨床検査	3(20.0)	13(56.5)	9 (52.9)
アラニンアミノトランスフェラーゼ増加	0	2(8.7)	3 (17.6)
アスパラギン酸アミノトランスフェラーゼ増加	1(6.7)	2(8.7)	4 (23.5)
血中アルカリホスファターゼ増加	0	4(17.4)	4 (23.5)
血中コレステロール増加	0	1(4.3)	0
血中クレアチンホスホキナーゼＭＢ増加	1(6.7)	0	0
血中クレアチンホスホキナーゼ増加	0	1(4.3)	0
血中クレアチニン増加	0	2(8.7)	0
血中免疫グロブリンＡ減少	0	1(4.3)	0
尿中血陽性	0	1(4.3)	0
脳性ナトリウム利尿ペプチド増加	0	2(8.7)	0
Ｃ－反応性蛋白増加	0	1(4.3)	2 (11.8)
心胸郭比増加	0	1(4.3)	0
心電図ＱＴ延長	1(6.7)	2(8.7)	2 (11.8)
心電図Ｔ波逆転	0	1(4.3)	0
好酸球数増加	0	1(4.3)	1 (5.9)
γ－グルタミルトランスフェラーゼ増加	1(6.7)	3(13.0)	4 (23.5)
リパーゼ増加	0	1(4.3)	0
体重減少	0	2(8.7)	4 (23.5)
体重増加	0	1(4.3)	0

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=15) n (%)	>=65 to <75 (N=23) n (%)	>=75 (N=17) n (%)
代謝および栄養障害	3(20.0)	11(47.8)	11 (64.7)
食欲減退	2(13.3)	4(17.4)	7 (41.2)
糖尿病	0	1(4.3)	0
高カリウム血症	0	0	1 (5.9)
高マグネシウム血症	0	0	1 (5.9)
高トリグリセリド血症	0	1(4.3)	0
低アルブミン血症	0	1(4.3)	4 (23.5)
低カルシウム血症	0	1(4.3)	2 (11.8)
低カリウム血症	1(6.7)	4(17.4)	0
低ナトリウム血症	0	0	2 (11.8)
低蛋白血症	0	0	1 (5.9)

Source: Listing 16.2.6 1 and 16 2.4.1
MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=15) n (%)	>=65 to <75 (N=23) n (%)	>=75 (N=17) n (%)
筋骨格系および結合組織障害	3(20.0)	9(39.1)	7 (41.2)
関節痛	0	1(4.3)	0
関節炎	0	1(4.3)	0
背部痛	1(6.7)	2(8.7)	2 (11.8)
出血性関節症	0	0	1 (5.9)
関節腫脹	0	1(4.3)	0
筋肉疲労	0	1(4.3)	1 (5.9)
筋痙縮	2(13.3)	2(8.7)	1 (5.9)
筋力低下	0	1(4.3)	0
筋骨格硬直	0	0	1 (5.9)
筋肉痛	1(6.7)	0	1 (5.9)
頚部痛	0	0	1 (5.9)
四肢痛	0	1(4.3)	0
肩回旋筋腱板症候群	0	1(4.3)	0
腱炎	0	1(4.3)	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1(6.7)	3(13.0)	0
末梢性Ｔ細胞性リンパ腫、組織型不明	0	1(4.3)	0
皮膚乳頭腫	0	1(4.3)	0
腫瘍疼痛	1(6.7)	1(4.3)	0

Source: Listing 16 2.6.1 and 16.2.4 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=15) n (%)	>=65 to <75 (N=23) n (%)	>=75 (N=17) n (%)
神経系障害	3(20.0)	4(17.4)	2 (11.8)
浮動性めまい	1(6.7)	0	0
味覚異常	0	1(4.3)	1 (5.9)
頭痛	3(20.0)	2(8.7)	1 (5.9)
感覚鈍麻	1(6.7)	0	0
末梢性感覚ニューロパチー	0	0	1 (5.9)
失神寸前の状態	0	1(4.3)	0
精神障害	0	4(17.4)	1 (5.9)
譫妄	0	1(4.3)	1 (5.9)
不眠症	0	4(17.4)	0

Source: Listing 16 2.6.1 and 16.2.4 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=15) n (%)	>=65 to <75 (N=23) n (%)	>=75 (N=17) n (%)
腎および尿路障害	0	0	2 (11.8)
急性腎障害	0	0	1 (5.9)
血尿	0	0	1 (5.9)
蛋白尿	0	0	1 (5.9)
生殖系および乳房障害	1(6.7)	0	0
陰嚢浮腫	1(6.7)	0	0
呼吸器、胸郭および縦隔障害	4(26.7)	11(47.8)	6 (35.3)
咳嗽	1(6.7)	2(8.7)	3 (17.6)
咽頭知覚不全	0	1(4.3)	0
発声障害	0	1(4.3)	0
呼吸困難	1(6.7)	2(8.7)	1 (5.9)
労作性呼吸困難	0	0	1 (5.9)
鼻出血	0	2(8.7)	0
しゃっくり	0	1(4.3)	0
間質性肺疾患	0	1(4.3)	0
口腔咽頭痛	3(20.0)	0	0
胸水	0	0	2 (11.8)
肺臓炎	1(6.7)	3(13.0)	0
湿性咳嗽	0	1(4.3)	0
アレルギー性鼻炎	0	0	1 (5.9)
鼻漏	0	0	1 (5.9)
上気道の炎症	0	0	1 (5.9)

Source: Listing 16.2.6.1 and 16.2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=15) n (%)	>=65 to <75 (N=23) n (%)	>=75 (N=17) n (%)
皮膚および皮下組織障害	6(40.0)	12(52.2)	5 (29.4)
褥瘡性潰瘍	0	0	1 (5.9)
ざ瘡様皮膚炎	0	1(4.3)	0
全身性剥脱性皮膚炎	0	0	1 (5.9)
皮膚乾燥	0	0	1 (5.9)
皮脂欠乏性湿疹	1(6.7)	0	0
紅斑	0	2(8.7)	0
多形紅斑	0	0	1 (5.9)
全身紅斑	0	1(4.3)	0
皮膚疼痛	0	1(4.3)	0
点状出血	0	1(4.3)	0
色素沈着障害	0	1(4.3)	0
全身性そう痒症	1(6.7)	1(4.3)	0
紫斑	0	2(8.7)	0
発疹	1(6.7)	3(13.0)	1 (5.9)
斑状丘疹状皮疹	0	2(8.7)	0
そう痒性皮疹	1(6.7)	0	0
蕁麻疹	2(13.3)	3(13.0)	0
血管障害	0	0	3 (17.6)
深部静脈血栓症	0	0	1 (5.9)
低血圧	0	0	1 (5.9)
末梢動脈閉塞性疾患	0	0	1 (5.9)

Source: Listing 16.2.6 1 and 16.2.4 1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-83　年齢別（65 歳未満、65 歳以上 75 歳未満、75 歳以上）の有害事象の概要（210 試験）（安全性解析対象集団）

Age group: <65

Description	40 mg (N=1) n (%)
Number of subjects with	
At least one TEAE	1 (100.0%)
At least one TEAE related to the study drug	1 (100.0%)
At least one serious TEAE	0 (0.0%)
At least one serious TEAE related to the study drug	0 (0.0%)
At least one TEAE leading to dose reduction or interruption	1 (100.0%)
At least one TEAE leading to study drug discontinuation	1 (100.0%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	1 (100.0%)
At least one TEAE with grade 3 or higher and related to the study drug	1 (100.0%)

Source: Listing 16.2.6 1 and 16 2.4.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

Age group: >=65 to <75

Description	40 mg (N=13) n (%)
Number of subjects with	
At least one TEAE	13 (100.0%)
At least one TEAE related to the study drug	13 (100.0%)
At least one serious TEAE	5 (38.5%)
At least one serious TEAE related to the study drug	4 (30.8%)
At least one TEAE leading to dose reduction or interruption	9 (69.2%)
At least one TEAE leading to study drug discontinuation	5 (38.5%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	11 (84.6%)
At least one TEAE with grade 3 or higher and related to the study drug	11 (84.6%)

Source: Listing 16.2.6 1 and 16 2.4.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

Age group: >=75

Description	40 mg (N=9) n (%)
Number of subjects with	
At least one TEAE	9 (100.0%)
At least one TEAE related to the study drug	9 (100.0%)
At least one serious TEAE	2 (22.2%)
At least one serious TEAE related to the study drug	2 (22.2%)
At least one TEAE leading to dose reduction or interruption	6 (66.7%)
At least one TEAE leading to study drug discontinuation	3 (33.3%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	6 (66.7%)
At least one TEAE with grade 3 or higher and related to the study drug	6 (66.7%)

Source: Listing 16.2.6 1 and 16 2.4.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

表 2.7.4.7-84　年齢別（65 歳未満、65 歳以上 75 歳未満、75 歳以上）の有害事象の発現割合（210 試験）（安全性解析対象集団）

System organ class Preferred term	<65 (N=1) n (%)	>=65 to <75 (N=13) n (%)	>=75 (N=9) n (%)
Number of subjects with at least one TEAE	1(100.0%)	13(100.0%)	9 (100.0%)
血液およびリンパ系障害	1(100.0%)	11(84.6%)	7 (77.8%)
貧血*	0	6(46.2%)	3 (33.3%)
好酸球増加症	0	0	1 (11.1%)
発熱性好中球減少症	0	1(7.7%)	0
白血球減少症*	1(100.0%)	7(53.8%)	2 (22.2%)
リンパ球減少症*	1(100.0%)	1(7.7%)	0
好中球減少症*	1(100.0%)	8(61.5%)	3 (33.3%)
血小板減少症*	0	11(84.6%)	7 (77.8%)
心臓障害	0	1(7.7%)	1 (11.1%)
第一度房室ブロック	0	0	1 (11.1%)
動悸	0	1(7.7%)	0
眼障害	0	0	1 (11.1%)
ドライアイ	0	0	1 (11.1%)
胃腸障害	0	4(30.8%)	5 (55.6%)
腹痛	0	1(7.7%)	2 (22.2%)
下痢	0	3(23.1%)	3 (33.3%)
悪心	0	2(15.4%)	1 (11.1%)
口内炎	0	0	1 (11.1%)

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=1) n (%)	>=65 to <75 (N=13) n (%)	>=75 (N=9) n (%)
一般・全身障害および投与部位の状態	0	7(53.8%)	6 (66.7%)
悪寒	0	1(7.7%)	0
疲労	0	0	3 (33.3%)
倦怠感	0	3(23.1%)	4 (44.4%)
非心臓性胸痛	0	1(7.7%)	0
末梢性浮腫	0	0	1 (11.1%)
発熱	0	3(23.1%)	0
感染症および寄生虫症	0	4(30.8%)	3 (33.3%)
細菌感染	0	1(7.7%)	0
サイトメガロウイルス感染	0	1(7.7%)	0
医療機器関連感染	0	1(7.7%)	0
麦粒腫	0	0	1 (11.1%)
口腔カンジダ症	0	0	1 (11.1%)
ニューモシスチス・イロベチイ肺炎	0	1(7.7%)	0
皮膚感染	0	1(7.7%)	0
扁桃炎	0	0	1 (11.1%)
上気道感染	0	1(7.7%)	0
尿路感染	0	0	1 (11.1%)

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=1) n (%)	>=65 to <75 (N=13) n (%)	>=75 (N=9) n (%)
傷害、中毒および処置合併症	0	0	1 (11.1%)
挫傷	0	0	1 (11.1%)
臨床検査	0	7(53.8%)	3 (33.3%)
アラニンアミノトランスフェラーゼ増加	0	1(7.7%)	0
アスパラギン酸アミノトランスフェラーゼ増加	0	2(15.4%)	0
血中アルカリホスファターゼ増加	0	1(7.7%)	0
血中乳酸脱水素酵素増加	0	1(7.7%)	0
脳性ナトリウム利尿ペプチド増加	0	0	1 (11.1%)
好酸球数増加	0	0	1 (11.1%)
γーグルタミルトランスフェラーゼ増加	0	2(15.4%)	0
リパーゼ増加	0	1(7.7%)	0
体重減少	0	3(23.1%)	1 (11.1%)

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=1) n (%)	>=65 to <75 (N=13) n (%)	>=75 (N=9) n (%)
代謝および栄養障害	0	7(53.8%)	6 (66.7%)
食欲減退	0	4(30.8%)	4 (44.4%)
高カルシウム血症	0	1(7.7%)	0
低アルブミン血症	0	1(7.7%)	2 (22.2%)
低カリウム血症	0	1(7.7%)	0
低ナトリウム血症	0	1(7.7%)	1 (11.1%)
低リン酸血症	0	1(7.7%)	0
筋骨格系および結合組織障害	0	5(38.5%)	2 (22.2%)
関節痛	0	1(7.7%)	0
背部痛	0	3(23.1%)	1 (11.1%)
脊椎すべり症	0	0	1 (11.1%)
尺骨突き上げ症候群	0	1(7.7%)	0

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=1) n (%)	>=65 to <75 (N=13) n (%)	>=75 (N=9) n (%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	0	0	1 (11.1%)
腫瘍疼痛	0	0	1 (11.1%)
神経系障害	0	4(30.8%)	5 (55.6%)
味覚消失	0	1(7.7%)	0
認知障害	0	0	1 (11.1%)
浮動性めまい	0	0	1 (11.1%)
味覚異常	0	3(23.1%)	1 (11.1%)
頭痛	0	0	2 (22.2%)
傾眠	0	0	1 (11.1%)
腎および尿路障害	0	1(7.7%)	0
尿瘻	0	1(7.7%)	0
呼吸器、胸郭および縦隔障害	0	3(23.1%)	1 (11.1%)
急性呼吸不全	0	1(7.7%)	0
鼻出血	0	1(7.7%)	0
間質性肺疾患	0	1(7.7%)	0
口腔咽頭痛	0	0	1 (11.1%)

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<65 (N=1) n (%)	>=65 to <75 (N=13) n (%)	>=75 (N=9) n (%)
皮膚および皮下組織障害	0	5(38.5%)	3 (33.3%)
接触皮膚炎	0	1(7.7%)	0
湿疹	0	1(7.7%)	0
紅斑	0	1(7.7%)	0
多形紅斑	0	0	1 (11.1%)
光線過敏性反応	0	0	1 (11.1%)
そう痒症	0	0	1 (11.1%)
発疹	0	1(7.7%)	0
皮膚剥脱	0	0	1 (11.1%)
皮膚潰瘍	0	1(7.7%)	0
血管障害	0	1(7.7%)	0
高血圧	0	1(7.7%)	0

Source: Listing 16.2.6 1 and 16 2.4.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by age category.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-85　PTCL サブセット別（再発、難治性）の有害事象の概要（203 試験）（安全性解析対象集団）

PTCL subtype: Refractory

Description	40 mg (N=23) n (%)
Number of subjects with	
At least one TEAE	23 (100.0)
At least one TEAE related to the study drug	21 (91.3)
At least one serious TEAE	4 (17.4)
At least one serious TEAE related to the study drug	2 (8.7)
At least one TEAE leading to dose reduction or interruption	17 (73.9)
At least one TEAE leading to study drug discontinuation	4 (17.4)
At least one TEAE leading to death	0 (0.0)
At least one TEAE with grade 3 or higher	17 (73.9)
At least one TEAE with grade 3 or higher and related to the study drug	16 (69.6)

Source: Listing 16.2.6 1 and 16 2.4.4

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL; n = number of subjects;
% = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE.　For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Subjects with refractory, recurrent and relapsed ATL are confirmed by Medical Expert.

PTCL subtype: Relapsed

Description	40 mg (N=32) n (%)
Number of subjects with	
At least one TEAE	32 (100.0)
At least one TEAE related to the study drug	30 (93.8)
At least one serious TEAE	10 (31.3)
At least one serious TEAE related to the study drug	8 (25.0)
At least one TEAE leading to dose reduction or interruption	23 (71.9)
At least one TEAE leading to study drug discontinuation	14 (43.8)
At least one TEAE leading to death	1 (3.1)
At least one TEAE with grade 3 or higher	29 (90.6)
At least one TEAE with grade 3 or higher and related to the study drug	26 (81.3)

Source: Listing 16.2.6 1 and 16 2.4.4

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL; n = number of subjects;
% = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Subjects with refractory, recurrent and relapsed ATL are confirmed by Medical Expert.

表 2.7.4.7-86　PTCL サブセット別（再発、難治性）の有害事象の発現割合（203 試験）（安全性解析対象集団）

System organ class Preferred term	Relapsed (N=32) n (%)	Refractory (N=23) n (%)
Number of subjects with at least one TEAE	32 (100.0)	23 (100.0)
血液およびリンパ系障害	30 (93.8)	22 (95.7)
貧血*	12 (37.5)	6 (26.1)
再生不良性貧血	0	1 (4.3)
好酸球増加症	0	1 (4.3)
発熱性好中球減少症	1 (3.1)	2 (8.7)
白血球減少症*	13 (40.6)	11 (47.8)
リンパ球減少症*	10 (31.3)	6 (26.1)
好中球減少症*	19 (59.4)	12 (52.2)
血小板減少症*	25 (78.1)	21 (91.3)
心臓障害	3 (9.4)	4 (17.4)
不安定狭心症	1 (3.1)	0
不整脈	0	1 (4.3)
心房細動	1 (3.1)	1 (4.3)
動悸	1 (3.1)	2 (8.7)
心嚢液貯留	0	1 (4.3)
耳および迷路障害	0	2 (8.7)
耳痛	0	1 (4.3)
回転性めまい	0	1 (4.3)

Source: Listing 16.2.6 1 and 16.2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Subjects with refractory and relapsed PTCL are confirmed by Medical Expert.

System organ class Preferred term	Relapsed (N=32)	Refractory (N=23)
	n (%)	n (%)
眼障害	2 (6.3)	3 (13.0)
白内障	0	1 (4.3)
結膜出血	0	1 (4.3)
ドライアイ	1 (3.1)	0
角膜炎	1 (3.1)	0
霧視	0	1 (4.3)

Source: Listing 16.2.6.1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Subjects with refractory and relapsed PTCL are confirmed by Medical Expert.

System organ class Preferred term	Relapsed (N=32)	Refractory (N=23)
	n (%)	n (%)
胃腸障害	16 (50.0)	16 (69.6)
腹部不快感	0	1 (4.3)
腹痛	2 (6.3)	1 (4.3)
上腹部痛	1 (3.1)	1 (4.3)
肛門出血	0	1 (4.3)
便秘	1 (3.1)	0
齲歯	2 (6.3)	0
下痢	8 (25.0)	9 (39.1)
消化不良	1 (3.1)	0
心窩部不快感	1 (3.1)	0
胃潰瘍	1 (3.1)	0
胃炎	0	1 (4.3)
痔出血	0	1 (4.3)
悪心	4 (12.5)	8 (34.8)
口腔粘膜血腫	1 (3.1)	0
口内炎	1 (3.1)	1 (4.3)
歯痛	0	1 (4.3)
嘔吐	0	3 (13.0)

Source: Listing 16.2.6.1 and 16.2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Subjects with refractory and relapsed PTCL are confirmed by Medical Expert.

System organ class Preferred term	Relapsed (N=32)	Refractory (N=23)
	n (%)	n (%)
一般・全身障害および投与部位の状態	15 (46.9)	12 (52.2)
無力症	0	2 (8.7)
カテーテル留置部位腫脹	1 (3.1)	0
胸部不快感	1 (3.1)	0
胸痛	1 (3.1)	0
溢出	1 (3.1)	0
疲労	4 (12.5)	2 (8.7)
歩行障害	0	1 (4.3)
インフルエンザ様疾患	1 (3.1)	1 (4.3)
倦怠感	4 (12.5)	4 (17.4)
末梢性浮腫	2 (6.3)	2 (8.7)
発熱	8 (25.0)	3 (13.0)
口渇	0	1 (4.3)
免疫系障害	0	1 (4.3)
薬物過敏症	0	1 (4.3)

Source: Listing 16.2.6.1 and 16.2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Subjects with refractory and relapsed PTCL are confirmed by Medical Expert.

System organ class Preferred term	Relapsed (N=32)	Refractory (N=23)
	n (%)	n (%)
感染症および寄生虫症	13 (40.6)	6 (26.1)
気管支炎	2 (6.3)	0
結膜炎	1 (3.1)	1 (4.3)
膀胱炎	0	1 (4.3)
サイトメガロウイルス感染	0	1 (4.3)
感染性小腸結腸炎	0	1 (4.3)
胃腸炎	1 (3.1)	0
帯状疱疹	0	1 (4.3)
膿痂疹	1 (3.1)	0
インフルエンザ	0	2 (8.7)
上咽頭炎	1 (3.1)	1 (4.3)
咽頭炎	3 (9.4)	0
ニューモシスチス・イロベチイ肺炎	1 (3.1)	0
肺炎	1 (3.1)	0
鼻炎	1 (3.1)	0
ブドウ球菌皮膚感染	0	1 (4.3)
上気道感染	4 (12.5)	0

Source: Listing 16.2.6.1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Subjects with refractory and relapsed PTCL are confirmed by Medical Expert.

System organ class Preferred term	Relapsed (N=32)	Refractory (N=23)
	n (%)	n (%)
傷害、中毒および処置合併症	2 (6.3)	1 (4.3)
胃瘻管部合併症	0	1 (4.3)
爪損傷	1 (3.1)	0
処置による疼痛	1 (3.1)	0

Source: Listing 16.2.6.1 and 16.2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Subjects with refractory and relapsed PTCL are confirmed by Medical Expert.

System organ class Preferred term	Relapsed (N=32)	Refractory (N=23)
	n (%)	n (%)
臨床検査	16 (50.0)	9 (39.1)
アラニンアミノトランスフェラーゼ増加	2 (6.3)	3 (13.0)
アスパラギン酸アミノトランスフェラーゼ増加	5 (15.6)	2 (8.7)
血中アルカリホスファターゼ増加	7 (21.9)	1 (4.3)
血中コレステロール増加	0	1 (4.3)
血中クレアチンホスホキナーゼ MB 増加	1 (3.1)	0
血中クレアチンホスホキナーゼ増加	1 (3.1)	0
血中クレアチニン増加	1 (3.1)	1 (4.3)
血中免疫グロブリン A 減少	0	1 (4.3)
尿中血陽性	1 (3.1)	0
脳性ナトリウム利尿ペプチド増加	1 (3.1)	1 (4.3)
Ｃ－反応性蛋白増加	3 (9.4)	0
心胸郭比増加	0	1 (4.3)
心電図 QT 延長	3 (9.4)	2 (8.7)
心電図 T 波逆転	1 (3.1)	0
好酸球数増加	1 (3.1)	1 (4.3)
γ－グルタミルトランスフェラーゼ増加	4 (12.5)	4 (17.4)
リパーゼ増加	1 (3.1)	0
体重減少	3 (9.4)	3 (13.0)
体重増加	0	1 (4.3)

Source: Listing 16.2.6.1 and 16.2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Subjects with refractory and relapsed PTCL are confirmed by Medical Expert.

System organ class Preferred term	Relapsed (N=32)	Refractory (N=23)
	n (%)	n (%)
代謝および栄養障害	13 (40.6)	12 (52.2)
食欲減退	7 (21.9)	6 (26.1)
糖尿病	1 (3.1)	0
高カリウム血症	0	1 (4.3)
高マグネシウム血症	0	1 (4.3)
高トリグリセリド血症	0	1 (4.3)
低アルブミン血症	2 (6.3)	3 (13.0)
低カルシウム血症	2 (6.3)	1 (4.3)
低カリウム血症	1 (3.1)	4 (17.4)
低ナトリウム血症	1 (3.1)	1 (4.3)
低蛋白血症	1 (3.1)	0

Source: Listing 16.2.6.1 and 16.2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Subjects with refractory and relapsed PTCL are confirmed by Medical Expert.

System organ class Preferred term	Relapsed (N=32)	Refractory (N=23)
	n (%)	n (%)
筋骨格系および結合組織障害	10 (31.3)	9 (39.1)
関節痛	1 (3.1)	0
関節炎	0	1 (4.3)
背部痛	1 (3.1)	4 (17.4)
出血性関節症	1 (3.1)	0
関節腫脹	1 (3.1)	0
筋肉疲労	1 (3.1)	1 (4.3)
筋痙縮	3 (9.4)	2 (8.7)
筋力低下	0	1 (4.3)
筋骨格硬直	1 (3.1)	0
筋肉痛	1 (3.1)	1 (4.3)
頚部痛	0	1 (4.3)
四肢痛	1 (3.1)	0
肩回旋筋腱板症候群	1 (3.1)	0
腱炎	1 (3.1)	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	2 (6.3)	2 (8.7)
末梢性 T 細胞性リンパ腫、組織型不明	1 (3.1)	0
皮膚乳頭腫	0	1 (4.3)
腫瘍疼痛	1 (3.1)	1 (4.3)

Source: Listing 16.2.6.1 and 16.2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Subjects with refractory and relapsed PTCL are confirmed by Medical Expert.

System organ class Preferred term	Relapsed (N=32)	Refractory (N=23)
	n (%)	n (%)
神経系障害	4 (12.5)	5 (21.7)
浮動性めまい	0	1 (4.3)
味覚異常	2 (6.3)	0
頭痛	2 (6.3)	4 (17.4)
感覚鈍麻	0	1 (4.3)
末梢性感覚ニューロパチー	0	1 (4.3)
失神寸前の状態	1 (3.1)	0
精神障害	1 (3.1)	4 (17.4)
譫妄	1 (3.1)	1 (4.3)
不眠症	1 (3.1)	3 (13.0)

Source: Listing 16.2.6.1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Subjects with refractory and relapsed PTCL are confirmed by Medical Expert.

System organ class Preferred term	Relapsed (N=32)	Refractory (N=23)
	n (%)	n (%)
腎および尿路障害	2 (6.3)	0
急性腎障害	1 (3.1)	0
血尿	1 (3.1)	0
蛋白尿	1 (3.1)	0
生殖系および乳房障害	0	1 (4.3)
陰嚢浮腫	0	1 (4.3)
呼吸器、胸郭および縦郭障害	14 (43.8)	7 (30.4)
咳嗽	5 (15.6)	1 (4.3)
咽頭知覚不全	0	1 (4.3)
発声障害	1 (3.1)	0
呼吸困難	3 (9.4)	1 (4.3)
労作性呼吸困難	1 (3.1)	0
鼻出血	1 (3.1)	1 (4.3)
しゃっくり	0	1 (4.3)
間質性肺疾患	1 (3.1)	0
口腔咽頭痛	2 (6.3)	1 (4.3)
胸水	1 (3.1)	1 (4.3)
肺臓炎	3 (9.4)	1 (4.3)
湿性咳嗽	0	1 (4.3)
アレルギー性鼻炎	1 (3.1)	0
鼻漏	1 (3.1)	0
上気道の炎症	1 (3.1)	0

Source: Listing 16.2.6.1 and 16.2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Subjects with refractory and relapsed PTCL are confirmed by Medical Expert.

System organ class Preferred term	Relapsed (N=32)	Refractory (N=23)
	n (%)	n (%)
皮膚および皮下組織障害	14 (43.8)	9 (39.1)
褥瘡性潰瘍	0	1 (4.3)
ざ瘡様皮膚炎	1 (3.1)	0
全身性剥脱性皮膚炎	1 (3.1)	0
皮膚乾燥	1 (3.1)	0
皮脂欠乏性湿疹	1 (3.1)	0
紅斑	1 (3.1)	1 (4.3)
多形紅斑	0	1 (4.3)
全身紅斑	1 (3.1)	0
皮膚疼痛	1 (3.1)	0
点状出血	1 (3.1)	0
色素沈着障害	0	1 (4.3)
全身性そう痒症	2 (6.3)	0
紫斑	0	2 (8.7)
発疹	3 (9.4)	2 (8.7)
斑状丘疹状皮疹	2 (6.3)	0
そう痒性皮疹	0	1 (4.3)
蕁麻疹	3 (9.4)	2 (8.7)
血管障害	1 (3.1)	2 (8.7)
深部静脈血栓症	1 (3.1)	0
低血圧	0	1 (4.3)
末梢動脈閉塞性疾患	0	1 (4.3)

Source: Listing 16.2.6.1 and 16.2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by refractory or relapsed PTCL.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Subjects with refractory and relapsed PTCL are confirmed by Medical Expert.

表 2.7.4.7-87　ECOG PS 別（0、1、2）の有害事象の概要（203 試験）（安全性解析対象集団）

ECOG performance status: 0

Description	40 mg (N=28) n (%)
Number of subjects with	
At least one TEAE	28 (100.0)
At least one TEAE related to the study drug	27 (96.4)
At least one serious TEAE	6 (21.4)
At least one serious TEAE related to the study drug	4 (14.3)
At least one TEAE leading to dose reduction or interruption	23 (82.1)
At least one TEAE leading to study drug discontinuation	8 (28.6)
At least one TEAE leading to death	0 (0.0)
At least one TEAE with grade 3 or higher	25 (89.3)
At least one TEAE with grade 3 or higher and related to the study drug	23 (82.1)

Source: Listing 16.2.6 1 and 16.2.11.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

ECOG performance status: 1

Description	40 mg (N=25) n (%)
Number of subjects with	
At least one TEAE	25 (100.0)
At least one TEAE related to the study drug	22 (88.0)
At least one serious TEAE	7 (28.0)
At least one serious TEAE related to the study drug	5 (20.0)
At least one TEAE leading to dose reduction or interruption	15 (60.0)
At least one TEAE leading to study drug discontinuation	10 (40.0)
At least one TEAE leading to death	1 (4.0)
At least one TEAE with grade 3 or higher	19 (76.0)
At least one TEAE with grade 3 or higher and related to the study drug	17 (68.0)

Source: Listing 16.2.6 1 and 16 2.11.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

ECOG performance status: 2

Description	40 mg (N=2) n (%)
Number of subjects with	
At least one TEAE	2 (100.0)
At least one TEAE related to the study drug	2 (100.0)
At least one serious TEAE	1 (50.0)
At least one serious TEAE related to the study drug	1 (50.0)
At least one TEAE leading to dose reduction or interruption	2 (100.0)
At least one TEAE leading to study drug discontinuation	0 (0.0)
At least one TEAE leading to death	0 (0.0)
At least one TEAE with grade 3 or higher	2 (100.0)
At least one TEAE with grade 3 or higher and related to the study drug	2 (100.0)

Source: Listing 16.2.6 1 and 16 2.11 1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

表 2.7.4.7-88　ECOG PS 別（0、1、2）の有害事象の発現割合（203 試験）（安全性解析対象集団）

System organ class Preferred term	ECOG Status: 0 (N=28) n (%)	ECOG Status: 1 (N=25) n (%)	ECOG Status: 2 (N=2) n (%)
Number of subjects with at least one TEAE	28(100.0)	25(100.0)	2(100.0)
血液およびリンパ系障害	28(100.0)	22(88.0)	2(100.0)
貧血*	9(32.1)	9(36.0)	0
再生不良性貧血	1(3.6)	0	0
好酸球増加症	0	0	1(50.0)
発熱性好中球減少症	0	2(8.0)	1(50.0)
白血球減少症*	17(60.7)	6(24.0)	1(50.0)
リンパ球減少症*	14(50.0)	2(8.0)	0
好中球減少症*	20(71.4)	10(40.0)	1(50.0)
血小板減少症*	27(96.4)	18(72.0)	1(50.0)
心臓障害	5(17.9)	1(4.0)	1(50.0)
不安定狭心症	1(3.6)	0	0
不整脈	1(3.6)	0	0
心房細動	1(3.6)	1(4.0)	0
動悸	3(10.7)	0	0
心嚢液貯留	0	0	1(50.0)
耳および迷路障害	0	1(4.0)	1(50.0)
耳痛	0	0	1(50.0)
回転性めまい	0	1(4.0)	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=28)	ECOG Status: 1 (N=25)	ECOG Status: 2 (N=2)
	n (%)	n (%)	n (%)
眼障害	4(14.3)	1(4.0)	0
白内障	0	1(4.0)	0
結膜出血	1(3.6)	0	0
ドライアイ	1(3.6)	0	0
角膜炎	1(3.6)	0	0
霧視	1(3.6)	0	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=28)	ECOG Status: 1 (N=25)	ECOG Status: 2 (N=2)
	n (%)	n (%)	n (%)
胃腸障害	19(67.9)	11(44.0)	2(100.0)
腹部不快感	1(3.6)	0	0
腹痛	2(7.1)	1(4.0)	0
上腹部痛	2(7.1)	0	0
肛門出血	1(3.6)	0	0
便秘	1(3.6)	0	0
齲歯	2(7.1)	0	0
下痢	9(32.1)	6(24.0)	2(100.0)
消化不良	0	1(4.0)	0
心窩部不快感	1(3.6)	0	0
胃潰瘍	1(3.6)	0	0
胃炎	0	1(4.0)	0
痔出血	1(3.6)	0	0
悪心	6(21.4)	4(16.0)	2(100.0)
口腔粘膜血腫	0	1(4.0)	0
口内炎	0	1(4.0)	1(50.0)
歯痛	1(3.6)	0	0
嘔吐	1(3.6)	1(4.0)	1(50.0)

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=28)	ECOG Status: 1 (N=25)	ECOG Status: 2 (N=2)
	n (%)	n (%)	n (%)
一般・全身障害および投与部位の状態	16(57.1)	9(36.0)	2(100.0)
無力症	0	1(4.0)	1(50.0)
カテーテル留置部位腫脹	1(3.6)	0	0
胸部不快感	1(3.6)	0	0
胸痛	1(3.6)	0	0
溢出	1(3.6)	0	0
疲労	3(10.7)	3(12.0)	0
歩行障害	1(3.6)	0	0
インフルエンザ様疾患	1(3.6)	1(4.0)	0
倦怠感	6(21.4)	1(4.0)	1(50.0)
末梢性浮腫	2(7.1)	1(4.0)	1(50.0)
発熱	5(17.9)	5(20.0)	1(50.0)
口渇	1(3.6)	0	0
免疫系障害	0	1(4.0)	0
薬物過敏症	0	1(4.0)	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=28)	ECOG Status: 1 (N=25)	ECOG Status: 2 (N=2)
	n (%)	n (%)	n (%)
感染症および寄生虫症	11(39.3)	8(32.0)	0
気管支炎	1(3.6)	1(4.0)	0
結膜炎	2(7.1)	0	0
膀胱炎	0	1(4.0)	0
サイトメガロウイルス感染	0	1(4.0)	0
感染性小腸結腸炎	0	1(4.0)	0
胃腸炎	1(3.6)	0	0
帯状疱疹	0	1(4.0)	0
膿痂疹	1(3.6)	0	0
インフルエンザ	1(3.6)	1(4.0)	0
上咽頭炎	2(7.1)	0	0
咽頭炎	2(7.1)	1(4.0)	0
ニューモシスチス・イロベチイ肺炎	0	1(4.0)	0
肺炎	0	1(4.0)	0
鼻炎	1(3.6)	0	0
ブドウ球菌皮膚感染	0	1(4.0)	0
上気道感染	2(7.1)	2(8.0)	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=28)	ECOG Status: 1 (N=25)	ECOG Status: 2 (N=2)
	n (%)	n (%)	n (%)
傷害、中毒および処置合併症	1(3.6)	2(8.0)	0
胃瘻管部合併症	0	1(4.0)	0
爪損傷	1(3.6)	0	0
処置による疼痛	0	1(4.0)	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.

N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.

n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;

TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.

* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.

TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=28)	ECOG Status: 1 (N=25)	ECOG Status: 2 (N=2)
	n (%)	n (%)	n (%)
臨床検査	15(53.6)	9(36.0)	1(50.0)
アラニンアミノトランスフェラーゼ増加	2(7.1)	2(8.0)	1(50.0)
アスパラギン酸アミノトランスフェラーゼ増加	5(17.9)	1(4.0)	1(50.0)
血中アルカリホスファターゼ増加	5(17.9)	3(12.0)	0
血中コレステロール増加	1(3.6)	0	0
血中クレアチンホスホキナーゼＭＢ増加	1(3.6)	0	0
血中クレアチンホスホキナーゼ増加	1(3.6)	0	0
血中クレアチニン増加	1(3.6)	1(4.0)	0
血中免疫グロブリンＡ減少	1(3.6)	0	0
尿中血陽性	1(3.6)	0	0
脳性ナトリウム利尿ペプチド増加	2(7.1)	0	0
Ｃ－反応性蛋白増加	2(7.1)	1(4.0)	0
心胸郭比増加	1(3.6)	0	0
心電図ＱＴ延長	2(7.1)	3(12.0)	0
心電図Ｔ波逆転	1(3.6)	0	0
好酸球数増加	0	2(8.0)	0
γ－グルタミルトランスフェラーゼ増加	4(14.3)	3(12.0)	1(50.0)
リパーゼ増加	1(3.6)	0	0
体重減少	5(17.9)	1(4.0)	0
体重増加	1(3.6)	0	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=28)	ECOG Status: 1 (N=25)	ECOG Status: 2 (N=2)
	n (%)	n (%)	n (%)
代謝および栄養障害	12(42.9)	11(44.0)	2(100.0)
食欲減退	6(21.4)	6(24.0)	1(50.0)
糖尿病	0	1(4.0)	0
高カリウム血症	0	1(4.0)	0
高マグネシウム血症	0	1(4.0)	0
高トリグリセリド血症	1(3.6)	0	0
低アルブミン血症	2(7.1)	2(8.0)	1(50.0)
低カルシウム血症	1(3.6)	2(8.0)	0
低カリウム血症	3(10.7)	2(8.0)	0
低ナトリウム血症	1(3.6)	0	1(50.0)
低蛋白血症	0	1(4.0)	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=28)	ECOG Status: 1 (N=25)	ECOG Status: 2 (N=2)
	n (%)	n (%)	n (%)
筋骨格系および結合組織障害	12(42.9)	6(24.0)	1(50.0)
関節痛	0	1(4.0)	0
関節炎	1(3.6)	0	0
背部痛	3(10.7)	1(4.0)	1(50.0)
出血性関節症	1(3.6)	0	0
関節腫脹	1(3.6)	0	0
筋肉疲労	1(3.6)	1(4.0)	0
筋痙縮	5(17.9)	0	0
筋力低下	0	1(4.0)	0
筋骨格硬直	1(3.6)	0	0
筋肉痛	2(7.1)	0	0
頚部痛	0	1(4.0)	0
四肢痛	1(3.6)	0	0
肩回旋筋腱板症候群	1(3.6)	0	0
腱炎	0	1(4.0)	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	3(10.7)	1(4.0)	0
末梢性Ｔ細胞性リンパ腫、組織型不明	1(3.6)	0	0
皮膚乳頭腫	1(3.6)	0	0
腫瘍疼痛	1(3.6)	1(4.0)	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=28)	ECOG Status: 1 (N=25)	ECOG Status: 2 (N=2)
	n (%)	n (%)	n (%)
神経系障害	6(21.4)	2(8.0)	1(50.0)
浮動性めまい	1(3.6)	0	0
味覚異常	1(3.6)	1(4.0)	0
頭痛	5(17.9)	0	1(50.0)
感覚鈍麻	1(3.6)	0	0
末梢性感覚ニューロパチー	0	1(4.0)	0
失神寸前の状態	1(3.6)	0	0
精神障害	1(3.6)	3(12.0)	1(50.0)
譫妄	0	1(4.0)	1(50.0)
不眠症	1(3.6)	3(12.0)	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=28)	ECOG Status: 1 (N=25)	ECOG Status: 2 (N=2)
	n (%)	n (%)	n (%)
腎および尿路障害	1(3.6)	1(4.0)	0
急性腎障害	0	1(4.0)	0
血尿	1(3.6)	0	0
蛋白尿	1(3.6)	0	0
生殖系および乳房障害	0	1(4.0)	0
陰嚢浮腫	0	1(4.0)	0
呼吸器、胸郭および縦隔障害	8(28.6)	11(44.0)	2(100.0)
咳嗽	2(7.1)	3(12.0)	1(50.0)
咽頭知覚不全	1(3.6)	0	0
発声障害	1(3.6)	0	0
呼吸困難	2(7.1)	1(4.0)	1(50.0)
労作性呼吸困難	0	1(4.0)	0
鼻出血	1(3.6)	1(4.0)	0
しゃっくり	0	1(4.0)	0
間質性肺疾患	0	1(4.0)	0
口腔咽頭痛	1(3.6)	2(8.0)	0
胸水	0	1(4.0)	1(50.0)
肺臓炎	1(3.6)	3(12.0)	0
湿性咳嗽	0	0	1(50.0)
アレルギー性鼻炎	0	1(4.0)	0
鼻漏	0	1(4.0)	0
上気道の炎症	1(3.6)	0	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=28)	ECOG Status: 1 (N=25)	ECOG Status: 2 (N=2)
	n (%)	n (%)	n (%)
皮膚および皮下組織障害	12(42.9)	9(36.0)	2(100.0)
褥瘡性潰瘍	0	0	1(50.0)
ざ瘡様皮膚炎	1(3.6)	0	0
全身性剥脱性皮膚炎	1(3.6)	0	0
皮膚乾燥	0	1(4.0)	0
皮脂欠乏性湿疹	1(3.6)	0	0
紅斑	1(3.6)	1(4.0)	0
多形紅斑	0	1(4.0)	0
全身紅斑	1(3.6)	0	0
皮膚疼痛	0	1(4.0)	0
点状出血	0	1(4.0)	0
色素沈着障害	1(3.6)	0	0
全身性そう痒症	2(7.1)	0	0
紫斑	2(7.1)	0	0
発疹	1(3.6)	4(16.0)	0
斑状丘疹状皮疹	2(7.1)	0	0
そう痒性皮疹	1(3.6)	0	0
蕁麻疹	1(3.6)	3(12.0)	1(50.0)
血管障害	0	3(12.0)	0
深部静脈血栓症	0	1(4.0)	0
低血圧	0	1(4.0)	0
末梢動脈閉塞性疾患	0	1(4.0)	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-89　ECOG PS 別（0、1、2）の有害事象の概要（210 試験）（安全性解析対象集団）

ECOG performance status: 0

Description	40 mg (N=12) n (%)
Number of subjects with	
At least one TEAE	12 (100.0%)
At least one TEAE related to the study drug	12 (100.0%)
At least one serious TEAE	5 (41.7%)
At least one serious TEAE related to the study drug	5 (41.7%)
At least one TEAE leading to dose reduction or interruption	11 (91.7%)
At least one TEAE leading to study drug discontinuation	7 (58.3%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	11 (91.7%)
At least one TEAE with grade 3 or higher and related to the study drug	11 (91.7%)

Source: Listing 16.2.6 1 and 16 2.11.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

ECOG performance status: 1

Description	40 mg (N=10) n (%)
Number of subjects with	
At least one TEAE	10 (100.0%)
At least one TEAE related to the study drug	10 (100.0%)
At least one serious TEAE	2 (20.0%)
At least one serious TEAE related to the study drug	1 (10.0%)
At least one TEAE leading to dose reduction or interruption	4 (40.0%)
At least one TEAE leading to study drug discontinuation	2 (20.0%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	6 (60.0%)
At least one TEAE with grade 3 or higher and related to the study drug	6 (60.0%)

Source: Listing 16.2.6 1 and 16.2.11.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

ECOG performance status: 2

Description	40 mg (N=1) n (%)
Number of subjects with	
At least one TEAE	1 (100.0%)
At least one TEAE related to the study drug	1 (100.0%)
At least one serious TEAE	0 (0.0%)
At least one serious TEAE related to the study drug	0 (0.0%)
At least one TEAE leading to dose reduction or interruption	1 (100.0%)
At least one TEAE leading to study drug discontinuation	0 (0.0%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	1 (100.0%)
At least one TEAE with grade 3 or higher and related to the study drug	1 (100.0%)

Source: Listing 16.2.6 1 and 16 2.11.1

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

表 2.7.4.7-90　ECOG PS 別（0、1、2）の有害事象の発現割合（210 試験）（安全性解析対象集団）

System organ class Preferred term	ECOG Status: 0 (N=12) n (%)	ECOG Status: 1 (N=10) n (%)	ECOG Status: 2 (N=1) n (%)
Number of subjects with at least one TEAE	12(100.0%)	10(100.0%)	1(100.0%)
血液およびリンパ系障害	10(83.3%)	8(80.0%)	1(100.0%)
貧血*	6(50.0%)	3(30.0%)	0
好酸球増加症	1(8.3%)	0	0
発熱性好中球減少症	1(8.3%)	0	0
白血球減少症*	7(58.3%)	2(20.0%)	1(100.0%)
リンパ球減少症*	2(16.7%)	0	0
好中球減少症*	9(75.0%)	3(30.0%)	0
血小板減少症*	9(75.0%)	8(80.0%)	1(100.0%)
心臓障害	1(8.3%)	1(10.0%)	0
第一度房室ブロック	0	1(10.0%)	0
動悸	1(8.3%)	0	0
眼障害	0	1(10.0%)	0
ドライアイ	0	1(10.0%)	0
胃腸障害	4(33.3%)	5(50.0%)	0
腹痛	1(8.3%)	2(20.0%)	0
下痢	3(25.0%)	3(30.0%)	0
悪心	1(8.3%)	2(20.0%)	0
口内炎	0	1(10.0%)	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=12)	ECOG Status: 1 (N=10)	ECOG Status: 2 (N=1)
	n (%)	n (%)	n (%)
一般・全身障害および投与部位の状態	7(58.3%)	5(50.0%)	1(100.0%)
悪寒	1(8.3%)	0	0
疲労	2(16.7%)	1(10.0%)	0
倦怠感	4(33.3%)	3(30.0%)	0
非心臓性胸痛	0	0	1(100.0%)
末梢性浮腫	0	1(10.0%)	0
発熱	2(16.7%)	1(10.0%)	0
感染症および寄生虫症	4(33.3%)	3(30.0%)	0
細菌感染	0	1(10.0%)	0
サイトメガロウイルス感染	1(8.3%)	0	0
医療機器関連感染	1(8.3%)	0	0
麦粒腫	1(8.3%)	0	0
口腔カンジダ症	0	1(10.0%)	0
ニューモシスチス・イロベチイ肺炎	1(8.3%)	0	0
皮膚感染	1(8.3%)	0	0
扁桃炎	0	1(10.0%)	0
上気道感染	1(8.3%)	0	0
尿路感染	1(8.3%)	0	0
傷害、中毒および処置合併症	0	1(10.0%)	0
挫傷	0	1(10.0%)	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=12)	ECOG Status: 1 (N=10)	ECOG Status: 2 (N=1)
	n (%)	n (%)	n (%)
臨床検査	6(50.0%)	4(40.0%)	0
アラニンアミノトランスフェラーゼ増加	1(8.3%)	0	0
アスパラギン酸アミノトランスフェラーゼ増加	1(8.3%)	1(10.0%)	0
血中アルカリホスファターゼ増加	1(8.3%)	0	0
血中乳酸脱水素酵素増加	0	1(10.0%)	0
脳性ナトリウム利尿ペプチド増加	1(8.3%)	0	0
好酸球数増加	0	1(10.0%)	0
γ－グルタミルトランスフェラーゼ増加	1(8.3%)	1(10.0%)	0
リパーゼ増加	0	1(10.0%)	0
体重減少	3(25.0%)	1(10.0%)	0
代謝および栄養障害	6(50.0%)	7(70.0%)	0
食欲減退	4(33.3%)	4(40.0%)	0
高カルシウム血症	0	1(10.0%)	0
低アルブミン血症	1(8.3%)	2(20.0%)	0
低カリウム血症	1(8.3%)	0	0
低ナトリウム血症	1(8.3%)	1(10.0%)	0
低リン酸血症	1(8.3%)	0	0
筋骨格系および結合組織障害	4(33.3%)	3(30.0%)	0
関節痛	1(8.3%)	0	0
背部痛	2(16.7%)	2(20.0%)	0
脊椎すべり症	0	1(10.0%)	0
尺骨突き上げ症候群	1(8.3%)	0	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=12)	ECOG Status: 1 (N=10)	ECOG Status: 2 (N=1)
	n (%)	n (%)	n (%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	0	1(10.0%)	0
腫瘍疼痛	0	1(10.0%)	0
神経系障害	3(25.0%)	6(60.0%)	0
味覚消失	0	1(10.0%)	0
認知障害	0	1(10.0%)	0
浮動性めまい	0	1(10.0%)	0
味覚異常	1(8.3%)	3(30.0%)	0
頭痛	1(8.3%)	1(10.0%)	0
傾眠	1(8.3%)	0	0
腎および尿路障害	1(8.3%)	0	0
尿瘻	1(8.3%)	0	0
呼吸器、胸郭および縦隔障害	2(16.7%)	2(20.0%)	0
急性呼吸不全	0	1(10.0%)	0
鼻出血	1(8.3%)	0	0
間質性肺疾患	1(8.3%)	0	0
口腔咽頭痛	0	1(10.0%)	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	ECOG Status: 0 (N=12)	ECOG Status: 1 (N=10)	ECOG Status: 2 (N=1)
	n (%)	n (%)	n (%)
皮膚および皮下組織障害	4(33.3%)	3(30.0%)	1(100.0%)
接触皮膚炎	0	0	1(100.0%)
湿疹	1(8.3%)	0	0
紅斑	0	1(10.0%)	0
多形紅斑	0	1(10.0%)	0
光線過敏性反応	0	1(10.0%)	0
そう痒症	1(8.3%)	0	0
発疹	1(8.3%)	0	0
皮膚剥脱	0	1(10.0%)	0
皮膚潰瘍	1(8.3%)	0	0
血管障害	1(8.3%)	0	0
高血圧	1(8.3%)	0	0

Source: Listing 16.2.6 1 and 16 2.11.1

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by ECOG performance status at baseline.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-91　前治療のレジメン数別（3 レジメン未満、3 レジメン以上）の有害事象の概要（203 試験）（安全性解析対象集団）

Number of Regimens Before the Study Treatment: Less than 3 regimens

Description	40 mg (N=35) n (%)
Number of subjects with	
At least one TEAE	35 (100.0)
At least one TEAE related to the study drug	32 (91.4)
At least one serious TEAE	10 (28.6)
At least one serious TEAE related to the study drug	7 (20.0)
At least one TEAE leading to dose reduction or interruption	25 (71.4)
At least one TEAE leading to study drug discontinuation	8 (22.9)
At least one TEAE leading to death	0 (0.0)
At least one TEAE with grade 3 or higher	31 (88.6)
At least one TEAE with grade 3 or higher and related to the study drug	28 (80.0)

Source: Listing 16.2.6 1 and 16 2.4.4

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

Number of Regimens Before the Study Treatment: 3 or more regimens

Description	40 mg (N=20)
	n (%)
Number of subjects with	
At least one TEAE	20 (100.0)
At least one TEAE related to the study drug	19 (95.0)
At least one serious TEAE	4 (20.0)
At least one serious TEAE related to the study drug	3 (15.0)
At least one TEAE leading to dose reduction or interruption	15 (75.0)
At least one TEAE leading to study drug discontinuation	10 (50.0)
At least one TEAE leading to death	1 (5.0)
At least one TEAE with grade 3 or higher	15 (75.0)
At least one TEAE with grade 3 or higher and related to the study drug	14 (70.0)

Source: Listing 16.2.6 1 and 16 2.4.4

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

表 2.7.4.7-92　前治療のレジメン数別（3 レジメン未満、3 レジメン以上）の有害事象の発現割合（203 試験）（安全性解析対象集団）

System organ class Preferred term	Less than 3 regimens (N=35) n (%)	3 or more regimens (N=20) n (%)
Number of subjects with at least one TEAE	35(100.0)	20(100.0)
血液およびリンパ系障害	34(97.1)	18(90.0)
貧血*	13(37.1)	5(25.0)
再生不良性貧血	0	1(5.0)
好酸球増加症	1(2.9)	0
発熱性好中球減少症	2(5.7)	1(5.0)
白血球減少症*	15(42.9)	9(45.0)
リンパ球減少症*	11(31.4)	5(25.0)
好中球減少症*	20(57.1)	11(55.0)
血小板減少症*	29(82.9)	17(85.0)
心臓障害	3(8.6)	4(20.0)
不安定狭心症	0	1(5.0)
不整脈	0	1(5.0)
心房細動	0	2(10.0)
動悸	2(5.7)	1(5.0)
心嚢液貯留	1(2.9)	0
耳および迷路障害	1(2.9)	1(5.0)
耳痛	1(2.9)	0
回転性めまい	0	1(5.0)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=35) n (%)	3 or more regimens (N=20) n (%)
眼障害	4(11.4)	1(5.0)
白内障	1(2.9)	0
結膜出血	0	1(5.0)
ドライアイ	1(2.9)	0
角膜炎	1(2.9)	0
霧視	1(2.9)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=35) n (%)	3 or more regimens (N=20) n (%)
胃腸障害	23(65.7)	9(45.0)
腹部不快感	0	1(5.0)
腹痛	2(5.7)	1(5.0)
上腹部痛	1(2.9)	1(5.0)
肛門出血	1(2.9)	0
便秘	1(2.9)	0
齲歯	2(5.7)	0
下痢	13(37.1)	4(20.0)
消化不良	1(2.9)	0
心窩部不快感	1(2.9)	0
胃潰瘍	1(2.9)	0
胃炎	0	1(5.0)
痔出血	0	1(5.0)
悪心	8(22.9)	4(20.0)
口腔粘膜血腫	1(2.9)	0
口内炎	2(5.7)	0
歯痛	1(2.9)	0
嘔吐	2(5.7)	1(5.0)

Source: Listing 16.2.6 1 and 16.2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=35) n (%)	3 or more regimens (N=20) n (%)
一般・全身障害および投与部位の状態	17(48.6)	10(50.0)
無力症	1(2.9)	1(5.0)
カテーテル留置部位腫脹	1(2.9)	0
胸部不快感	1(2.9)	0
胸痛	0	1(5.0)
溢出	1(2.9)	0
疲労	2(5.7)	4(20.0)
歩行障害	1(2.9)	0
インフルエンザ様疾患	2(5.7)	0
倦怠感	5(14.3)	3(15.0)
末梢性浮腫	4(11.4)	0
発熱	7(20.0)	4(20.0)
口渇	1(2.9)	0
免疫系障害	1(2.9)	0
薬物過敏症	1(2.9)	0

Source: Listing 16 2.6.1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=35) n (%)	3 or more regimens (N=20) n (%)
感染症および寄生虫症	15(42.9)	4(20.0)
気管支炎	2(5.7)	0
結膜炎	2(5.7)	0
膀胱炎	1(2.9)	0
サイトメガロウイルス感染	1(2.9)	0
感染性小腸結腸炎	0	1(5.0)
胃腸炎	1(2.9)	0
帯状疱疹	1(2.9)	0
膿痂疹	1(2.9)	0
インフルエンザ	1(2.9)	1(5.0)
上咽頭炎	1(2.9)	1(5.0)
咽頭炎	3(8.6)	0
ニューモシスチス・イロベチイ肺炎	1(2.9)	0
肺炎	0	1(5.0)
鼻炎	1(2.9)	0
ブドウ球菌皮膚感染	0	1(5.0)
上気道感染	2(5.7)	2(10.0)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=35) n (%)	3 or more regimens (N=20) n (%)
傷害、中毒および処置合併症	2(5.7)	1(5.0)
胃瘻管部合併症	0	1(5.0)
爪損傷	1(2.9)	0
処置による疼痛	1(2.9)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=35)	3 or more regimens (N=20)
	n (%)	n (%)
臨床検査	17(48.6)	8(40.0)
アラニンアミノトランスフェラーゼ増加	4(11.4)	1(5.0)
アスパラギン酸アミノトランスフェラーゼ増加	7(20.0)	0
血中アルカリホスファターゼ増加	5(14.3)	3(15.0)
血中コレステロール増加	1(2.9)	0
血中クレアチンホスホキナーゼＭＢ増加	1(2.9)	0
血中クレアチンホスホキナーゼ増加	1(2.9)	0
血中クレアチニン増加	2(5.7)	0
血中免疫グロブリンＡ減少	0	1(5.0)
尿中血陽性	1(2.9)	0
脳性ナトリウム利尿ペプチド増加	0	2(10.0)
Ｃ－反応性蛋白増加	2(5.7)	1(5.0)
心胸郭比増加	0	1(5.0)
心電図ＱＴ延長	3(8.6)	2(10.0)
心電図Ｔ波逆転	1(2.9)	0
好酸球数増加	1(2.9)	1(5.0)
γ－グルタミルトランスフェラーゼ増加	6(17.1)	2(10.0)
リパーゼ増加	0	1(5.0)
体重減少	5(14.3)	1(5.0)
体重増加	1(2.9)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=35)	3 or more regimens (N=20)
	n (%)	n (%)
代謝および栄養障害	17(48.6)	8(40.0)
食欲減退	10(28.6)	3(15.0)
糖尿病	1(2.9)	0
高カリウム血症	0	1(5.0)
高マグネシウム血症	0	1(5.0)
高トリグリセリド血症	1(2.9)	0
低アルブミン血症	3(8.6)	2(10.0)
低カルシウム血症	2(5.7)	1(5.0)
低カリウム血症	2(5.7)	3(15.0)
低ナトリウム血症	2(5.7)	0
低蛋白血症	0	1(5.0)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=35) n (%)	3 or more regimens (N=20) n (%)
筋骨格系および結合組織障害	14(40.0)	5(25.0)
関節痛	1(2.9)	0
関節炎	1(2.9)	0
背部痛	3(8.6)	2(10.0)
出血性関節症	1(2.9)	0
関節腫脹	1(2.9)	0
筋肉疲労	1(2.9)	1(5.0)
筋痙縮	4(11.4)	1(5.0)
筋力低下	1(2.9)	0
筋骨格硬直	1(2.9)	0
筋肉痛	1(2.9)	1(5.0)
頚部痛	1(2.9)	0
四肢痛	1(2.9)	0
肩回旋筋腱板症候群	1(2.9)	0
腱炎	1(2.9)	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	4(11.4)	0
末梢性Ｔ細胞性リンパ腫、組織型不明	1(2.9)	0
皮膚乳頭腫	1(2.9)	0
腫瘍疼痛	2(5.7)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=35) n (%)	3 or more regimens (N=20) n (%)
神経系障害	6(17.1)	3(15.0)
浮動性めまい	0	1(5.0)
味覚異常	1(2.9)	1(5.0)
頭痛	5(14.3)	1(5.0)
感覚鈍麻	0	1(5.0)
末梢性感覚ニューロパチー	1(2.9)	0
失神寸前の状態	0	1(5.0)
精神障害	4(11.4)	1(5.0)
譫妄	2(5.7)	0
不眠症	3(8.6)	1(5.0)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=35)	3 or more regimens (N=20)
	n (%)	n (%)
腎および尿路障害	1(2.9)	1(5.0)
急性腎障害	0	1(5.0)
血尿	1(2.9)	0
蛋白尿	1(2.9)	0
生殖系および乳房障害	0	1(5.0)
陰嚢浮腫	0	1(5.0)
呼吸器、胸郭および縦隔障害	18(51.4)	3(15.0)
咳嗽	6(17.1)	0
咽頭知覚不全	1(2.9)	0
発声障害	1(2.9)	0
呼吸困難	3(8.6)	1(5.0)
労作性呼吸困難	1(2.9)	0
鼻出血	2(5.7)	0
しゃっくり	1(2.9)	0
間質性肺疾患	1(2.9)	0
口腔咽頭痛	2(5.7)	1(5.0)
胸水	1(2.9)	1(5.0)
肺臓炎	2(5.7)	2(10.0)
湿性咳嗽	1(2.9)	0
アレルギー性鼻炎	1(2.9)	0
鼻漏	1(2.9)	0
上気道の炎症	1(2.9)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=35)	3 or more regimens (N=20)
	n (%)	n (%)
皮膚および皮下組織障害	17(48.6)	6(30.0)
褥瘡性潰瘍	1(2.9)	0
ざ瘡様皮膚炎	1(2.9)	0
全身性剥脱性皮膚炎	1(2.9)	0
皮膚乾燥	0	1(5.0)
皮脂欠乏性湿疹	1(2.9)	0
紅斑	2(5.7)	0
多形紅斑	0	1(5.0)
全身紅斑	0	1(5.0)
皮膚疼痛	1(2.9)	0
点状出血	1(2.9)	0
色素沈着障害	1(2.9)	0
全身性そう痒症	2(5.7)	0
紫斑	2(5.7)	0
発疹	5(14.3)	0
斑状丘疹状皮疹	1(2.9)	1(5.0)
そう痒性皮疹	0	1(5.0)
蕁麻疹	4(11.4)	1(5.0)
血管障害	2(5.7)	1(5.0)
深部静脈血栓症	1(2.9)	0
低血圧	0	1(5.0)
末梢動脈閉塞性疾患	1(2.9)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-93　前治療のレジメン数別（3 レジメン未満、3 レジメン以上）の有害事象の概要（210 試験）（安全性解析対象集団）

Number of Regimens Before the Study Treatment: Less than 3 regimens

Description	40 mg (N=11) n (%)
Number of subjects with	
At least one TEAE	11 (100.0%)
At least one TEAE related to the study drug	11 (100.0%)
At least one serious TEAE	5 (45.5%)
At least one serious TEAE related to the study drug	5 (45.5%)
At least one TEAE leading to dose reduction or interruption	7 (63.6%)
At least one TEAE leading to study drug discontinuation	3 (27.3%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	8 (72.7%)
At least one TEAE with grade 3 or higher and related to the study drug	8 (72.7%)

Source: Listing 16 2.6.1 and 16 2.4.4

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

Number of Regimens Before the Study Treatment: 3 or more regimens

Description	40 mg (N=12) n (%)
Number of subjects with	
At least one TEAE	12 (100.0%)
At least one TEAE related to the study drug	12 (100.0%)
At least one serious TEAE	2 (16.7%)
At least one serious TEAE related to the study drug	1 (8.3%)
At least one TEAE leading to dose reduction or interruption	9 (75.0%)
At least one TEAE leading to study drug discontinuation	6 (50.0%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	10 (83.3%)
At least one TEAE with grade 3 or higher and related to the study drug	10 (83.3%)

Source: Listing 16.2.6 1 and 16 2.4.4

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

表 2.7.4.7-94　前治療のレジメン数別（3 レジメン未満、3 レジメン以上）の有害事象の発現割合（210 試験）（安全性解析対象集団）

System organ class Preferred term	Less than 3 regimens (N=11) n (%)	3 or more regimens (N=12) n (%)
Number of subjects with at least one TEAE	11(100.0%)	12(100.0%)
血液およびリンパ系障害	8(72.7%)	11(91.7%)
貧血*	2(18.2%)	7(58.3%)
好酸球増加症	1(9.1%)	0
発熱性好中球減少症	0	1(8.3%)
白血球減少症*	3(27.3%)	7(58.3%)
リンパ球減少症*	0	2(16.7%)
好中球減少症*	5(45.5%)	7(58.3%)
血小板減少症*	8(72.7%)	10(83.3%)
心臓障害	2(18.2%)	0
第一度房室ブロック	1(9.1%)	0
動悸	1(9.1%)	0
眼障害	1(9.1%)	0
ドライアイ	1(9.1%)	0
胃腸障害	4(36.4%)	5(41.7%)
腹痛	1(9.1%)	2(16.7%)
下痢	2(18.2%)	4(33.3%)
悪心	1(9.1%)	2(16.7%)
口内炎	1(9.1%)	0

Source: Listing 16 2.6.1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=11)	3 or more regimens (N=12)
	n (%)	n (%)
一般・全身障害および投与部位の状態	6(54.5%)	7(58.3%)
悪寒	0	1(8.3%)
疲労	2(18.2%)	1(8.3%)
倦怠感	4(36.4%)	3(25.0%)
非心臓性胸痛	0	1(8.3%)
末梢性浮腫	1(9.1%)	0
発熱	1(9.1%)	2(16.7%)
感染症および寄生虫症	4(36.4%)	3(25.0%)
細菌感染	1(9.1%)	0
サイトメガロウイルス感染	0	1(8.3%)
医療機器関連感染	0	1(8.3%)
麦粒腫	1(9.1%)	0
口腔カンジダ症	1(9.1%)	0
ニューモシスチス・イロベチイ肺炎	1(9.1%)	0
皮膚感染	0	1(8.3%)
扁桃炎	0	1(8.3%)
上気道感染	1(9.1%)	0
尿路感染	1(9.1%)	0
傷害、中毒および処置合併症	1(9.1%)	0
挫傷	1(9.1%)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=11)	3 or more regimens (N=12)
	n (%)	n (%)
臨床検査	8(72.7%)	2(16.7%)
アラニンアミノトランスフェラーゼ増加	1(9.1%)	0
アスパラギン酸アミノトランスフェラーゼ増加	2(18.2%)	0
血中アルカリホスファターゼ増加	1(9.1%)	0
血中乳酸脱水素酵素増加	1(9.1%)	0
脳性ナトリウム利尿ペプチド増加	1(9.1%)	0
好酸球数増加	1(9.1%)	0
γーグルタミルトランスフェラーゼ増加	2(18.2%)	0
リパーゼ増加	1(9.1%)	0
体重減少	2(18.2%)	2(16.7%)
代謝および栄養障害	7(63.6%)	6(50.0%)
食欲減退	5(45.5%)	3(25.0%)
高カルシウム血症	1(9.1%)	0
低アルブミン血症	1(9.1%)	2(16.7%)
低カリウム血症	1(9.1%)	0
低ナトリウム血症	0	2(16.7%)
低リン酸血症	1(9.1%)	0
筋骨格系および結合組織障害	5(45.5%)	2(16.7%)
関節痛	0	1(8.3%)
背部痛	3(27.3%)	1(8.3%)
脊椎すべり症	1(9.1%)	0
尺骨突き上げ症候群	1(9.1%)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=11)	3 or more regimens (N=12)
	n (%)	n (%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	0	1(8.3%)
腫瘍疼痛	0	1(8.3%)
神経系障害	5(45.5%)	4(33.3%)
味覚消失	1(9.1%)	0
認知障害	0	1(8.3%)
浮動性めまい	1(9.1%)	0
味覚異常	2(18.2%)	2(16.7%)
頭痛	1(9.1%)	1(8.3%)
傾眠	1(9.1%)	0
腎および尿路障害	0	1(8.3%)
尿瘻	0	1(8.3%)
呼吸器、胸郭および縦隔障害	2(18.2%)	2(16.7%)
急性呼吸不全	0	1(8.3%)
鼻出血	1(9.1%)	0
間質性肺疾患	0	1(8.3%)
口腔咽頭痛	1(9.1%)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

System organ class Preferred term	Less than 3 regimens (N=11)	3 or more regimens (N=12)
	n (%)	n (%)
皮膚および皮下組織障害	4(36.4%)	4(33.3%)
接触皮膚炎	0	1(8.3%)
湿疹	1(9.1%)	0
紅斑	0	1(8.3%)
多形紅斑	1(9.1%)	0
光線過敏性反応	1(9.1%)	0
そう痒症	1(9.1%)	0
発疹	1(9.1%)	0
皮膚剥脱	0	1(8.3%)
皮膚潰瘍	0	1(8.3%)
血管障害	0	1(8.3%)
高血圧	0	1(8.3%)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the number of regimens before the start of study treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.

表 2.7.4.7-95　直近のがん治療からの期間別（3 ヵ月未満、3 ヵ月以上）の有害事象の概要（203 試験）（安全性解析対象集団）

Days from End of the Last Immediate Previous Treatment: < 3 months

Description	40 mg (N=27) n (%)
Number of subjects with	
At least one TEAE	27 (100.0)
At least one TEAE related to the study drug	25 (92.6)
At least one serious TEAE	5 (18.5)
At least one serious TEAE related to the study drug	4 (14.8)
At least one TEAE leading to dose reduction or interruption	18 (66.7)
At least one TEAE leading to study drug discontinuation	7 (25.9)
At least one TEAE leading to death	0 (0.0)
At least one TEAE with grade 3 or higher	20 (74.1)
At least one TEAE with grade 3 or higher and related to the study drug	19 (70.4)

Source: Listing 16.2.6 1 and 16 2.4.4

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment; n = number of subjects;
% = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

Days from End of the Last Immediate Previous Treatment: >=3 months

Description	40 mg (N=28) n (%)
Number of subjects with	
At least one TEAE	28 (100.0)
At least one TEAE related to the study drug	26 (92.9)
At least one serious TEAE	9 (32.1)
At least one serious TEAE related to the study drug	6 (21.4)
At least one TEAE leading to dose reduction or interruption	22 (78.6)
At least one TEAE leading to study drug discontinuation	11 (39.3)
At least one TEAE leading to death	1 (3.6)
At least one TEAE with grade 3 or higher	26 (92.9)
At least one TEAE with grade 3 or higher and related to the study drug	23 (82.1)

Source: Listing 16.2.6 1 and 16 2.4.4

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment; n = number of subjects;
% = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

表 2.7.4.7-96　直近のがん治療からの期間別（3 ヵ月未満、3 ヵ月以上）の有害事象の発現割合（203 試験）（安全性解析対象集団）

System organ class Preferred term	< 3months (N=27) n (%)	>= 3months (N=28) n (%)
Number of subjects with at least one TEAE	27(100.0)	28(100.0)
血液およびリンパ系障害	25(92.6)	27(96.4)
貧血*	9(33.3)	9(32.1)
再生不良性貧血	1(3.7)	0
好酸球増加症	1(3.7)	0
発熱性好中球減少症	3(11.1)	0
白血球減少症*	13(48.1)	11(39.3)
リンパ球減少症*	7(25.9)	9(32.1)
好中球減少症*	15(55.6)	16(57.1)
血小板減少症*	22(81.5)	24(85.7)
心臓障害	4(14.8)	3(10.7)
不安定狭心症	0	1(3.6)
不整脈	1(3.7)	0
心房細動	1(3.7)	1(3.6)
動悸	2(7.4)	1(3.6)
心嚢液貯留	1(3.7)	0
耳および迷路障害	2(7.4)	0
耳痛	1(3.7)	0
回転性めまい	1(3.7)	0

Source: Listing 16.2.6 1 and 16 2.4.4
MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

System organ class Preferred term	< 3months (N=27) n (%)	>= 3months (N=28) n (%)
眼障害	3(11.1)	2(7.1)
白内障	1(3.7)	0
結膜出血	1(3.7)	0
ドライアイ	0	1(3.6)
角膜炎	0	1(3.6)
霧視	1(3.7)	0

Source: Listing 16.2.6.1 and 16.2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

System organ class Preferred term	< 3months (N=27) n (%)	>= 3months (N=28) n (%)
胃腸障害	16(59.3)	16(57.1)
腹部不快感	1(3.7)	0
腹痛	1(3.7)	2(7.1)
上腹部痛	1(3.7)	1(3.6)
肛門出血	1(3.7)	0
便秘	0	1(3.6)
齲歯	0	2(7.1)
下痢	10(37.0)	7(25.0)
消化不良	0	1(3.6)
心窩部不快感	0	1(3.6)
胃潰瘍	0	1(3.6)
胃炎	1(3.7)	0
痔出血	1(3.7)	0
悪心	7(25.9)	5(17.9)
口腔粘膜血腫	0	1(3.6)
口内炎	1(3.7)	1(3.6)
歯痛	1(3.7)	0
嘔吐	2(7.4)	1(3.6)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

System organ class Preferred term	< 3months (N=27)	>= 3months (N=28)
	n (%)	n (%)
一般・全身障害および投与部位の状態	15(55.6)	12(42.9)
無力症	2(7.4)	0
カテーテル留置部位腫脹	0	1(3.6)
胸部不快感	0	1(3.6)
胸痛	0	1(3.6)
溢出	0	1(3.6)
疲労	3(11.1)	3(10.7)
歩行障害	1(3.7)	0
インフルエンザ様疾患	0	2(7.1)
倦怠感	5(18.5)	3(10.7)
末梢性浮腫	1(3.7)	3(10.7)
発熱	6(22.2)	5(17.9)
口渇	1(3.7)	0
免疫系障害	1(3.7)	0
薬物過敏症	1(3.7)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

System organ class Preferred term	< 3months (N=27)	>= 3months (N=28)
	n (%)	n (%)
感染症および寄生虫症	4(14.8)	15(53.6)
気管支炎	0	2(7.1)
結膜炎	1(3.7)	1(3.6)
膀胱炎	1(3.7)	0
サイトメガロウイルス感染	1(3.7)	0
感染性小腸結腸炎	0	1(3.6)
胃腸炎	0	1(3.6)
帯状疱疹	0	1(3.6)
膿痂疹	0	1(3.6)
インフルエンザ	2(7.4)	0
上咽頭炎	1(3.7)	1(3.6)
咽頭炎	0	3(10.7)
ニューモシスチス・イロベチイ肺炎	0	1(3.6)
肺炎	0	1(3.6)
鼻炎	0	1(3.6)
ブドウ球菌皮膚感染	0	1(3.6)
上気道感染	0	4(14.3)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

System organ class Preferred term	< 3months (N=27) n (%)	>= 3months (N=28) n (%)
傷害、中毒および処置合併症	0	3(10.7)
胃瘻管部合併症	0	1(3.6)
爪損傷	0	1(3.6)
処置による疼痛	0	1(3.6)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

System organ class Preferred term	< 3months (N=27) n (%)	>= 3months (N=28) n (%)
臨床検査	11(40.7)	14(50.0)
アラニンアミノトランスフェラーゼ増加	3(11.1)	2(7.1)
アスパラギン酸アミノトランスフェラーゼ増加	3(11.1)	4(14.3)
血中アルカリホスファターゼ増加	2(7.4)	6(21.4)
血中コレステロール増加	1(3.7)	0
血中クレアチンホスホキナーゼＭＢ増加	0	1(3.6)
血中クレアチンホスホキナーゼ増加	0	1(3.6)
血中クレアチニン増加	1(3.7)	1(3.6)
血中免疫グロブリンＡ減少	1(3.7)	0
尿中血陽性	0	1(3.6)
脳性ナトリウム利尿ペプチド増加	1(3.7)	1(3.6)
Ｃ－反応性蛋白増加	1(3.7)	2(7.1)
心胸郭比増加	1(3.7)	0
心電図ＱＴ延長	2(7.4)	3(10.7)
心電図Ｔ波逆転	0	1(3.6)
好酸球数増加	1(3.7)	1(3.6)
γ－グルタミルトランスフェラーゼ増加	4(14.8)	4(14.3)
リパーゼ増加	0	1(3.6)
体重減少	2(7.4)	4(14.3)
体重増加	1(3.7)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

System organ class Preferred term	< 3months (N=27) n (%)	>= 3months (N=28) n (%)
代謝および栄養障害	14(51.9)	11(39.3)
食欲減退	8(29.6)	5(17.9)
糖尿病	0	1(3.6)
高カリウム血症	1(3.7)	0
高マグネシウム血症	1(3.7)	0
高トリグリセリド血症	1(3.7)	0
低アルブミン血症	4(14.8)	1(3.6)
低カルシウム血症	1(3.7)	2(7.1)
低カリウム血症	3(11.1)	2(7.1)
低ナトリウム血症	1(3.7)	1(3.6)
低蛋白血症	1(3.7)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

System organ class Preferred term	< 3months (N=27) n (%)	>= 3months (N=28) n (%)
筋骨格系および結合組織障害	8(29.6)	11(39.3)
関節痛	0	1(3.6)
関節炎	1(3.7)	0
背部痛	4(14.8)	1(3.6)
出血性関節症	0	1(3.6)
関節腫脹	0	1(3.6)
筋肉疲労	1(3.7)	1(3.6)
筋痙縮	2(7.4)	3(10.7)
筋力低下	1(3.7)	0
筋骨格硬直	0	1(3.6)
筋肉痛	1(3.7)	1(3.6)
頚部痛	0	1(3.6)
四肢痛	0	1(3.6)
肩回旋筋腱板症候群	0	1(3.6)
腱炎	0	1(3.6)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	2(7.4)	2(7.1)
末梢性Ｔ細胞性リンパ腫、組織型不明	0	1(3.6)
皮膚乳頭腫	1(3.7)	0
腫瘍疼痛	1(3.7)	1(3.6)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

System organ class Preferred term	< 3months (N=27) n (%)	>= 3months (N=28) n (%)
神経系障害	5(18.5)	4(14.3)
浮動性めまい	1(3.7)	0
味覚異常	1(3.7)	1(3.6)
頭痛	4(14.8)	2(7.1)
感覚鈍麻	1(3.7)	0
末梢性感覚ニューロパチー	0	1(3.6)
失神寸前の状態	0	1(3.6)
精神障害	4(14.8)	1(3.6)
譫妄	1(3.7)	1(3.6)
不眠症	3(11.1)	1(3.6)
腎および尿路障害	1(3.7)	1(3.6)
急性腎障害	1(3.7)	0
血尿	0	1(3.6)
蛋白尿	0	1(3.6)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

System organ class Preferred term	< 3months (N=27) n (%)	>= 3months (N=28) n (%)
生殖系および乳房障害	1(3.7)	0
陰嚢浮腫	1(3.7)	0
呼吸器、胸郭および縦隔障害	10(37.0)	11(39.3)
咳嗽	1(3.7)	5(17.9)
咽頭知覚不全	1(3.7)	0
発声障害	0	1(3.6)
呼吸困難	2(7.4)	2(7.1)
労作性呼吸困難	0	1(3.6)
鼻出血	1(3.7)	1(3.6)
しゃっくり	1(3.7)	0
間質性肺疾患	0	1(3.6)
口腔咽頭痛	2(7.4)	1(3.6)
胸水	2(7.4)	0
肺臓炎	3(11.1)	1(3.6)
湿性咳嗽	1(3.7)	0
アレルギー性鼻炎	0	1(3.6)
鼻漏	0	1(3.6)
上気道の炎症	0	1(3.6)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

System organ class Preferred term	< 3months (N=27)	>= 3months (N=28)
	n (%)	n (%)
皮膚および皮下組織障害	10(37.0)	13(46.4)
褥瘡性潰瘍	1(3.7)	0
ざ瘡様皮膚炎	0	1(3.6)
全身性剥脱性皮膚炎	0	1(3.6)
皮膚乾燥	1(3.7)	0
皮脂欠乏性湿疹	0	1(3.6)
紅斑	1(3.7)	1(3.6)
多形紅斑	1(3.7)	0
全身紅斑	0	1(3.6)
皮膚疼痛	0	1(3.6)
点状出血	0	1(3.6)
色素沈着障害	1(3.7)	0
全身性そう痒症	0	2(7.1)
紫斑	2(7.4)	0
発疹	1(3.7)	4(14.3)
斑状丘疹状皮疹	0	2(7.1)
そう痒性皮疹	1(3.7)	0
蕁麻疹	3(11.1)	2(7.1)
血管障害	1(3.7)	2(7.1)
深部静脈血栓症	0	1(3.6)
低血圧	1(3.7)	0
末梢動脈閉塞性疾患	0	1(3.6)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects within a subgroup in the analysis set;
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
TEAE of overdose is not included in this analysis.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375.

表 2.7.4.7-97　直近のがん治療からの期間別（3 ヵ月未満、3 ヵ月以上）の有害事象の概要（210 試験）（安全性解析対象集団）

Days from End of the Last Immediate Previous Treatment: < 3 months

Description	40 mg (N=12) n (%)
Number of subjects with	
At least one TEAE	12 (100.0%)
At least one TEAE related to the study drug	12 (100.0%)
At least one serious TEAE	3 (25.0%)
At least one serious TEAE related to the study drug	2 (16.7%)
At least one TEAE leading to dose reduction or interruption	7 (58.3%)
At least one TEAE leading to study drug discontinuation	4 (33.3%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	9 (75.0%)
At least one TEAE with grade 3 or higher and related to the study drug	9 (75.0%)

Source: Listing 16.2.6 1 and 16 2.4.4

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment; n = number of subjects;
% = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

Days from End of the Last Immediate Previous Treatment: >=3 months

Description	40 mg (N=11) n (%)
Number of subjects with	
At least one TEAE	11 (100.0%)
At least one TEAE related to the study drug	11 (100.0%)
At least one serious TEAE	4 (36.4%)
At least one serious TEAE related to the study drug	4 (36.4%)
At least one TEAE leading to dose reduction or interruption	9 (81.8%)
At least one TEAE leading to study drug discontinuation	5 (45.5%)
At least one TEAE leading to death	0 (0.0%)
At least one TEAE with grade 3 or higher	9 (81.8%)
At least one TEAE with grade 3 or higher and related to the study drug	9 (81.8%)

Source: Listing 16.2.6 1 and 16 2.4.4

Severities are graded using NCI-CTCAE Version 4.03.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment; n = number of subjects;
% = percentages of subjects are calculated relative to the total number of subjects in a subgroup in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
Subjects with more than one TEAE are counted once in the worst severity or strongest relationship category.
TEAE related to study drug is defined as a TEAE with a relationship of possible, probable or definite to study drug.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375
TEAE of overdose is not included in this analysis.
For TEAE leading to dose reduction or interruption, the worst action taken is considered for a derived TEAE. For example, if the actions taken for a derived AE consisted of dose reduction/interruption and study drug discontinuation, the worst action taken of TEAE leading to study drug discontinuation will be considered, and dose reduction/interruption will not be counted for this derived AE.
If TEAE leading to dose reduction/interruption and AE leading to study drug discontinuation occurred to different derived TEAEs, these actions taken will be counted separately.

表 2.7.4.7-98　直近のがん治療からの期間別（3 ヵ月未満、3 ヵ月以上）の有害事象の発現割合（210 試験）（安全性解析対象集団）

System organ class Preferred term	<3months (N=12) n (%)	>= 3months (N=11) n (%)
Number of subjects with at least one TEAE	12(100.0%)	11(100.0%)
血液およびリンパ系障害	9(75.0%)	10(90.9%)
貧血*	5(41.7%)	4(36.4%)
好酸球増加症	0	1(9.1%)
発熱性好中球減少症	1(8.3%)	0
白血球減少症*	5(41.7%)	5(45.5%)
リンパ球減少症*	1(8.3%)	1(9.1%)
好中球減少症*	5(41.7%)	7(63.6%)
血小板減少症*	9(75.0%)	9(81.8%)
心臓障害	1(8.3%)	1(9.1%)
第一度房室ブロック	1(8.3%)	0
動悸	0	1(9.1%)
眼障害	1(8.3%)	0
ドライアイ	1(8.3%)	0
胃腸障害	5(41.7%)	4(36.4%)
腹痛	2(16.7%)	1(9.1%)
下痢	3(25.0%)	3(27.3%)
悪心	3(25.0%)	0
口内炎	1(8.3%)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<3months (N=12) n (%)	>= 3months (N=11) n (%)
一般・全身障害および投与部位の状態	7(58.3%)	6(54.5%)
悪寒	1(8.3%)	0
疲労	0	3(27.3%)
倦怠感	4(33.3%)	3(27.3%)
非心臓性胸痛	1(8.3%)	0
末梢性浮腫	1(8.3%)	0
発熱	2(16.7%)	1(9.1%)
感染症および寄生虫症	5(41.7%)	2(18.2%)
細菌感染	1(8.3%)	0
サイトメガロウイルス感染	1(8.3%)	0
医療機器関連感染	1(8.3%)	0
麦粒腫	0	1(9.1%)
口腔カンジダ症	1(8.3%)	0
ニューモシスチス・イロベチイ肺炎	0	1(9.1%)
皮膚感染	1(8.3%)	0
扁桃炎	1(8.3%)	0
上気道感染	0	1(9.1%)
尿路感染	0	1(9.1%)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<3months (N=12) n (%)	>= 3months (N=11) n (%)
傷害、中毒および処置合併症	1(8.3%)	0
挫傷	1(8.3%)	0
臨床検査	5(41.7%)	5(45.5%)
アラニンアミノトランスフェラーゼ増加	1(8.3%)	0
アスパラギン酸アミノトランスフェラーゼ増加	1(8.3%)	1(9.1%)
血中アルカリホスファターゼ増加	0	1(9.1%)
血中乳酸脱水素酵素増加	1(8.3%)	0
脳性ナトリウム利尿ペプチド増加	0	1(9.1%)
好酸球数増加	1(8.3%)	0
γーグルタミルトランスフェラーゼ増加	0	2(18.2%)
リパーゼ増加	1(8.3%)	0
体重減少	1(8.3%)	3(27.3%)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<3months (N=12) n (%)	>= 3months (N=11) n (%)
代謝および栄養障害	6(50.0%)	7(63.6%)
食欲減退	3(25.0%)	5(45.5%)
高カルシウム血症	1(8.3%)	0
低アルブミン血症	1(8.3%)	2(18.2%)
低カリウム血症	0	1(9.1%)
低ナトリウム血症	2(16.7%)	0
低リン酸血症	0	1(9.1%)
筋骨格系および結合組織障害	3(25.0%)	4(36.4%)
関節痛	0	1(9.1%)
背部痛	2(16.7%)	2(18.2%)
脊椎すべり症	1(8.3%)	0
尺骨突き上げ症候群	0	1(9.1%)

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
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Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<3months (N=12) n (%)	>= 3months (N=11) n (%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1(8.3%)	0
腫瘍疼痛	1(8.3%)	0
神経系障害	6(50.0%)	3(27.3%)
味覚消失	1(8.3%)	0
認知障害	1(8.3%)	0
浮動性めまい	1(8.3%)	0
味覚異常	3(25.0%)	1(9.1%)
頭痛	1(8.3%)	1(9.1%)
傾眠	0	1(9.1%)
腎および尿路障害	1(8.3%)	0
尿瘻	1(8.3%)	0

Source: Listing 16.2.6.1 and 16.2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375
TEAE of overdose is not included in this analysis.

System organ class Preferred term	<3months (N=12) n (%)	>= 3months (N=11) n (%)
呼吸器、胸郭および縦隔障害	3(25.0%)	1(9.1%)
急性呼吸不全	1(8.3%)	0
鼻出血	0	1(9.1%)
間質性肺疾患	1(8.3%)	0
口腔咽頭痛	1(8.3%)	0
皮膚および皮下組織障害	4(33.3%)	4(36.4%)
接触皮膚炎	1(8.3%)	0
湿疹	0	1(9.1%)
紅斑	1(8.3%)	0
多形紅斑	1(8.3%)	0
光線過敏性反応	1(8.3%)	0
そう痒症	0	1(9.1%)
発疹	0	1(9.1%)
皮膚剥脱	0	1(9.1%)
皮膚潰瘍	1(8.3%)	0
血管障害	1(8.3%)	0
高血圧	1(8.3%)	0

Source: Listing 16.2.6 1 and 16 2.4.4

MedDRA Version 21.1 was used to code adverse events.
N = number of subjects in the Safety Analysis Set by the duration from end of last immediate previous treatment.
n = number of subjects; % = percentages of subjects are calculated relative to the number of subjects in each subtype in the analysis set.
TEAE = treatment-emergent adverse event is defined as AEs that started or worsened in severity on or after the first study drug administration.
* Hematological adverse events are defined as grouped AEs where anemia is combined with haemoglobin decreased; thrombocytopenia is combined with platelet count decreased; leukopenia is combined with white blood cell count decreased; lymphopenia is combined with lymphocyte count decreased; neutropenia is combined with neutrophil count decreased and granulocytopenia.
Days from end of the last immediate previous treatment (months) = (date of first study drug - end date of the last immediate previous treatment +1)/ 30.4375
TEAE of overdose is not included in this analysis.

ツシジノスタット
ハイヤスタ錠 10mg

第 2 部 CTD の概要

2.7 臨床概要
2.7.5 参考文献

Huya Japan 合同会社

2.7.5 参考文献

2.7.5.1 2.7.1 生物薬剤学及び関連する分析法の概要で引用した参考文献

該当なし

2.7.5.2 2.7.2 臨床薬理試験で引用した参考文献

該当なし

2.7.5.3 2.7.3 臨床的有効性で引用した参考文献

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2.7.5.4 2.7.4 臨床的安全性で引用した文献

該当なし