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略語一覧

略語又は用語	定義／説明
AI/Pen	AI/Pen Autoinjector/pen（ペン型プレフィルド自己注射器）
ALP	Alkaline phosphatase（アルカリホスファターゼ）
ALT	Alanine aminotransferase（アラニンアミノトランスフェラーゼ）
AMQ	Amgen MedDRA Query（Amgen社が定義したMedDRA検索式）
AST	Aspartate aminotransferase（アスパラギン酸アミノトランスフェラーゼ）
BUN	Blood urea nitrogen（血中尿素窒素）
CGRP	Calcitonin gene-related peptide（カルシトニン遺伝子関連ペプチド）
CHU	Clinical home use（在宅での臨床使用）
CM	Chronic migraine（慢性片頭痛）
C_{max}	Maximum observed concentration（最高血清中濃度）
C-SSRS	Columbia-Suicide Severity Rating Scale（コロンビア自殺企図評価尺度）
CTCAE	Common Terminology Criteria for Adverse Events（有害事象共通用語規準）
eGFR	Estimated glemerular filtration rate（推算糸球体濾過値）
EM	Episodic migraine（反復性片頭痛）
EU	European Union（欧州連合）
FDA	Food and Drug Administration（米国食品医薬品局）
iSAP	Integrated statistical analysis plan（併合統計解析計画書）
MedDRA	Medical Dictionary for Regulatory Activities（国際医薬用語集）
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese translation（国際医薬用語集日本語版）
PBRER	Periodic benefit risk evaluation report（定期的ベネフィット・リスク評価報告）
PSUR	Periodic safety update report（定期的安全性最新報告）
PT	Preferred term（基本語）
SAP	Statistical analysis plan（統計解析計画書）
SD	Standard deviation（標準偏差）
SMQ	Standardized MedDRA Query（MedDRA標準検索式）
SOC	System organ class（器官別大分類）
ULN	Upper limit of normal（基準値上限）

1. 医薬品への曝露

1.1 総括的安全性評価計画及び安全性試験の記述

エレヌマブ（開発コード：AMG 334）の安全性は、主として国内で実施した反復性片頭痛（EM）患者を対象とした第II相試験（20120309試験）、並びにEM患者及び慢性片頭痛（CM）患者を対象とした第III相試験（20170609試験）の併合解析の結果に基づき評価した（表 1）。海外で実施したEM患者を対象とした第II相試験（20120178試験）、CM患者を対象とした第II相試験（20120295試験）及びその継続試験（20130255試験）、並びにEM患者を対象とした第III相の2試験（20120296試験及び20120297試験）の併合解析の結果は参考資料として用いた（表 2）。本概要では、評価資料である国内試験の併合解析の結果を中心に示し、海外試験の併合解析の結果はその概要を2.1.1.2項に参考として示す。

また、個々の試験における安全性の結果、並びに本概要に含まない安定狭心症患者を対象にエレヌマブを投与した第IIa相試験（20140254試験）及び第I相の8試験（20120130試験、20101267試験、20101268試験、20140477試験、20140255試験、20150149試験、20150334試験、20160349試験）の安全性の結果はモジュール2.7.6に示した。

表 1　安全性評価に用いた国内試験（評価資料）

試験番号	試験の目的	試験デザイン 対照の種類	投与方法	安全性評価例数	対象患者及び 主な組入基準	投与 期間	試験の進行状況 報告書の種類 CSR添付場所
20120309	有効性、安全性、忍容性	第II相、無作為化、二重盲検、プラセボ対照	プラセボ、エレヌマブ28、70、又は140 mgをQ4WでSC投与	プラセボ：136 28 mg：66 70 mg：135 140 mg：137	MMDが4日以上15日未満、かつ月間頭痛日数が15日未満のEM患者 年齢：20～65歳	24週	完了 主要解析の完全な報告書 5.3.5.1-1.1
		非盲検	エレヌマブ70又は140 mgをQ4WでSC投与	70/140 mg：459	20120309試験の二重盲検投与期の投与及びWeek 24の来院を完了した被験者	76週	完了 最終解析の簡略化された報告書 5.3.5.1-1.2
20170609	有効性、安全性、忍容性	第III相、無作為化、二重盲検、プラセボ対照	プラセボ又はエレヌマブ70 mgをQ4WでSC投与	プラセボ：131 70 mg：130	MMDが4日以上15日未満、かつ月間頭痛日数が15日未満のEM患者及び MMDが8日以上、かつ月間頭痛日数が15日以上のCM患者 年齢：20～65歳	24週	継続 主要解析の完全な報告書 5.3.5.1-2
		非盲検	エレヌマブ70 mgをQ4WでSC投与	70 mg：継続	20170609試験の二重盲検投与期の投与及びWeek 24の来院を完了した被験者	28週	

CM = 慢性片頭痛、EM = 反復性片頭痛、MMD = 月間片頭痛日数、Q4W = 4週に1回、SC = 皮下

表２　安全性評価に用いた海外試験（参考資料）

試験番号	試験の目的	試験デザイン 対照の種類	投与方法	安全性評価例数	対象患者及び 主な組入基準	投与 期間	試験の進行状況 報告書の種類 CSR添付場所
20120178	有効性、安全性、忍容性	第II相、無作為化、二重盲検、プラセボ対照	プラセボ、エレヌマブ7、21、又は70 mgをQ4WでSC投与	プラセボ：153 7 mg：108 21 mg：105 70 mg：106	MMDが4日以上14日以下、かつ月間頭痛日数が15日未満のEM患者 年齢：18～60歳	12週	完了 主要解析の完全な報告書 5.3.5.1-3.1
		非盲検、単群、延長	エレヌマブ70又は140 mgをQ4WでSC投与	70/140 mg：383	20120178試験の二重盲検投与期の治験薬投与、及びWeek 12の来院を完了した被験者	最大256週	完了 中間解析のシノプシス報告書 5.3.5.1-3.2 最終解析の簡略化された報告書 5.3.5.1-3.3
20120295	有効性、安全性、忍容性	第II相、無作為化、二重盲検、プラセボ対照	プラセボ、エレヌマブ70、又は140 mgをQ4WでSC投与	プラセボ：282 70 mg：190 140 mg：188	MMDが8日以上、かつ月間頭痛日数が15日以上のCM患者 年齢：18～65歳	12週	完了 完全な報告書 5.3.5.1-4
20120296	有効性、安全性、忍容性	第III相、無作為化、二重盲検、プラセボ対照	プラセボ、エレヌマブ70、又は140 mgをQ4WでSC投与	プラセボ：319 70 mg：314 140 mg：319	MMDが4日以上15日未満、かつ月間頭痛日数が15日未満のEM患者 年齢：18～65歳	24週	完了 主要解析の完全な報告書 5.3.5.1-5.1
		非盲検（エレヌマブの投与量に対する盲検性は維持）	エレヌマブ70又は140 mgをQ4WでSC投与	70/140 mg：845	20120296試験のプラセボ対照二重盲検投与期の治験薬投与、及びWeek 24の来院を完了した被験者	28週	完了 最終解析の簡略化された報告書 5.3.5.1-5.2

表 2　安全性評価に用いた海外試験（参考資料）（続き）

試験番号	試験の目的	試験デザイン 対照の種類	投与方法	安全性評価例数	対象患者及び 主な組入基準	投与 期間	試験の進行状況 報告書の種類 CSR添付場所
20120297	有効性、安全性、忍容性	第III相、無作為化、二重盲検、プラセボ対照	プラセボ又はエレヌマブ70 mgをQ4WでSC投与	プラセボ：289 70 mg：283	MMDが4日以上15日未満、かつ月間頭痛日数が15日未満のEM患者 年齢：18～65歳	12週	完了 主要解析の完全な報告書 5.3.5.1-6.1
		非盲検、単群、延長	エレヌマブ70 mgをQ4WでSC投与	70 mg：538	20120297試験の二重盲検投与期の治験薬投与、及びWeek 12の来院を完了した被験者	28週	完了 最終解析の簡略化された報告書 5.3.5.1-6.2
20130255	長期の有効性、安全性、忍容性	第II相、非盲検	エレヌマブ70又は140 mgをQ4WでSC投与	70/140 mg：609	20120295試験のWeek 12の評価を完了し、プラセボ対照二重盲検投与期に治験薬の投与を中止していない被験者	52週	完了 最終解析の完全な報告書 5.3.5.2-1

CM = 慢性片頭痛、EM = 反復性片頭痛、MMD = 月間片頭痛日数、Q4W = 4週に1回、SC = 皮下

1.1.1　安全性の評価項目及び評価方法

本項では、評価資料である20120309試験及び20170609試験について記載する。

1.1.1.1　有害事象

試験中被験者に発現したあらゆる好ましくない医療上の出来事、又は試験開始前から存在した医学的状態の悪化を有害事象とした。有害事象のうち、死亡に至るもの、生命を脅かすもの、治療のため入院又は入院期間の延長が必要となるもの、永続的又は顕著な障害・機能不全に陥るもの、先天異常を来たすもの、又はその他の医学的に重要な重篤な事象を重篤な有害事象とした。

重篤な有害事象に関する情報は、同意説明文書への署名後から試験終了［治験薬最終投与の16週（20120309試験）又は12週後（20170609試験）］までの期間にわたり収集した。非重篤な有害事象に関する情報は、治験薬の初回投与後から試験終了までの期間にわたり収集した。

本概要では、すべての有害事象、死亡、重篤な有害事象、治験薬の投与中止に至った有害事象、重症度別の有害事象、注目すべき有害事象（1.1.1.1.1項参照）、発現時期別の有害事象、機器関連の有害事象、及び部分集団別の有害事象（1.1.1.1.2項参照）について評価した。有害事象の重症度は有害事象共通用語規準（CTCAE）バージョン4.03に従って判定された。治験薬又は機器との因果関係は、「関連あり」（治験薬又は機器と有害事象に合理的な因果関係がある）又は「関連なし」（治験薬又は機器と有害事象に合理的な因果関係がない）のいずれかで判定された。また、機器関連の有害事象は医療機器（プレフィルドシリンジ）の使用に関連したあらゆる有害事象と定義され、これには、使用上の説明が不十分又は不適切であったことにより発現した有害事象、機器の誤作動による有害事象、機器の使用ミスや意図的な誤使用による有害事象等が含まれた。

報告された有害事象は、国際医薬用語集（MedDRA）を用いてコード化し、集計した。国内試験の併合解析で使用されたMedDRAのバージョンは22.1であり、本概要ではMedDRA/Jの同一バージョンを用いてそれぞれの器官別大分類（SOC）及び基本語（PT）を和訳した。

1.1.1.1.1　注目すべき有害事象

エレヌマブの注目すべき有害事象は以下のいずれかに基づいて選択された：タンパク製剤投与に関連する事象（過敏症、免疫原性及び注射部位反応）、カルシトニン遺伝子関連ペプチド（CGRP）阻害と理論上関連する可能性のある事象（心臓、脳血管及び血管障害、並びに胃腸障害）、臨床開発の過程又は市販後の使用経験から検出された事象（便秘関連事象）、及びその他エレヌマブの安全性プロファイルを検討する上で重要と考えられる事象（表 3参照）。

注目すべき有害事象ではMedDRA SOC、又はMedDRA標準検索式（SMQ）若しくはAmgen社が定義したAmgen MedDRA Query（AMQ）を用いた検索式により有害事象を特定した。選択された注目すべき有害事象及び検索法を表 3に示す。また、各SMQ又はAMQを構成する検索用語の詳細を8.1項に示す。

表 3　選択された注目すべき有害事象及び検索法

器官別又は症候群別有害事象	検索法
免疫系障害	・　免疫系障害SOC ・　皮膚および皮下組織障害SOC ・　過敏症SMQ（狭域及び広域） ・　アナフィラキシー反応SMQ（狭域及び広域） ・　免疫原性[a]
一般・全身障害及び投与部位の状態	・　一般・全身障害および投与部位の状態SOC ・　注射部位反応AMQ（狭域及び広域）
胃腸障害	・　胃腸障害SOC ・　便秘AMQ（狭域及び広域）
心臓、脳血管及び血管障害	・　心臓障害SOC ・　虚血性中枢神経系血管障害SMQ（狭域） ・　虚血性心疾患SMQ（狭域及び広域） ・　末梢動脈疾患AMQ（狭域及び広域） ・　高血圧SMQ（狭域及び広域）
その他	・　精神障害SOC ・　肝胆道系障害SOC ・　神経系障害SOC ・　良性、悪性および詳細不明の新生物SOC ・　筋骨格系および結合組織障害SOC

[a] 免疫原性については1.1.1.2項参照

1.1.1.1.2　部分集団解析

部分集団別の有害事象では、内因性又は外因性要因として次の部分集団について解析を行い、安全性を評価した。

- 内因性要因：ベースライン時の性別（男、女）、年齢（中央値未満、以上）、体重（中央値未満、以上）、片頭痛の種類（EM、CM）、心血管リスク因子数（0、1、2以上）、腎機能障害（有、無）*
- 外因性要因：片頭痛予防薬の治療不成功歴［有、無（使用なしも含む）］

* 推算糸球体濾過値（eGFR：mL/min/1.73 m^2）が60未満を障害ありとした。

1.1.1.2　免疫原性

タンパク製剤の投与は免疫反応を誘発し、安全性又は有効性に影響を及ぼす可能性がある（FDA Guidance for Industry, 2009）。

抗エレヌマブ結合抗体は、治験実施計画書で規定した時点に血液検体を採取し測定された。結合抗体陽性の被験者では中和抗体についても検査した。なお、中和抗体が陽性の場合も、盲検維持のため結果は実施医療機関に通知されず、当該被験者は試験を継続した。

本概要では抗エレヌマブ抗体の発現状況とその発現が影響すると考えられる有害事象（主に過敏症及び注射部位反応等）との関連を評価し、安全性への影響を検討した。

1.1.1.3 臨床検査

臨床検査では、以下の血液学的及び生化学的検査項目について評価した。肝機能検査値の重症度はCTCAEバージョン4.03を用いて分類された。臨床検査値異常は、治験責任医師等の判断により有害事象としても報告された。

- 血液学的検査：好中球絶対数、赤血球数、ヘモグロビン量、平均赤血球容積、平均赤血球ヘモグロビン量、平均赤血球ヘモグロビン濃度、血小板数、白血球数
- 生化学的検査
  - 肝機能：ALT、AST、総ビリルビン、ALP
  - 腎機能：クレアチニン、BUN、総蛋白、アルブミン
  - 代謝及び筋：糖、ナトリウム、カリウム、クロール、重炭酸、カルシウム

エレヌマブの薬物性肝障害の可能性は、以下のHy's law（US FDA Guidance for Industry, 2009）の基準に該当する被験者を特定することにより評価した。

- ALT又はASTが基準値上限（ULN）の3倍超、総ビリルビンがULNの2倍超かつALPがULNの2倍未満

1.1.1.4 バイタルサイン

バイタルサインでは、収縮期／拡張期血圧及び心拍数について、以下のカテゴリーに該当する被験者を評価した。バイタルサイン値異常は、治験責任医師等の判断により有害事象としても報告された。

- 拡張期血圧
  - ベースラインから10 mmHg以上の変化があり、90 mmHg以下
  - ベースラインから10 mmHg以上の変化があり、90 mmHg超
- 収縮期血圧
  - ベースラインから20 mmHg以上の変化があり、140 mmHg以下
  - ベースラインから20 mmHg以上の変化があり、140 mmHg超
- 心拍数
  - ベースラインから15拍／分（bpm）以上の増加があり、120 bpm以上
  - ベースラインから15 bpm以上の減少があり、50 bpm以下

1.1.1.5 心電図

心電図検査は潜在的なQTc作用の評価を目的とはせず、通常の安全性モニタリングとして実施した。20120309試験では中央検査機関の読影者が心電図を評価し、20170609試験では治験責任医師又は実施医療機関で指定された医師が心電図を評価した。心電図の異常は治験責任医師等の判断により有害事象としても報告された。

1.1.1.6　コロンビア自殺企図評価尺度

コロンビア自殺企図評価尺度（C-SSRS）は自殺の危険性の評価尺度であり、自殺行動や自殺念慮について評価する手法である。米国食品医薬品局（FDA）のDivision of Neurology Productsで開発される製品に関するすべての治験実施計画書には、適応症を問わず、自殺に関するプロスペクティブ評価を含めなければならないというFDAガイダンスに従い、設定された。C-SSRSは治験責任医師又はその指名者が被験者に質問することにより評価した。実行の意図を伴う自殺念慮（重症度が4又は5）の報告、実際の自殺未遂あるいはその中止や中断の報告、又は自殺を試行するための準備行動は被験者の自殺のリスクが高いことを示す。なお、これらがスクリーニング時に確認された患者は試験対象から除外された。

本概要ではC-SSRSはベースラインから最も悪化したときのシフトテーブルにより評価した。

1.1.2　統計学的手法

国内併合データの統計解析は、国内併合統計解析計画書［J-iSAP（モジュール5.3.5.3-1.1）］に基づき実施した。海外併合データの統計解析は、海外併合統計解析計画書［G-iSAP（モジュール5.3.5.3-2.1）］に基づき実施した。以下に実施した統計解析の概要を示す。

1.1.2.1　解析対象集団

安全性の併合解析対象集団は、併合データ又は各試験に含まれる被験者のうち、治験薬の投与を1回以上受けた被験者とした。本集団を対象とした解析は各試験の統計解析計画書（SAP）の定義に従い、実際に受けた投与群別又はランダム化された投与群別に行った。それぞれの併合データセットの定義は1.1.2.2.1及び1.1.2.2.2項に記載する。

1.1.2.2　併合解析

1.1.2.2.1　国内併合データ

国内併合データではEM患者を対象とした第II相試験（20120309試験）、並びにEM患者及びCM患者を対象とした第III相試験（20170609試験）のデータを併合した。20120309試験では24週間のプラセボ対照の二重盲検投与期及び76週間の非盲検投与期の最終解析までのデータが含まれ、20170609試験では24週間のプラセボ対照の二重盲検投与期のデータが含まれた。

併合データセットの定義

国内併合解析では2つの併合データセットを設定した。それぞれに含まれる解析データ及び解析対象集団を以下に定義する。

- プラセボ対照併合データ
  - Pool J-ISS-1：24週間の二重盲検プラセボ対照期の併合データ
    20120309試験及び20170609試験で24週間の二重盲検投与期にランダム化され、治験薬の投与を1回以上受けた被験者を含む。プラセボと比較し、エレヌマブの短期間の安全性を評価する。

- 長期投与併合データ
  - Pool J-ISS-2：全投与期のエレヌマブ70 mg又は140 mg併合データ
    20120309試験の二重盲検又は非盲検投与期にエレヌマブ70 mg又は140 mgの投与を1回以上受けた被験者を含む。本Poolでは、エレヌマブ70 mg又は140 mgの初回投与から被験者が試験を終了した時点までの70 mg又は140 mg投与のデータが含まれ、エレヌマブの長期の安全性を評価する。

    本Poolで認められた有害事象は、被験者が有害事象の発現日に投与していたエレヌマブの用量別（70 mg又は140 mg）に要約される。本Poolでは被験者が2つの異なる投与量間の切り替えを異なる順序で行った可能性があるため、投与量間の発現頻度の差の解釈には注意を要する。例えば、ある被験者がエレヌマブ70 mg投与中に有害事象を発現し、140 mgに切り替えた後にも新たに同じ有害事象を発現した場合には、有害事象は両投与量群で発現例数としてそれぞれ集計される。

1.1.2.2.2 海外併合データ

海外併合データでは以下の5試験のデータを併合した：EM患者を対象とした第II相試験（20120178試験）、CM患者を対象とした第II相試験（20120295試験）及びその非盲検継続試験（20130255試験）、EM患者を対象とした第III相試験（20120296試験及び20120297試験）。20120178試験、20120295試験及び20120297試験には12週間の二重盲検投与期が含まれ、20120296試験には24週間の二重盲検投与期が含まれた。また、20120296試験及び20120297試験には28週間の盲検下の実薬投与期及び非盲検投与期、20130255試験では52週間の非盲検投与期、20120178試験には256週間の非盲検投与期が含まれた。

海外併合解析に用いた各試験のデータを表 4に示す。20120178試験以外の4試験では最終解析までのデータが本併合解析に含まれ、20120178試験については12週間の二重盲検投与期及び約3年の非盲検投与期のデータが含まれた。なお、20120178試験の非盲検投与期の最終解析までの最長5年超の安全性の結果はモジュール2.7.6　12項に示した。

表 4　海外併合解析に用いた各試験のデータ

Study	Analysis data
20120295	12W DBTP [final data]
20130255	52W OLTP [final data]
20120178	12W DBTP and 3-yr OLTP data (Data Cut-off Date: [redacted] 20[redacted])
20120296	24W DBTP and 28W ATP [final data]
20120297	12W DBTP and 28W OLTP [final data]

ATP = 実薬投与期、DBTP = 二重盲検投与期、OLTP = 非盲検投与期

併合データセットの定義

海外併合解析では4つの併合データセットを設定した（図 1）。それぞれに含まれる解析データ及び解析対象集団を以下に定義する。

- プラセボ対照併合データ
  - Pool A：12週間の二重盲検プラセボ対照期の併合データ
    20120178試験、20120295試験、20120296試験及び20120297試験で12週間の二重盲検投与期にランダム化され、治験薬の投与を1回以上受けた被験者を含む。20120296試験のデータは

12週以降の結果は含めなかった。本Poolでは、二重盲検投与期の最初の12週間のデータをプラセボと比較し、エレヌマブの短期間の安全性を評価する。

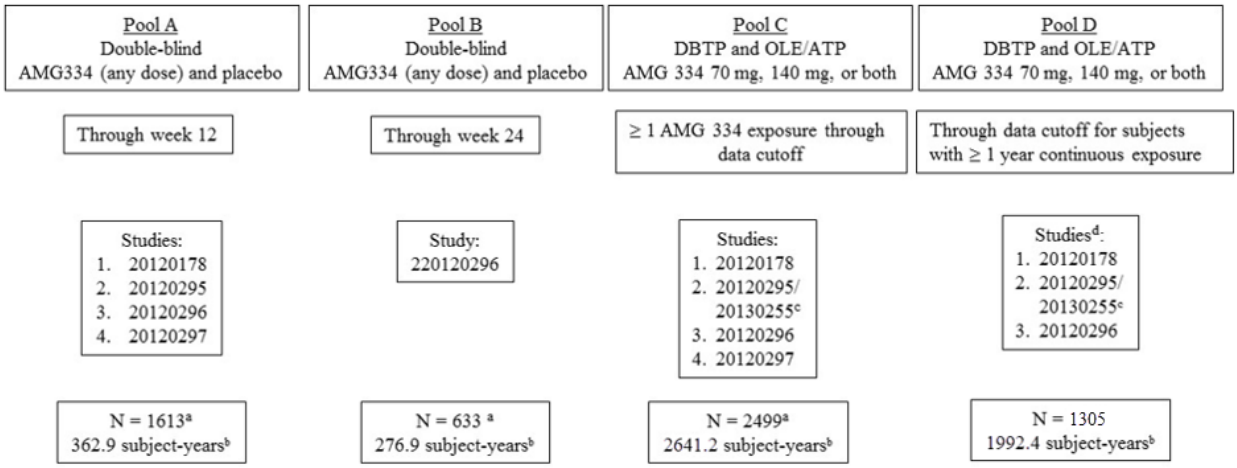
- Pool B：24週間の二重盲検プラセボ対照期の併合データ
  20120296試験で24週間の二重盲検投与期にランダム化され、治験薬の投与を1回以上受けた被験者を含む。本Poolの集計期間及び集計対象は、国内併合データのPool J-ISS-1と同じである。

• 長期投与併合データ

- Pool C：全投与期のエレヌマブ70 mg又は140 mg併合データ
  5つの試験（20120178試験、20120295試験／20130255試験、20120296試験及び20120297試験）の二重盲検又は非盲検／実薬投与期に、エレヌマブ70 mg又は140 mgの投与を1回以上受けた被験者を含む。本Poolの集計期間及び集計対象は、国内併合データのPool J-ISS-2と同じである。

- Pool D：1年以上の長期投与併合データ
  Pool DはPool Cのサブセットであり、エレヌマブの70 mg又は140 mgを継続して1年以上（二重盲検及び非盲検／実薬投与期の合算）投与された被験者を含む。なお、20120297試験におけるエレヌマブの最長投与期間は40週間であるため、当該試験の被験者は本Poolには含まれない。

図 1　海外併合データセット



ATP = 実薬投与期、DBTP = 二重盲検投与期、OLTP = 非盲検投与期

[a] For Pools A and B, N represents number of subjects who received ≥ 1 dose of investigational product. For Pool C, N represents the number of subjects as of the data cut-off date who received at least 1 dose of AMG 334 (70 mg/140 mg).

[b] Represents subject-years of exposure.

[c] Study 20130255 is the long-term extension of Study 20120295.

[d] Study 20120297 is not included in the long-term pool because the maximum exposure is 40 weeks.

1.2　全般的な曝露状況

国内併合解析における曝露状況を以下に示す。曝露期間は治験薬の初回投与日から最終投与日までの期間に投与間隔の28日を加算した期間として算出した。また、曝露期間の単位として使用している1カ月は28日換算で算出した。

1.2.1 二重盲検プラセボ対照期

Pool J-ISS-1における曝露状況を表 5に示す。

本Poolでは468例がエレヌマブの投与を受け（エレヌマブ70 mg群265例、28 mg群66例、140 mg群137例）、267例がプラセボの投与を受けた。

ほとんどの被験者（エレヌマブ70 mg群95.8%、28 mg群98.5%、140 mg群97.1%、プラセボ群97.4%）は治験実施計画書で規定されている6回の治験薬投与を受けた。曝露期間の平均値［標準偏差（SD）］はエレヌマブ70 mg群で23.5（2.5）週であり、プラセボ群［23.6（2.0）週］と比較して同程度で、その他のエレヌマブ群［エレヌマブ28 mg群23.8（0.6）週、140 mg群23.6（2.5）週］とも同程度であった。

表 5 曝露状況（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (N = 267)	28 mg QM (N = 66)	70 mg QM (N = 265)	140 mg QM (N = 137)	Overall (N = 468)
Total number of investigational product doses received - n (%)					
1	0 (0.0)	0 (0.0)	2 (0.8)	2 (1.5)	4 (0.9)
2	3 (1.1)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
3	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
4	2 (0.7)	0 (0.0)	2 (0.8)	1 (0.7)	3 (0.6)
5	1 (0.4)	1 (1.5)	3 (1.1)	1 (0.7)	5 (1.1)
6	260 (97.4)	65 (98.5)	254 (95.8)	133 (97.1)	452 (96.6)
Duration of exposure to investigational product (weeks)[a]					
n	267	66	265	137	468
Mean	23.6	23.8	23.5	23.6	23.6
SD	2.0	0.6	2.5	2.5	2.4
Median	24.0	24.0	24.0	24.0	24.0
Q1, Q3	23.9, 24.0	23.7, 24.0	23.9, 24.0	23.9, 24.0	23.9, 24.0
Min, Max	8, 24	20, 24	4, 25	4, 24	4, 25

N = Number of subjects in the analysis set
n = Number of subjects with observed data
% = n / N * 100
[a] Duration of exposure to investigational product (IP) in double-blind treatment period (DBTP) is calculated as (minimum [last DBTP dose date + 27, first open-label treatment period (OLTP) dose date - 1] - first DBTP dose date + 1) / 7 for subjects who receive OLTP IP dose, and (minimum [last DBTP dose date + 27, end of study date] - first DBTP dose date + 1) / 7 for subjects who did not receive any OLTP IP dose.

[redacted]

1.2.2 全投与期

Pool J-ISS-2での曝露期間はエレヌマブ70 mg又は140 mgの初回投与日及び最終投与日に基づいて算出した。本期間中に70 mg及び140 mg両方の投与を受けた被験者については用量ごとに曝露期間を算出しそれぞれの総曝露期間に含めた。

Pool J-ISS-2における曝露状況を表 6に示す。

本Poolでは計470例がエレヌマブ70 mg又は140 mgの投与を受け、このうち70 mgの投与を1回以上受けた被験者は414例、140 mgの投与を1回以上受けた被験者は269例であった。

エレヌマブ70 mg又は140 mgの曝露期間の平均値（SD）は21.2（5.0）カ月であり、投与量別では70 mgの曝露期間が14.7（8.1）カ月、140 mgの曝露期間が14.5（6.6）カ月であった。エレヌマブ

70 mg又は140 mgの投与を受けた470例のうち、453例（96.4%）が6カ月以上、444例（94.5%）が12カ月以上、437例（93.0%）が18カ月以上の曝露を受けた。エレヌマブ70 mgの投与を受けた414例では、321例（77.5%）が6カ月以上、259例（62.6%）が12カ月以上、249例（60.1%）が18カ月以上の曝露を受けた。

表 6　曝露状況（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (N = 414)	140 mg QM (N = 269)	Combined (N = 470)
Duration of exposure by time - n (%)			
≥ 1 month	406 (98.1)	269 (100.0)	470 (100.0)
≥ 3 months	374 (90.3)	266 (98.9)	463 (98.5)
≥ 6 months	321 (77.5)	237 (88.1)	453 (96.4)
≥ 12 months	259 (62.6)	184 (68.4)	444 (94.5)
≥ 18 months	249 (60.1)	118 (43.9)	437 (93.0)
Total number of investigational product doses received - n (%)			
1	22 (5.3)	3 (1.1)	5 (1.1)
2 - 3	33 (8.0)	0 (0.0)	5 (1.1)
4 - 6	71 (17.1)	79 (29.4)	8 (1.7)
7 - 13	34 (8.2)	18 (6.7)	10 (2.1)
14 - 20	179 (43.2)	130 (48.3)	196 (41.7)
≥ 21	75 (18.1)	39 (14.5)	246 (52.3)
Duration of exposure to investigational product (months)			
n	414	269	470
Mean	14.7	14.5	21.2
SD	8.1	6.6	5.0
Median	18.9	16.1	24.7
Q1, Q3	6.0, 19.1	6.0, 19.0	19.0, 25.0
Min, Max	1, 25	1, 25	1, 25

N = Number of subjects in the analysis set
n = Number of subjects with observed data
% = n / N * 100
Duration of exposure to investigational product (IP) in double-blind treatment period (DBTP) is calculated as (minimum [last DBTP dose date + 27, first open-label treatment period (OLTP) dose date - 1] - first DBTP dose date + 1) / 28 for subjects who received OLTP IP, or (minimum [last DBTP dose date + 27, end of study (EOS) date] - first DBTP dose date + 1) / 28 for subjects who did not receive any OLTP IP.
Duration of exposure to IP in OLTP is calculated as (minimum [last OLTP dose date + 27, EOS date] - first OLTP dose date + 1) / 28 for the subjects receiving only 70 mg or 140 mg during OLTP.
For subjects who received both 70 mg and 140 mg during OLTP:
1. 70 mg duration = (minimum [first 140 mg dose date - 1, last 70 mg dose date + 27] - first 70 mg dose date + 1) / 28;
2. 140 mg duration = (minimum [last 140 mg dose date + 27, EOS date] - first 140 mg dose date + 1) / 28.
For subjects who received IP in both DBTP and OLTP, duration of exposure for the dose level of interest will be sum of the exposure in DBTP and OLTP.

[redacted]

1.3　人口統計学的特性及びその他の特性

20120309試験及び20170609試験では、20歳以上65歳以下のCM患者及びEM患者を組み入れた。通常よく見られる心血管疾患のリスク因子（糖尿病、高血圧及び高脂血症等）を有する被験者は試験対象集団から除外しなかった。ベースライン時に医学的に重要なバイタルサイン異常、臨床検査値異常あるいは心電図異常所見がある患者、又は重大な心血管疾患（スクリーニング前12カ月以内の

心筋梗塞、脳卒中、一過性脳虚血発作、不安定狭心症又は冠動脈バイパス手術の既往等）がある患者は除外された。

国内併合解析集団における人口統計学的特性及びベースライン時のその他の特性を以下に示す。

1.3.1 人口統計学的特性

Pool J-ISS-1における人口統計学的特性を表 7に示す。

本Poolの安全性解析対象集団735例のうち85.3%が女性であり、年齢の中央値は45.0歳（範囲20～64歳）、体重の中央値は54.40 kg（範囲32.1～102.0 kg）であった。人口統計学的特性はいずれの投与群でも同様であった。

表 7 人口統計学的特性（J-ISS-1：安全性解析対象集団）

	Placebo (N = 267)	AMG 334 28 mg QM (N = 66)	AMG 334 70 mg QM (N = 265)	AMG 334 140 mg QM (N = 137)	Total (N = 735)
Sex - n (%)					
Male	33 (12.4)	11 (16.7)	39 (14.7)	25 (18.2)	108 (14.7)
Female	234 (87.6)	55 (83.3)	226 (85.3)	112 (81.8)	627 (85.3)
Age (years)					
n	267	66	265	137	735
Mean	44.1	42.8	44.0	45.0	44.1
SD	9.2	6.9	8.8	8.3	8.7
Median	45.0	43.0	44.0	45.0	45.0
Q1, Q3	39.0, 51.0	39.0, 48.0	39.0, 50.0	41.0, 50.0	39.0, 50.0
Min, Max	20, 64	22, 57	20, 64	23, 64	20, 64
Age group - n (%)					
< Median	126 (47.2)	38 (57.6)	135 (50.9)	61 (44.5)	360 (49.0)
≥ Median	141 (52.8)	28 (42.4)	130 (49.1)	76 (55.5)	375 (51.0)
Weight (kg)					
n	267	66	265	137	735
Mean	55.82	57.59	56.43	57.67	56.54
SD	9.98	10.19	10.64	10.96	10.43
Median	54.00	56.70	54.00	55.20	54.40
Q1, Q3	48.70, 61.70	50.70, 61.80	49.30, 61.20	49.10, 64.30	49.10, 62.00
Min, Max	38.5, 98.5	40.5, 91.7	32.1, 102.0	39.8, 99.7	32.1, 102.0
Weight group - n (%)					
< Median	140 (52.4)	31 (47.0)	134 (50.6)	58 (42.3)	363 (49.4)
≥ Median	127 (47.6)	35 (53.0)	131 (49.4)	79 (57.7)	372 (50.6)
Body mass index (BMI, kg/m^2)					
n	267	66	265	137	735
Mean	21.85	22.06	21.89	22.05	21.92
SD	3.42	3.55	3.46	3.51	3.46
Median	21.52	21.27	21.33	21.36	21.39
Q1, Q3	19.35, 23.76	19.48, 23.73	19.56, 23.45	19.53, 24.25	19.48, 23.77
Min, Max	15.3, 38.1	14.8, 34.6	13.9, 36.0	15.6, 36.1	13.9, 38.1

N = Number of subjects in the analysis set
n = Number of subjects with observed data
% = n / N * 100

[redacted]

Pool J-ISS-2における人口統計学的特性は表 付録-1に示す。

1.3.2 ベースライン時のその他の特性

Pool J-ISS-1におけるベースライン時のその他の特性を表 8に示す。

本Poolの安全性解析対象集団735例のうち86.1%がEM患者、13.9%がCM患者であった。エレヌマブ70 mg群におけるEM患者の割合は80.4%、CM患者の割合は19.6%であり、プラセボ群と同程度であった（EM：81.3%、CM：18.7%）。20120309試験ではEM患者のみを対象としたため、エレヌマブ28 mg群及び140 mg群ではCM患者はいなかった。心血管リスク因子は半数以上の被験者で認められ、心血管リスク因子が1つのみであった被験者は41.5%、2つ以上の被験者は16.3%であった。最も多く認められた心血管リスク因子はコレステロール高値であった。腎機能では被験者の約90%でeGFRが60以上であった。ベースライン時の特性はエレヌマブ70 mg群とプラセボ群で同様であり、エレヌマブの投与群間でも28 mg群及び140 mg群でCM患者がいなかったことを除き、明らかな違いはなく、おおむね同様であった。

表 8　ベースライン時のその他の特性（J-ISS-1：安全性解析対象集団）

Factor Category	Placebo (N = 267) n (%)	AMG 334 28 mg QM (N = 66) n (%)	 70 mg QM (N = 265) n (%)	 140 mg QM (N = 137) n (%)	Total (N = 735) n (%)
Migraine type					
EM	217 (81.3)	66 (100.0)	213 (80.4)	137 (100.0)	633 (86.1)
CM	50 (18.7)	0 (0.0)	52 (19.6)	0 (0.0)	102 (13.9)
Renal impairment					
Yes	26 (9.7)	3 (4.5)	27 (10.2)	10 (7.3)	66 (9.0)
No	241 (90.3)	63 (95.5)	238 (89.8)	127 (92.7)	669 (91.0)
CKD stages					
eGFR ≥ 90 mL/min/1.73 m^2	40 (15.0)	16 (24.2)	45 (17.0)	13 (9.5)	114 (15.5)
eGFR ≥ 60 to < 90 mL/min/1.73 m^2	201 (75.3)	47 (71.2)	193 (72.8)	114 (83.2)	555 (75.5)
eGFR ≥ 30 to < 60 mL/min/1.73 m^2	26 (9.7)	3 (4.5)	27 (10.2)	10 (7.3)	66 (9.0)
eGFR ≥ 15 to < 30 mL/min/1.73 m^2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
eGFR < 15 mL/min/1.73 m^2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of baseline cardiovascular risk factors					
0	124 (46.4)	25 (37.9)	115 (43.4)	46 (33.6)	310 (42.2)
1	103 (38.6)	31 (47.0)	108 (40.8)	63 (46.0)	305 (41.5)
≥ 2	40 (15.0)	10 (15.2)	42 (15.8)	28 (20.4)	120 (16.3)
Treatment failure of migraine preventive medication					
Yes	102 (38.2)	20 (30.3)	102 (38.5)	54 (39.4)	278 (37.8)
No	165 (61.8)	46 (69.7)	163 (61.5)	83 (60.6)	457 (62.2)

N = Number of subjects in the analysis set
n = Number of subjects with observed data
% = n / N * 100
EM = Episodic migraine
CM = Chronic migraine
Renal impairment: eGRF < 60 mL/min/1.73 m^2
Summary of migraine criteria is based on actual data collected instead of randomization stratification.
Baseline cardiovascular risk factors include: diabetes mellitus, hypertension and / or high blood pressure, history of smoking, history of dyslipidemia / high cholesterol level / high lipid levels, BMI > 30, coronary artery disease and cerebrovascular and peripheral artery disease.

[redacted]

Pool J-ISS-2におけるベースライン時のその他の特性は表 付録-2に示す。

2.　有害事象

2.1　有害事象の解析

2.1.1　有害事象の要約

2.1.1.1　国内併合解析

1.　二重盲検プラセボ対照期

Pool J-ISS-1における有害事象の要約を以下に示す（表 9）。

- すべての有害事象の発現割合はエレヌマブ70 mg群で68.3%であり、プラセボ群（64.0%）と同程度であった。その他のエレヌマブ群の発現割合は28 mg群で60.6%、140 mg群で71.5%であった。

- 有害事象の重症度はほとんどがグレード2以下であった。グレード3以上の有害事象の発現割合はエレヌマブ70 mg群で2.6%であり、プラセボ群（2.2%）と比較して同程度で、エレヌマブの投与群間で用量依存的な傾向は認められなかった（28 mg群1.5%、140 mg群0.0%）。グレード4の有害事象はエレヌマブ70 mg群の1例［全身性エリテマトーデス（2.1.2.2項参照）］及びプラセボ群の1例のみに発現した。
- 死亡は認められなかった。
- 重篤な有害事象の発現割合はエレヌマブ70 mg群で1.1%であり、プラセボ群（2.2%）と比較して同程度で、その他のエレヌマブ群（28 mg群1.5%、140 mg群0.7%）とも同程度であった。
- 治験薬の投与中止に至った有害事象の発現割合はエレヌマブ70 mg群で0.8%であり、プラセボ群（0.4%）と比較して同程度であった。その他のエレヌマブ群では治験薬の投与中止に至った有害事象は認められなかった。

表 9　有害事象の要約（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
All treatment-emergent adverse events	171 (64.0)	40 (60.6)	181 (68.3)	98 (71.5)	319 (68.2)
Grade ≥ 2	129 (48.3)	33 (50.0)	139 (52.5)	65 (47.4)	237 (50.6)
Grade ≥ 3	6 (2.2)	1 (1.5)	7 (2.6)	0 (0.0)	8 (1.7)
Grade ≥ 4	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Serious adverse events	6 (2.2)	1 (1.5)	3 (1.1)	1 (0.7)	5 (1.1)
Leading to discontinuation of investigational product	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	11 (4.1)	5 (7.6)	28 (10.6)	13 (9.5)	46 (9.8)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03

[redacted]

Pool J-ISS-1における曝露期間で調整した発現頻度を算出した有害事象の要約は表 付録-3に示す。

2.　全投与期

Pool J-ISS-2では、有害事象は曝露期間で調整した発現頻度（100人年あたりの被験者数）を用いて要約した。曝露期間で調整した発現頻度は、解析対象期間においてある事象を少なくとも1件発現した被験者数を当該期間の観察人年で割った値と定義される。有害事象を発現した被験者では、それぞれの用量における曝露期間は、当該有害事象の発現前のそれぞれの用量での投与期間と同一である（注：被験者が有害事象発現前に当該用量を投与した期間は継続的でない可能性があり、そのため、有害事象発現以前に当該用量を投与していたすべての期間が含まれる）。なお、すべての要約表について、分母は各投与量群で当該用量の投与を1回以上受けた被験者の数を示す。よって、エ

レヌマブの2つ以上の用量を投与した被験者は、両方の投与量群の分母に含まれ、要約表の「Combined」の欄の値は、各投与群に含まれる被験者の総数とはならない場合がある。

Pool J-ISS-2における有害事象の要約を以下に示す（表 10）。

- すべての有害事象の発現頻度はエレヌマブ70 mg投与期間で223.1例／100人年、140 mg投与期間で239.4例／100人年であった。
- 有害事象の重症度はほとんどがグレード2以下であった。グレード3以上の有害事象の発現頻度はエレヌマブ70 mg投与期間で4.3例／100人年、140 mg投与期間で2.7例／100人年であった。グレード4の有害事象は、二重盲検プラセボ対照期にエレヌマブ70 mg群の1例に発現した全身性エリテマトーデスのみであった。
- 死亡は認められなかった。
- 重篤な有害事象の発現頻度はエレヌマブ70 mg投与期間で3.7例／100人年、140 mg投与期間で3.0例／100人年であった。
- 治験薬の投与中止に至った有害事象の発現頻度はエレヌマブ70 mg投与期間で1.1例／100人年、140 mg投与期間で0.6例／100人年であった。
- これらの有害事象の発現頻度は、二重盲検プラセボ対照期と比較し明らかな増加は認められなかった（表 付録-3）。

表 10　有害事象の要約（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent adverse events	328 (79.2) / 147.0 [223.1]	230 (85.5) / 96.1 [239.4]	439 (93.4) / 192.6 [227.9]
Grade ≥ 2	267 (64.5) / 238.9 [111.7]	191 (71.0) / 153.6 [124.3]	375 (79.8) / 348.8 [107.5]
Grade ≥ 3	22 (5.3) / 510.2 [4.3]	9 (3.3) / 335.3 [2.7]	31 (6.6) / 842.1 [3.7]
Grade ≥ 4	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
Serious adverse events	19 (4.6) / 512.8 [3.7]	10 (3.7) / 334.0 [3.0]	29 (6.2) / 846.8 [3.4]
Leading to discontinuation of investigational product	6 (1.4) / 527.4 [1.1]	2 (0.7) / 343.2 [0.6]	8 (1.7) / 870.6 [0.9]
Fatal adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Treatment-related treatment-emergent adverse events	42 (10.1) / 480.0 [8.8]	26 (9.7) / 315.1 [8.3]	64 (13.6) / 775.5 [8.3]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Grading categories determined using CTCAE version 4.03

[redacted]

2.1.1.2　海外併合データ

本併合解析では有害事象はMedDRAバージョン22.0を用いてコード化された。また、一部の有害事象の集計表では国内併合解析と同一のMedDRAバージョン22.1も用いた。海外併合解析のすべての解析結果はモジュール5.3.5.3-2.2に添付した。

1. Pool A

12週間の二重盲検プラセボ対照期における有害事象の要約を以下に示す（表 11）。

- Pool Aでは1613例（エレヌマブ7 mg又は21 mg群213例、70 mg群893例、140 mg群507例）がエレヌマブの投与を受け、1043例がプラセボの投与を受けた。
- エレヌマブを投与された1613例での曝露期間の平均値（SD）は、11.7（1.2）週であった。
- すべての有害事象の発現割合はエレヌマブ70 mg群で47.6%、140 mg群で46.0%、プラセボ群で48.9%であり、投与群間で同程度であった。
- 有害事象の重症度はほとんどがグレード2以下であった。グレード3以上の有害事象の発現割合はエレヌマブ70 mg群で3.5%、140 mg群で3.4%、プラセボ群3.3%であり、投与群間で同程度であった。グレード4の有害事象はエレヌマブ70 mg群及び140 mg群の各1例（それぞれ、肋軟骨炎及び血中クレアチンホスホキナーゼ増加）のみに発現した。
- 死亡は認められなかった。
- 重篤な有害事象の発現割合はエレヌマブ70 mg群で1.7%、140 mg群で1.4%、プラセボ群で1.6%であり、投与群間で同程度であった。
- 治験薬の投与中止に至った有害事象の発現割合はエレヌマブ70 mg群で1.7%、140 mg群で2.0%、プラセボ群で1.0%であり、投与群間で同程度であった。
- 発現した重篤又は治験薬の投与中止に至った有害事象に一定の傾向は認められなかった（モジュール5.3.5.3-2.2　表14-6.3.1及び表14-6.4）。
- 全エレヌマブ群で3%以上の被験者に認められた有害事象は上咽頭炎（エレヌマブ70 mg群5.9%、140 mg群5.5%、プラセボ群7.3%、以下同順）、上気道感染（4.5%、2.8%、3.1%）であった。個々の有害事象において、エレヌマブ70 mg群、140 mg群及びプラセボ群の投与群間で発現割合に明らかな違いが認められた事象はなかった。

表 11　有害事象の要約及び高頻度の有害事象（Pool A：安全性解析対象集団）

		AMG 334			
	Placebo (N = 1043) n (%)	7 mg or 21 mg (N = 213) n (%)	70 mg (N = 893) n (%)	140 mg (N = 507) n (%)	All (N = 1613) n (%)
All treatment-emergent adverse events	510 (48.9)	112 (52.6)	425 (47.6)	233 (46.0)	770 (47.7)
Grade ≥ 2	286 (27.4)	56 (26.3)	220 (24.6)	125 (24.7)	401 (24.9)
Grade ≥ 3	34 (3.3)	6 (2.8)	31 (3.5)	17 (3.4)	54 (3.3)
Grade ≥ 4	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	2 (0.1)
Serious adverse events	17 (1.6)	1 (0.5)	15 (1.7)	7 (1.4)	23 (1.4)
Leading to discontinuation of investigational product	10 (1.0)	4 (1.9)	15 (1.7)	10 (2.0)	29 (1.8)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Frequent treatment-emergent adverse events (≥ 2% in the All AMG 334 group)					
上咽頭炎	76 (7.3)	16 (7.5)	53 (5.9)	28 (5.5)	97 (6.0)
上気道感染	32 (3.1)	3 (1.4)	40 (4.5)	14 (2.8)	57 (3.5)
注射部位疼痛	18 (1.7)	2 (0.9)	33 (3.7)	9 (1.8)	44 (2.7)
疲労	18 (1.7)	7 (3.3)	20 (2.2)	10 (2.0)	37 (2.3)
悪心	27 (2.6)	4 (1.9)	21 (2.4)	10 (2.0)	35 (2.2)

Integrated safety analysis set (ISAS): all subjects in the studies/pool who have received at least one dose of IP.
12-Week Placebo-controlled Pool: all subjects from studies 20120178, 20120295, 20120296, and 20120297 in the ISAS.
N = Number of subjects in the analysis set; n = Number of subjects reporting at least one occurrence of an adverse event;
% = n/N * 100.
Grading categories determined using CTCAE version 4.03.
Coded using MedDRA version 22.1.

[redacted]

2. Pool B

24週間の二重盲検プラセボ対照期における有害事象の要約を以下に示す（表 12）。

- Pool Bでは633例（エレヌマブ70 mg群314例、140 mg群319例）がエレヌマブの投与を受け、319例がプラセボの投与を受けた。
- エレヌマブを投与された633例での曝露期間の平均値（SD）は、22.8（3.9）週であった。
- すべての有害事象の発現割合はエレヌマブ70 mg群で57.6%、140 mg群で56.1%、プラセボ群で63.3%であり、投与群間で明らかな違いは認められなかった。
- 有害事象の重症度はほとんどがグレード2以下であった。グレード3以上の有害事象の発現割合はエレヌマブ70 mg群で5.4%、140 mg群で5.6%、プラセボ群5.0%であり、投与群間で同程度であった。グレード4の有害事象はプラセボ群及びエレヌマブ140 mg群の各1例（エレヌマブ群140 mg群の1例はPool Aに認められた血中クレアチンホスホキナーゼ増加と同一）に発現した。
- 死亡は認められなかった。
- 重篤な有害事象の発現割合はエレヌマブ70 mg群で2.5%、140 mg群で2.5%、プラセボ群で2.2%であり、投与群間で同程度であった。
- 治験薬の投与中止に至った有害事象の発現割合はエレヌマブ70 mg群で2.2%、140 mg群で3.1%、プラセボ群2.5%であり、投与群間で明らかな違いは認められなかった。
- 発現した重篤又は治験薬の投与中止に至った有害事象に一定の傾向は認められなかった（モジュール5.3.5.3-2.2　表14-6.63.1及び表14-6.64）。

- 全エレヌマブ群で3%以上の被験者に認められた有害事象はPool Aと同様、上咽頭炎（エレヌマブ70 mg群9.9%、140 mg群11.0%、プラセボ群10.7%、以下同順）、上気道感染（6.7%、4.7%、6.0%）であった。個々の有害事象において、便秘はプラセボ群（1.3%）又はエレヌマブ70 mg群（1.9%）に比較して140 mg群（3.8%）で発現割合が高かったが、その他、エレヌマブ70 mg群、140 mg群及びプラセボ群の投与群間で発現割合に明らかな違いが認められた事象はなかった。

表 12　有害事象の要約及び高頻度の有害事象（Pool B：安全性解析対象集団）

		AMG 334		
	Placebo (N = 319) n (%)	70 mg (N = 314) n (%)	140 mg (N = 319) n (%)	All (N = 633) n (%)
All treatment-emergent adverse events	202 (63.3)	181 (57.6)	179 (56.1)	360 (56.9)
Grade ≥ 2	126 (39.5)	111 (35.4)	111 (34.8)	222 (35.1)
Grade ≥ 3	16 (5.0)	17 (5.4)	18 (5.6)	35 (5.5)
Grade ≥ 4	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.2)
Serious adverse events	7 (2.2)	8 (2.5)	8 (2.5)	16 (2.5)
Leading to discontinuation of investigational product	8 (2.5)	7 (2.2)	10 (3.1)	17 (2.7)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Frequent treatment-emergent adverse events (≥ 2% in the All AMG 334 group)				
上咽頭炎	34 (10.7)	31 (9.9)	35 (11.0)	66 (10.4)
上気道感染	19 (6.0)	21 (6.7)	15 (4.7)	36 (5.7)
便秘	4 (1.3)	6 (1.9)	12 (3.8)	18 (2.8)
副鼻腔炎	7 (2.2)	7 (2.2)	11 (3.4)	18 (2.8)
インフルエンザ	5 (1.6)	4 (1.3)	10 (3.1)	14 (2.2)
関節痛	6 (1.9)	7 (2.2)	7 (2.2)	14 (2.2)
疲労	8 (2.5)	6 (1.9)	7 (2.2)	13 (2.1)
背部痛	6 (1.9)	6 (1.9)	7 (2.2)	13 (2.1)
悪心	6 (1.9)	7 (2.2)	6 (1.9)	13 (2.1)

Integrated safety analysis set (ISAS): all subjects in the studies/pool who have received at least one dose of IP.
24-Week Placebo-controlled Pool: all subjects from study 20120296 in the ISAS.
N = Number of subjects in the analysis set; n = Number of subjects reporting at least one occurrence of an adverse event;
% = n/N * 100.
Grading categories determined using CTCAE version 4.03.
Coded using MedDRA version 22.1.

[redacted]

3. Pool C

全投与期における有害事象の要約を以下に示す（表 13）。

- Pool Cでは計2499例がエレヌマブ70 mg又は140 mg投与を受け、このうちエレヌマブ70 mgを1回以上投与された被験者は2128例、140 mgを1回以上投与された被験者は1223例であった。
- エレヌマブを投与された2499例での曝露期間の平均値（SD）は、55.1（43.8）週であった。
- すべての有害事象の発現頻度はエレヌマブ70 mg投与期間で158.9例／100人年、140 mg投与期間で147.0例／100人年であった。
- 有害事象の重症度はほとんどがグレード2以下であった。グレード3以上の有害事象の発現頻度はエレヌマブ70 mg投与期間で8.9例／100人年、140 mg投与期間で6.8例／100人年であった。グ

レード4の有害事象はエレヌマブ70 mg投与期間で4例［肺炎球菌性菌血症、急性呼吸窮迫症候群、心房細動及び心筋虚血（同一被験者で発現）、高血圧性心疾患、肋軟骨炎、乳頭様甲状腺癌、各1例］、140 mg投与期間で4例（血中クレアチンホスホキナーゼ増加2例、硬膜下血腫1例、卵管卵巣膿瘍1例）に発現した。

- 死亡に至った有害事象は2例に報告され、エレヌマブ70 mg投与期間で1例（動脈硬化症）、140 mg投与期間で1例（不整脈原性右室異形成症）に認められた（詳細は2.1.3項参照）。
- 重篤な有害事象の発現頻度はエレヌマブ70 mg投与期間で4.3例／100人年、140 mg投与期間で4.7例／100人年であった。
- 治験薬の投与中止に至った有害事象の発現頻度は、エレヌマブ70 mg投与期間で2.8例／100人年、140 mg投与期間で3.0例／100人年であった。
- Pool A及びPool Bと同様に、発現した重篤又は治験薬の投与中止に至った有害事象に一定の傾向は認められなかった（モジュール5.3.5.3-2.2　表14-6.30及び表14-6.31）。
- エレヌマブ70 mg又は140mgの全投与期で100人年あたり5例以上に認められた有害事象は、上咽頭炎（エレヌマブ70 mg投与期間15.8例／100人年、140 mg投与期間15.4例／100人年、以下同順）、上気道感染（9.8例／100人年、8.4例／100人年）、副鼻腔炎（4.7例／100人年、5.5例／100人年）であった。発現した有害事象の種類はPool A及びPool Bとおおむね一致しており、個々の有害事象においてPool Aに比較して発現頻度が顕著に増加した事象は認められなかった（モジュール5.3.5.3-2.2　表14-6.18.1）。

表 13　有害事象の要約及び高頻度の有害事象（Pool C：安全性解析対象集団）

	AMG 334		
	70 mg (Subj-yr = 2068.2) (N = 2128) n (%) / e [r]	140 mg (Subj-yr = 1016.4) (N = 1223) n (%) / e [r]	Combined (Subj-yr = 3084.6) (N = 2499) n (%) / e [r]
All treatment-emergent adverse events	1425 (67.0) / 896.5 [158.9]	754 (61.7) / 513.0 [147.0]	1792 (71.7) / 1181.1 [151.7]
Grade ≥ 2	1024 (48.1) / 1297.6 [78.9]	506 (41.4) / 697.0 [72.6]	1322 (52.9) / 1777.9 [74.4]
Grade ≥ 3	173 (8.1) / 1949.7 [8.9]	67 (5.5) / 981.9 [6.8]	229 (9.2) / 2867.5 [8.0]
Grade ≥ 4	4 (0.2) / 2066.2 [0.2]	5 (0.4) / 1014.7 [0.5]	9 (0.4) / 3080.1 [0.3]
Serious adverse events	87 (4.1) / 2014.6 [4.3]	47 (3.8) / 995.4 [4.7]	129 (5.2) / 2982.6 [4.3]
Leading to discontinuation of investigational product	58 (2.7) / 2052.9 [2.8]	30 (2.5) / 1006.8 [3.0]	88 (3.5) / 3059.7 [2.9]
Fatal adverse events	1 (<0.1) / 2068.2 [<0.1]	1 (<0.1) / 1016.4 [<0.1]	2 (<0.1) / 3084.6 [<0.1]
Frequent treatment-emergent adverse events (≥ 2 per 100 subject years in the All AMG 334 group)			
上咽頭炎	293 (13.8) / 1851.6 [15.8]	143 (11.7) / 927.8 [15.4]	398 (15.9) / 2691.0 [14.8]
上気道感染	189 (8.9) / 1934.4 [9.8]	81 (6.6) / 968.9 [8.4]	242 (9.7) / 2843.4 [8.5]
副鼻腔炎	93 (4.4) / 1992.7 [4.7]	54 (4.4) / 985.2 [5.5]	142 (5.7) / 2936.4 [4.8]
インフルエンザ	92 (4.3) / 1999.0 [4.6]	30 (2.5) / 998.8 [3.0]	115 (4.6) / 2958.9 [3.9]
関節痛	82 (3.9) / 1999.5 [4.1]	33 (2.7) / 1000.1 [3.3]	114 (4.6) / 2968.2 [3.8]
背部痛	83 (3.9) / 1997.2 [4.2]	32 (2.6) / 1002.1 [3.2]	111 (4.4) / 2960.7 [3.7]
尿路感染	78 (3.7) / 2019.2 [3.9]	37 (3.0) / 994.8 [3.7]	110 (4.4) / 2989.4 [3.7]
悪心	68 (3.2) / 2017.7 [3.4]	45 (3.7) / 985.4 [4.6]	109 (4.4) / 2986.6 [3.6]
疲労	61 (2.9) / 2016.9 [3.0]	43 (3.5) / 987.3 [4.4]	102 (4.1) / 2977.7 [3.4]
片頭痛	73 (3.4) / 2031.8 [3.6]	32 (2.6) / 998.0 [3.2]	101 (4.0) / 3016.3 [3.3]
注射部位反応	83 (3.9) / 2000.1 [4.1]	19 (1.6) / 999.4 [1.9]	97 (3.9) / 2980.2 [3.3]
浮動性めまい	55 (2.6) / 2027.9 [2.7]	23 (1.9) / 1003.5 [2.3]	76 (3.0) / 3010.8 [2.5]
気管支炎	53 (2.5) / 2030.5 [2.6]	21 (1.7) / 1005.6 [2.1]	74 (3.0) / 3016.5 [2.5]
便秘	37 (1.7) / 2036.9 [1.8]	37 (3.0) / 992.9 [3.7]	73 (2.9) / 3011.5 [2.4]
咳嗽	46 (2.2) / 2041.4 [2.3]	20 (1.6) / 1000.8 [2.0]	63 (2.5) / 3019.2 [2.1]
口腔咽頭痛	45 (2.1) / 2038.2 [2.2]	15 (1.2) / 1008.0 [1.5]	59 (2.4) / 3024.3 [2.0]

Integrated safety analysis set (ISAS): all subjects in the studies/pool who have received at least one dose of IP.
AMG 334 through OLE pool: all subjects enrolled in studies 20120178, 20120295, 20130255, 20120296, and 20120297 who received at least one dose of AMG 334 (70 mg or 140 mg).
N = Number of subjects in the analysis set exposed to each dose level; n = Number of subjects reporting at least one occurrence of an adverse event; % = n/N * 100; e = Sum across all subjects, the total time at risk in years. Total time at risk is the time from first dose of AMG 334 (70 mg or 140 mg) through to onset of first event or the min (end of study date, data cutoff date, last IP dose + 84/112) if no event. r = Exposure-adjusted subject incidence rate per 100 subject years (n/e*100).
AEs are presented at the dose level at which the AE occurred so subjects who receive IP at more than one dose level will be counted in both dose levels of AMG 334. Therefore, the All AMG 334 column may not be the sum of the subjects included in each of the individual dose levels.
Multiple occurrences of the same event for a subject are counted as single events within a dose level.
OLE = Open Label Extension. Grading categories determined using CTCAE version 4.03.
Coded using MedDRA version 22.1.



4. Pool D

1年以上の長期投与被験者における有害事象の要約を以下に示す（表 14）。

- Pool Dでは計1305例がエレヌマブ70 mg又は140 mg投与を受け、このうちエレヌマブ70 mgを1回以上投与された被験者は1147例、エレヌマブ140 mgを1回以上投与された被験者は923例であった。
- エレヌマブを投与された1305例での曝露期間の平均値（SD）は、79.7（48.2）週であった。
- すべての有害事象の発現頻度は、エレヌマブ70 mg投与期間で137.1例／100人年、140 mg投与期間で140.9例／100人年であった。
- 有害事象の重症度はほとんどがグレード2以下であった。グレード3以上の有害事象の発現頻度はエレヌマブ70 mg投与期間で7.7例／100人年、140 mg投与期間で6.4例／100人年であった。グレード4の有害事象はエレヌマブ70 mg投与期間で2例（高血圧性心疾患、肋軟骨炎、各1例）、140 mg投与期間で2例（血中クレアチンホスホキナーゼ増加、卵管卵巣膿瘍、各1例）に発現した。
- 死亡に至った有害事象はエレヌマブ70 mg投与期間の1例（動脈硬化症）で報告された。
- 重篤な有害事象の発現頻度はエレヌマブ70 mg投与期間で4.1例／100人年、140 mg投与期間で4.3例／100人年であった。
- 治験薬の投与中止に至った有害事象の発現頻度はエレヌマブ70 mg投与期間で0.7例／100人年、140 mg投与期間で0.2例／100人年であった。
- エレヌマブを長期投与した場合でも、発現した重篤又は治験薬の投与中止に至った有害事象に一定の傾向は認められなかった（モジュール5.3.5.3-2.2　表14-6.47及び表14-6.48）。
- エレヌマブ70 mg又は140 mgの全投与期で100人年あたり5例以上に認められた有害事象は、上咽頭炎（エレヌマブ70 mg投与期間15.2例／100人年、140 mg投与期間15.3例／100人年、以下同順）、上気道感染（8.6例／100人年、8.8例／100人年）、副鼻腔炎（5.6例／100人年、5.5例／100人年）であった。エレヌマブを長期間投与した本Poolにおいても発現した有害事象の種類はPool A及びPool Bとおおむね一致しており、個々の有害事象において発現頻度がPool Aに比較して顕著に増加した事象は認められなかった（モジュール5.3.5.3-2.2　表 14-6.18.1）。

表 14　有害事象の要約及び高頻度の有害事象（Pool D：安全性解析対象集団）

	AMG 334		
	70 mg (Subj-yr = 1395.7) (N = 1147) n (%) / e [r]	140 mg (Subj-yr = 840.4) (N = 923) n (%) / e [r]	Combined (Subj-yr = 2236.1) (N = 1305) n (%) / e [r]
All treatment-emergent adverse events	785 (68.4) / 572.5 [137.1]	586 (63.5) / 416.0 [140.9]	1011 (77.5) / 765.3 [132.1]
Grade ≥ 2	574 (50.0) / 839.1 [68.4]	406 (44.0) / 563.2 [72.1]	783 (60.0) / 1190.7 [65.8]
Grade ≥ 3	101 (8.8) / 1305.8 [7.7]	52 (5.6) / 811.9 [6.4]	143 (11.0) / 2054.5 [7.0]
Grade ≥ 4	2 (0.2) / 1394.4 [0.1]	2 (0.2) / 839.5 [0.2]	4 (0.3) / 2233.1 [0.2]
Serious adverse events	55 (4.8) / 1352.7 [4.1]	35 (3.8) / 822.3 [4.3]	85 (6.5) / 2148.3 [4.0]
Leading to discontinuation of investigational product	10 (0.9) / 1393.0 [0.7]	2 (0.2) / 839.5 [0.2]	12 (0.9) / 2232.5 [0.5]
Fatal adverse events	1 (<0.1) / 1395.7 [<0.1]	0 (0.0) / 840.4 [0.0]	1 (<0.1) / 2236.1 [<0.1]
Frequent treatment-emergent adverse events (≥ 2 per 100 subject years in the All AMG 334 group)			
上咽頭炎	186 (16.2) / 1226.9 [15.2]	117 (12.7) / 763.9 [15.3]	266 (20.4) / 1903.8 [14.0]
上気道感染	112 (9.8) / 1299.4 [8.6]	70 (7.6) / 798.9 [8.8]	155 (11.9) / 2039.9 [7.6]
副鼻腔炎	74 (6.5) / 1328.8 [5.6]	45 (4.9) / 812.9 [5.5]	114 (8.7) / 2100.7 [5.4]
インフルエンザ	66 (5.8) / 1341.0 [4.9]	22 (2.4) / 826.2 [2.7]	81 (6.2) / 2128.6 [3.8]
背部痛	58 (5.1) / 1337.8 [4.3]	23 (2.5) / 828.8 [2.8]	77 (5.9) / 2128.4 [3.6]
尿路感染	49 (4.3) / 1357.9 [3.6]	33 (3.6) / 820.2 [4.0]	77 (5.9) / 2153.6 [3.6]
関節痛	52 (4.5) / 1340.3 [3.9]	24 (2.6) / 827.5 [2.9]	75 (5.7) / 2137.0 [3.5]
悪心	33 (2.9) / 1363.4 [2.4]	33 (3.6) / 814.0 [4.1]	63 (4.8) / 2160.9 [2.9]
疲労	33 (2.9) / 1360.2 [2.4]	29 (3.1) / 817.2 [3.5]	60 (4.6) / 2151.4 [2.8]
気管支炎	39 (3.4) / 1363.5 [2.9]	18 (2.0) / 830.6 [2.2]	57 (4.4) / 2174.6 [2.6]
注射部位疼痛	38 (3.3) / 1357.9 [2.8]	16 (1.7) / 825.5 [1.9]	49 (3.8) / 2164.0 [2.3]
便秘	23 (2.0) / 1372.9 [1.7]	27 (2.9) / 820.7 [3.3]	49 (3.8) / 2175.8 [2.3]
咳嗽	33 (2.9) / 1375.5 [2.4]	19 (2.1) / 825.2 [2.3]	49 (3.8) / 2177.8 [2.3]
片頭痛	30 (2.6) / 1375.8 [2.2]	22 (2.4) / 826.2 [2.7]	48 (3.7) / 2188.9 [2.2]

Integrated safety analysis set (ISAS): all subjects in the studies/pool who have received at least one dose of IP.
AMG 334 long-term pool: all subjects in the AMG 334 through open label extension (OLE) pool who have a minimum of 1 year's continuous exposure (phases combined) to AMG 334 (70 mg, 140 mg or both).
N = Number of subjects in the analysis set exposed to each dose level; n = Number of subjects reporting at least one occurrence of an adverse event; % = n/N * 100; e = Sum across all subjects, the total time at risk in years. Total time at risk is the time from first dose of AMG 334 (70 mg or 140 mg) through to onset of first event or the min (end of study date, data cutoff date, last IP dose + 84/112) if no event. r = Exposure-adjusted subject incidence rate per 100 subject years (n/e*100).
AEs are presented at the dose level at which the AE occurred so subjects who receive IP at more than one dose level will be counted in both dose levels of AMG 334. Therefore, the All AMG 334 column may not be the sum of the subjects included in each of the individual dose levels.
Multiple occurrences of the same event for a subject are counted as single events within a dose level.
Grading categories determined using CTCAE version 4.03.
Coded using MedDRA version 22.1.



2.1.2　比較的よく見られる有害事象

本項では国内併合解析の結果を示す。

2.1.2.1　高頻度に認められた有害事象

1.　二重盲検プラセボ対照期

Pool J-ISS-1においてエレヌマブ70 mg群で1%以上の被験者に認められた有害事象を表 15に示す。Pool J-ISS-1に認められたすべての有害事象を表 付録-4に、曝露期間で調整した発現頻度を算出したすべての有害事象を表 付録-5、治験薬との関連がある有害事象を表 付録-6に示す。

エレヌマブ70 mg群で2%以上の被験者に認められた有害事象は、上咽頭炎（エレヌマブ70 mg群27.9%、プラセボ群29.2%、以下同順）、背部痛（5.3%、3.0%）、便秘（4.9%、1.5%）、齲歯（4.2%、1.9%）、咽頭炎（3.8%、2.6%）、胃腸炎（2.6%、3.0%）、上腹部痛（2.6%、0.7%）、口内炎（2.3%、1.1%）、及び筋骨格硬直（2.3%、1.1%）であった。全体的にこれらの事象はエレヌマブ70 mg群でプラセボ群に比較して発現割合が高かったものの、エレヌマブの投与群間では用量依存的な傾向は認められなかったが、便秘においてはプラセボ群（1.5%）及びエレヌマブ28 mg群（0.0%）に比較して、70 mg群（4.9%）及び140 mg群（5.1%）で発現割合が高かった。

表 15　エレヌマブ70 mg群で1%以上の被験者に認められた有害事象
（J-ISS-1：安全性解析対象集団）

		AMG 334			
Preferred Term	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
Number of subjects reporting treatment-emergent adverse events that occurred in ≥ 1% of subjects in 70 mg group	113 (42.3)	32 (48.5)	145 (54.7)	65 (47.4)	242 (51.7)
上咽頭炎	78 (29.2)	22 (33.3)	74 (27.9)	45 (32.8)	141 (30.1)
背部痛	8 (3.0)	3 (4.5)	14 (5.3)	1 (0.7)	18 (3.8)
便秘	4 (1.5)	0 (0.0)	13 (4.9)	7 (5.1)	20 (4.3)
齲歯	5 (1.9)	2 (3.0)	11 (4.2)	2 (1.5)	15 (3.2)
咽頭炎	7 (2.6)	3 (4.5)	10 (3.8)	3 (2.2)	16 (3.4)
胃腸炎	8 (3.0)	2 (3.0)	7 (2.6)	5 (3.6)	14 (3.0)
上腹部痛	2 (0.7)	1 (1.5)	7 (2.6)	2 (1.5)	10 (2.1)
口内炎	3 (1.1)	2 (3.0)	6 (2.3)	1 (0.7)	9 (1.9)
筋骨格硬直	3 (1.1)	1 (1.5)	6 (2.3)	1 (0.7)	8 (1.7)
胃炎	5 (1.9)	0 (0.0)	5 (1.9)	3 (2.2)	8 (1.7)
湿疹	2 (0.7)	0 (0.0)	5 (1.9)	2 (1.5)	7 (1.5)
下痢	2 (0.7)	0 (0.0)	5 (1.9)	1 (0.7)	6 (1.3)
傾眠	1 (0.4)	0 (0.0)	5 (1.9)	0 (0.0)	5 (1.1)
インフルエンザ	6 (2.2)	1 (1.5)	4 (1.5)	1 (0.7)	6 (1.3)
筋肉痛	1 (0.4)	0 (0.0)	4 (1.5)	1 (0.7)	5 (1.1)
口腔咽頭痛	1 (0.4)	0 (0.0)	4 (1.5)	1 (0.7)	5 (1.1)
腱鞘炎	0 (0.0)	0 (0.0)	4 (1.5)	0 (0.0)	4 (0.9)
膀胱炎	4 (1.5)	1 (1.5)	3 (1.1)	2 (1.5)	6 (1.3)
感覚鈍麻	2 (0.7)	1 (1.5)	3 (1.1)	1 (0.7)	5 (1.1)
不眠症	2 (0.7)	1 (1.5)	3 (1.1)	1 (0.7)	5 (1.1)
変形性脊椎症	1 (0.4)	0 (0.0)	3 (1.1)	1 (0.7)	4 (0.9)
蕁麻疹	1 (0.4)	0 (0.0)	3 (1.1)	1 (0.7)	4 (0.9)
腹痛	1 (0.4)	1 (1.5)	3 (1.1)	0 (0.0)	4 (0.9)
鼻漏	1 (0.4)	1 (1.5)	3 (1.1)	0 (0.0)	4 (0.9)
挫傷	2 (0.7)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.6)
足底筋膜炎	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.6)
耳鳴	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.6)
歯痛	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.6)
腹部不快感	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.6)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1

[redacted]

2.　全投与期

Pool J-ISS-2においてエレヌマブ70 mg投与期間で100人年あたり2例以上に認められた有害事象を表 16に示す。Pool J-ISS-2に認められたすべての有害事象を表 付録-7に、治験薬との関連がある有害事象を表 付録-8に示す。

エレヌマブ70 mg投与期間で100人年あたり5例以上の頻度で認められた有害事象は、上咽頭炎（エレヌマブ70 mg投与期間60.1例／100人年、140 mg投与期間68.8例／100人年、以下同順）、インフル

エンザ（10.0例／100人年、9.5例／100人年）、背部痛（6.8例／100人年、2.4例／100人年）、胃腸炎（5.8例／100人年、5.8例／100人年）であった。

発現した有害事象の種類はPool J-ISS-1とおおむね同様であった。Pool J-ISS-1に比較して発現頻度に増加傾向がみられた有害事象はインフルエンザであった［Pool J-ISS-2：エレヌマブ70 mg投与期間10.0例／100人年、Pool J-ISS-1：エレヌマブ70 mg群3.3例／100人年（表 付録-5）］（2.1.2.3項　発現時期別の有害事象参照）。その他、Pool J-ISS-1に比較して発現頻度が顕著に増加した事象は認められなかった。

表 16　エレヌマブ70 mg投与期間で100人年あたり2例以上に認められた有害事象
（J-ISS-2：安全性解析対象集団）

	AMG 334		
Preferred Term	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent adverse events that occurred in ≥ 2 subjects per 100 subject years in 70 mg group	275 (66.4) / 218.2 [126.1]	186 (69.1) / 155.3 [119.8]	390 (83.0) / 318.5 [122.4]
上咽頭炎	191 (46.1) / 317.6 [60.1]	143 (53.2) / 207.9 [68.8]	299 (63.6) / 490.6 [60.9]
インフルエンザ	49 (11.8) / 489.6 [10.0]	30 (11.2) / 317.4 [9.5]	78 (16.6) / 805.4 [9.7]
背部痛	34 (8.2) / 498.4 [6.8]	8 (3.0) / 335.2 [2.4]	41 (8.7) / 827.7 [5.0]
胃腸炎	29 (7.0) / 502.5 [5.8]	19 (7.1) / 328.6 [5.8]	46 (9.8) / 822.4 [5.6]
咽頭炎	26 (6.3) / 502.5 [5.2]	10 (3.7) / 333.9 [3.0]	34 (7.2) / 831.1 [4.1]
上腹部痛	24 (5.8) / 506.1 [4.7]	6 (2.2) / 339.5 [1.8]	29 (6.2) / 833.4 [3.5]
齲歯	24 (5.8) / 506.8 [4.7]	11 (4.1) / 331.7 [3.3]	34 (7.2) / 830.4 [4.1]
便秘	21 (5.1) / 505.1 [4.2]	12 (4.5) / 334.2 [3.6]	32 (6.8) / 824.7 [3.9]
膀胱炎	19 (4.6) / 514.5 [3.7]	9 (3.3) / 337.0 [2.7]	27 (5.7) / 844.3 [3.2]
気管支炎	16 (3.9) / 515.1 [3.1]	8 (3.0) / 335.1 [2.4]	24 (5.1) / 847.1 [2.8]
口腔咽頭痛	15 (3.6) / 517.1 [2.9]	2 (0.7) / 341.5 [0.6]	17 (3.6) / 857.2 [2.0]
湿疹	14 (3.4) / 516.0 [2.7]	11 (4.1) / 333.5 [3.3]	25 (5.3) / 846.8 [3.0]
胃炎	13 (3.1) / 511.9 [2.5]	10 (3.7) / 336.5 [3.0]	22 (4.7) / 845.6 [2.6]
アレルギー性鼻炎	13 (3.1) / 515.9 [2.5]	3 (1.1) / 340.1 [0.9]	16 (3.4) / 856.0 [1.9]
口内炎	12 (2.9) / 517.0 [2.3]	4 (1.5) / 341.2 [1.2]	15 (3.2) / 857.0 [1.8]
下痢	12 (2.9) / 517.8 [2.3]	5 (1.9) / 340.6 [1.5]	17 (3.6) / 854.2 [2.0]
上気道の炎症	12 (2.9) / 518.5 [2.3]	11 (4.1) / 334.8 [3.3]	23 (4.9) / 849.3 [2.7]
浮動性めまい	12 (2.9) / 523.1 [2.3]	6 (2.2) / 337.1 [1.8]	18 (3.8) / 857.0 [2.1]
不眠症	11 (2.7) / 519.0 [2.1]	4 (1.5) / 340.1 [1.2]	15 (3.2) / 857.7 [1.7]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1

[redacted]

2.1.2.2　グレード3以上の有害事象

1.　二重盲検プラセボ対照期

Pool J-ISS-1に認められたグレード3以上の有害事象を表 17に示す。

グレード3以上の有害事象の発現割合はエレヌマブ70 mg群で2.6%（7/265例）であり、プラセボ群［2.2%（6/267例）］と比較して同程度で、エレヌマブの投与群間で用量依存的な傾向は認められなかった［28 mg群1.5%（1/66例）、140 mg群0.0%（0/137例）］。

エレヌマブを投与された被験者で計8例に認められたグレード3以上の有害事象は、エレヌマブ28 mg群で発現した手骨折、エレヌマブ70 mg群で発現した齲歯、椎間板突出、全身性エリテマトーデス、浮動性めまい、くも膜下出血、薬疹及び特発性蕁麻疹であり、いずれも各1例での発現であった。このうち、グレード4の有害事象は全身性エリテマトーデスのみであった。本事象は関節リウマチの既往がある4[redacted]歳の女性でDay 146に発現し、治験薬の投与は中止された。本事象は治験薬との関連ありと判断された。当該被験者における抗エレヌマブ結合抗体は陰性であった。これらのグレード3以上の有害事象のうち、重篤な有害事象と判定されたのは手骨折、椎間板突出、全身性エリテマトーデス及びくも膜下出血であり、治験薬の投与中止に至った又は治験薬との関連ありと判断された事象は全身性エリテマトーデスのみであった。

表 17　グレード3以上の有害事象（J-ISS-1：安全性解析対象集団）

System Organ Class Preferred Term	Placebo (N = 267) n (%)	AMG 334 28 mg QM (N = 66) n (%)	AMG 334 70 mg QM (N = 265) n (%)	AMG 334 140 mg QM (N = 137) n (%)	AMG 334 Overall (N = 468) n (%)
Number of subjects reporting grade ≥ 3 treatment-emergent adverse events	6 (2.2)	1 (1.5)	7 (2.6)	0 (0.0)	8 (1.7)
胃腸障害	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
齲歯	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
痔核	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
感染症および寄生虫症	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
虫垂炎	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
傷害、中毒および処置合併症	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
手骨折	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
筋骨格系および結合組織障害	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
椎間板突出	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
全身性エリテマトーデス	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
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 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
卵巣腺腫	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
腎細胞癌	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
神経系障害	2 (0.7)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
浮動性めまい	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
くも膜下出血	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
頭痛	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
片頭痛	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚および皮下組織障害	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
薬疹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
特発性蕁麻疹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1
Grading categories determined using CTCAE version 4.03

[redacted]

2.　全投与期

Pool J-ISS-2に認められたグレード3以上の有害事象を表 18に示す。

グレード3以上の有害事象の発現頻度はエレヌマブ70 mg投与期間で4.3例／100人年であり、Pool J-ISS-1のエレヌマブ70 mg群（5.8例／100人年、表 付録-3）と同程度であった。140 mg投与期間のグレード3以上の有害事象の発現頻度は2.7例／100人年であった。

エレヌマブを投与された被験者で計31例に認められたグレード3以上の有害事象のうち、2例以上に発現したグレード3以上の事象は咽頭炎（70 mg投与期間に2例）のみであった。その他の事象は各

1例の発現であり、グレード3以上の有害事象に一定の傾向は認められなかった。グレード4の有害事象は、二重盲検プラセボ対照期に1例に発現した全身性エリテマトーデスのみであった。

表 18　グレード3以上の有害事象（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (Subj-yr = 528.8)	140 mg QM (Subj-yr = 343.8)	Combined (Subj-yr = 872.7)
System Organ Class Preferred Term	(N = 414) n (%) / e [r]	(N = 269) n (%) / e [r]	(N = 470) n (%) / e [r]
All grade ≥ 3 treatment-emergent adverse events	22 (5.3) / 510.2 [4.3]	9 (3.3) / 335.3 [2.7]	31 (6.6) / 842.1 [3.7]
耳および迷路障害	1 (0.2) / 527.2 [0.2]	1 (0.4) / 343.4 [0.3]	2 (0.4) / 870.6 [0.2]
突発性難聴	1 (0.2) / 527.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.0 [0.1]
頭位性回転性めまい	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.4 [0.3]	1 (0.2) / 872.2 [0.1]
眼障害	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.8 [0.3]	1 (0.2) / 871.6 [0.1]
眼瞼下垂	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.8 [0.3]	1 (0.2) / 871.6 [0.1]
胃腸障害	4 (1.0) / 525.7 [0.8]	0 (0.0) / 343.8 [0.0]	4 (0.9) / 867.8 [0.5]
齲歯	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.6 [0.1]
出血性腸憩室	1 (0.2) / 527.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
腸炎	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
痔核	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.5 [0.1]
感染症および寄生虫症	3 (0.7) / 525.5 [0.6]	1 (0.4) / 342.5 [0.3]	4 (0.9) / 868.1 [0.5]
咽頭炎	2 (0.5) / 526.2 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 870.1 [0.2]
ウイルス性髄膜炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.5 [0.3]	1 (0.2) / 871.4 [0.1]
扁桃炎	1 (0.2) / 527.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
憩室炎	1 (0.2) / 528.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.0 [0.1]
傷害、中毒および処置合併症	5 (1.2) / 524.4 [1.0]	1 (0.4) / 342.5 [0.3]	6 (1.3) / 866.9 [0.7]
歯牙破折	1 (0.2) / 527.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]
手骨折	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.5 [0.3]	1 (0.2) / 871.3 [0.1]
鎖骨骨折	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
筋断裂	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
腱断裂	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
軟骨損傷	1 (0.2) / 528.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.1 [0.1]
術後イレウス	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
臨床検査	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.1 [0.3]	1 (0.2) / 872.0 [0.1]
血中尿酸増加	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.1 [0.3]	1 (0.2) / 872.0 [0.1]
代謝および栄養障害	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
脱水	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
筋骨格系および結合組織障害	2 (0.5) / 527.8 [0.4]	2 (0.7) / 341.3 [0.6]	4 (0.9) / 869.1 [0.5]
軟骨疾患	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.2 [0.3]	1 (0.2) / 871.1 [0.1]
骨壊死	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.9 [0.3]	1 (0.2) / 871.8 [0.1]
四肢拘縮	1 (0.2) / 528.1 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.9 [0.1]
全身性エリテマトーデス	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
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 (0.7) / 526.9 [0.6]	0 (0.0) / 343.8 [0.0]	3 (0.6) / 870.7 [0.3]
大腸腺腫	1 (0.2) / 527.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
乳癌	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
乳管内増殖性病変	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]

表 18　グレード3以上の有害事象（J-ISS-2：安全性解析対象集団）（続き）

	AMG 334		
System Organ Class Preferred Term	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
神経系障害	3 (0.7) / 527.5 [0.6]	2 (0.7) / 342.8 [0.6]	5 (1.1) / 868.6 [0.6]
浮動性めまい	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.6 [0.1]
脊髄症	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
頭蓋内動脈瘤	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.0 [0.3]	1 (0.2) / 871.8 [0.1]
頭痛	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.7 [0.3]	1 (0.2) / 872.5 [0.1]
片頭痛	1 (0.2) / 528.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.6 [0.1]
生殖系および乳房障害	1 (0.2) / 527.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]
子宮頚部上皮異形成	1 (0.2) / 527.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]
血管障害	1 (0.2) / 527.3 [0.2]	1 (0.4) / 343.6 [0.3]	2 (0.4) / 870.9 [0.2]
高血圧	1 (0.2) / 527.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]
起立性低血圧	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.6 [0.3]	1 (0.2) / 872.4 [0.1]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1
Grading categories determined using CTCAE version 4.03

[redacted]

2.1.2.3　発現時期別の有害事象

本解析では、J-ISS-2においてエレヌマブ70 mg又は140 mgの初回投与からの投与期間を1～3カ月、3超～6カ月、6超～12カ月、12超～18カ月、18超～24カ月、24カ月超と設定し、発現時期に基づいて有害事象を集計した。各集計期間で被験者が同一の有害事象を複数回発現した場合には、その集計期間で最初に発現した事象のみが集計された。また、被験者が同一の有害事象を異なる集計期間に新たに発現した場合には、これらの事象は各集計期間に含まれた。各期間のいずれかで1%以上かつ2例以上の被験者に発現した発現時期別の有害事象を表 19に示す。

すべての有害事象の発現割合は、初回投与後6超～12カ月及び12超～18カ月の期間に増加し、18カ月超以降に減少する傾向が認められた。個々の有害事象では、上咽頭炎及びインフルエンザの発現割合が初回投与後6超～12カ月及び12超～18カ月の期間に増加した。したがって、初回投与後6超～18カ月に有害事象の発現割合が増加した理由として、観察期間の違い（最初の1～6カ月は3カ月ごと、6カ月超からは6カ月ごと）に加え、季節性の事象の増加による可能性が考えられた。その他、発現割合が経時的に顕著に増加した又は新たに発現した事象は認められなかった。なお、便秘の発現割合は初回投与後1～3カ月の期間に最も高かったが（4.0%）、それ以降は低頻度であった（3超～6カ月：1.1%、6超～12カ月：0.7%、12超～8カ月：0.4%、18超～24カ月：0.9%、24カ月超：0.0%）。

表 19　発現時期別（各期間のいずれかで発現割合1%以上かつ2例以上）の有害事象（J-ISS-2：安全性解析対象集団）

	AMG 334 70/140mg QM					
Preferred Term	1 to 3 months (N = 470) n (%)	>3 to 6 months (N = 470) n (%)	>6 to 12 months (N = 459) n (%)	>12 to 18 months (N = 445) n (%)	>18 to 24 months (N = 434) n (%)	>24 months (N = 239) n (%)
Number of subjects reporting treatment-emergent adverse events with ≥ 1% subject incidence and reported by ≥ 2 subjects in any intervals	178 (37.9)	164 (34.9)	253 (55.1)	238 (53.5)	158 (36.4)	32 (13.4)
上咽頭炎	93 (19.8)	80 (17.0)	136 (29.6)	137 (30.8)	100 (23.0)	15 (6.3)
便秘	19 (4.0)	5 (1.1)	3 (0.7)	2 (0.4)	4 (0.9)	0 (0.0)
咽頭炎	12 (2.6)	3 (0.6)	14 (3.1)	8 (1.8)	5 (1.2)	0 (0.0)
上腹部痛	10 (2.1)	5 (1.1)	12 (2.6)	5 (1.1)	4 (0.9)	1 (0.4)
背部痛	9 (1.9)	6 (1.3)	13 (2.8)	8 (1.8)	5 (1.2)	2 (0.8)
インフルエンザ	8 (1.7)	7 (1.5)	21 (4.6)	26 (5.8)	15 (3.5)	4 (1.7)
胃腸炎	6 (1.3)	9 (1.9)	17 (3.7)	8 (1.8)	12 (2.8)	0 (0.0)
齲歯	6 (1.3)	8 (1.7)	9 (2.0)	10 (2.2)	4 (0.9)	0 (0.0)
胃炎	6 (1.3)	2 (0.4)	9 (2.0)	5 (1.1)	3 (0.7)	0 (0.0)
膀胱炎	6 (1.3)	2 (0.4)	6 (1.3)	9 (2.0)	6 (1.4)	1 (0.4)
悪心	5 (1.1)	2 (0.4)	4 (0.9)	2 (0.4)	1 (0.2)	0 (0.0)
口腔咽頭痛	4 (0.9)	2 (0.4)	5 (1.1)	9 (2.0)	0 (0.0)	1 (0.4)
アレルギー性鼻炎	4 (0.9)	2 (0.4)	2 (0.4)	6 (1.3)	4 (0.9)	0 (0.0)
湿疹	3 (0.6)	6 (1.3)	9 (2.0)	4 (0.9)	4 (0.9)	2 (0.8)
注射部位反応	3 (0.6)	4 (0.9)	6 (1.3)	2 (0.4)	0 (0.0)	0 (0.0)
気管支炎	3 (0.6)	3 (0.6)	7 (1.5)	8 (1.8)	4 (0.9)	1 (0.4)
上気道感染	3 (0.6)	2 (0.4)	5 (1.1)	4 (0.9)	1 (0.2)	0 (0.0)
注射部位紅斑	2 (0.4)	8 (1.7)	5 (1.1)	1 (0.2)	0 (0.0)	0 (0.0)
蕁麻疹	2 (0.4)	4 (0.9)	5 (1.1)	5 (1.1)	2 (0.5)	0 (0.0)
口内炎	2 (0.4)	2 (0.4)	7 (1.5)	7 (1.6)	4 (0.9)	0 (0.0)
季節性アレルギー	2 (0.4)	0 (0.0)	5 (1.1)	2 (0.4)	3 (0.7)	0 (0.0)
下痢	1 (0.2)	4 (0.9)	8 (1.7)	5 (1.1)	3 (0.7)	0 (0.0)
胃食道逆流性疾患	1 (0.2)	4 (0.9)	4 (0.9)	5 (1.1)	1 (0.2)	0 (0.0)
上気道の炎症	1 (0.2)	3 (0.6)	9 (2.0)	9 (2.0)	2 (0.5)	0 (0.0)

表 19　発現時期別（各期間のいずれかで発現割合1%以上かつ2例以上）の有害事象（J-ISS-2：安全性解析対象集団）（続き）

	AMG 334 70/140mg QM					
Preferred Term	1 to 3 months (N = 470) n (%)	>3 to 6 months (N = 470) n (%)	>6 to 12 months (N = 459) n (%)	>12 to 18 months (N = 445) n (%)	>18 to 24 months (N = 434) n (%)	>24 months (N = 239) n (%)
挫傷	1 (0.2)	3 (0.6)	6 (1.3)	5 (1.1)	4 (0.9)	0 (0.0)
浮動性めまい	1 (0.2)	3 (0.6)	3 (0.7)	8 (1.8)	3 (0.7)	1 (0.4)
副鼻腔炎	1 (0.2)	2 (0.4)	3 (0.7)	6 (1.3)	2 (0.5)	2 (0.8)
頚部痛	1 (0.2)	2 (0.4)	3 (0.7)	5 (1.1)	2 (0.5)	1 (0.4)
ざ瘡	1 (0.2)	1 (0.2)	6 (1.3)	0 (0.0)	3 (0.7)	0 (0.0)
関節痛	0 (0.0)	3 (0.6)	6 (1.3)	4 (0.9)	0 (0.0)	1 (0.4)
片頭痛	0 (0.0)	2 (0.4)	8 (1.7)	3 (0.7)	5 (1.2)	2 (0.8)
結膜炎	0 (0.0)	2 (0.4)	6 (1.3)	5 (1.1)	1 (0.2)	0 (0.0)
高血圧	0 (0.0)	1 (0.2)	3 (0.7)	3 (0.7)	5 (1.2)	0 (0.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1
Months 1 to 3 (≤ 91 days), months > 3 to 6 (> 91 days and ≤ 182 days), months > 6 to 12 (> 182 days and ≤ 365 days), months >12 to 18 (> 365 days and ≤ 547 days), months > 18 to 24 (> 547 days and ≤ 730 days) and > 24 months (> 730 days).

[redacted]

2.1.3　死亡

20120309試験及び20170609試験では死亡例は認められなかった。

海外試験では3例の死亡が報告された。死亡一覧を表 付録-9及び表 付録-10に示す。

1例目は20120178試験において二重盲検投与期にエレヌマブ7 mg、非盲検投与期にエレヌマブ70 mgを投与され、動脈硬化症及び高血圧性心疾患を発現し死亡に至った。エレヌマブの最終投与日はDay 641であり、本事象が発現したのはDay 650であった。2例目は20120296試験において二重盲検投与期にエレヌマブ70 mg、非盲検投与期にエレヌマブ140 mgを投与され、不整脈原性右室異形成症／心筋症（死後に診断）による心不全を発現し死亡に至った。エレヌマブの最終投与日はDay 253であり、本事象が発現したのはDay 275であった。3例目は20120178試験において二重盲検投与期にエレヌマブ7 mg、非盲検投与期にエレヌマブ140 mgを投与され、死因不明の立会者のいない死亡であった。エレヌマブの最終投与日はDay 1848であり、本事象が発現したのはDay 1943であった。

1例目及び2例目は両事象とも心原性であったが、両被験者ともリスク因子を有しており、様々な原因があったことが明らかになった。1例目は高血圧、重度の冠動脈硬化症の既往歴があり、死亡時、アルコール及び強心薬が検出された。2例目は、それまでは未確認であった心血管系の遺伝性疾患が認められ、心突然死のリスクが高かったことが判明した。3例目は剖検を実施しなかったため、死因を特定できなかったが、いずれの死亡も治験薬との関連なしと判断された。したがって、これら3例の死亡はエレヌマブ投与と関連のある安全性シグナルを示すものではないと判断された。

2.1.4　その他の重篤な有害事象

20120309試験及び20170609試験で認められた重篤な有害事象を発現した被験者一覧を表 付録-11及び表 付録-12に示す。また、海外試験である20120178試験、20120295試験、20130255試験、20120296試験及び20120297試験で認められた重篤な有害事象を発現した被験者一覧をそれぞれ表 付録-13、表 付録-14、表 付録-15、表 付録-16及び表 付録-17に示す。

20120309試験及び20170609試験で認められた重篤な有害事象の叙述をモジュール2.7.6　付録1に示す。

本項では国内併合解析の結果を示す。

1.　二重盲検プラセボ対照期

Pool J-ISS-1に認められた重篤な有害事象を表 20に示す。

重篤な有害事象の発現割合はエレヌマブ70 mg群で1.1%（3/265例）であり、プラセボ群［2.2%（6/267例）］と比較して同程度であり、その他のエレヌマブ群とも同程度であった［28 mg群1.5%（1/66例）、140 mg群0.7%（1/137例）］。

エレヌマブを投与された被験者で計5例に認められた重篤な有害事象は、エレヌマブ28 mg群で発現した手骨折、エレヌマブ70 mg群で発現したくも膜下出血、創傷、脳挫傷、鎖骨骨折及び頭蓋骨骨折（同一被験者に発現）、椎間板突出、全身性エリテマトーデス、エレヌマブ140 mg群で発現した胃腸炎及び腸結核（同一被験者に発現）のいずれも各1例であった。

このうち、重症度がグレード3以上の事象はくも膜下出血、椎間板突出及び全身性エリテマトーデス（グレード4）であり、治験薬の投与中止に至った又は治験薬と関連ありと判断された重篤な事象は全身性エリテマトーデスのみであった。

表 20　重篤な有害事象（J-ISS-1：安全性解析対象集団）

		AMG 334			
System Organ Class Preferred Term	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
Number of subjects reporting serious treatment-emergent adverse events	6 (2.2)	1 (1.5)	3 (1.1)	1 (0.7)	5 (1.1)
心臓障害	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
プリンツメタル狭心症	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
胃腸障害	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
痔核	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
感染症および寄生虫症	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
胃腸炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
腸結核	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
虫垂炎	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
傷害、中毒および処置合併症	0 (0.0)	1 (1.5)	1 (0.4)	0 (0.0)	2 (0.4)
脳挫傷	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
鎖骨骨折	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
頭蓋骨骨折	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
創傷	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
手骨折	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
筋骨格系および結合組織障害	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
椎間板突出	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
全身性エリテマトーデス	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
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 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
卵巣腺腫	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
腎細胞癌	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
神経系障害	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
くも膜下出血	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
片頭痛	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1

[redacted]

2. 全投与期

Pool J-ISS-2に認められた重篤な有害事象を表 21に示す。

重篤な有害事象の発現頻度はエレヌマブ70 mg投与期間で3.7例／100人年であり、Pool J-ISS-1のエレヌマブ70 mg群（2.5例/100人年、表 付録-3）と同程度であった。140 mg投与期間の重篤な有害事象の発現頻度は3.0例／100人年であった。

エレヌマブを投与された被験者で計29例に認められた重篤な有害事象は、いずれの事象も各1例のみの発現であり、一定の傾向は認められなかった。これらの重篤な有害事象の多くはグレード3以上であったが、治験薬の投与中止に至った事象は全身性エリテマトーデス、乳癌及び乳管内増殖性病変（いずれもエレヌマブ70 mg投与期間に発現）、治験薬との関連ありと判断された事象は全身性エリテマトーデス、出血性腸憩室（2.1.6.3.1項参照）及び乳癌（エレヌマブ70 mg投与期間に発現）、並びにマイコバクテリア感染（エレヌマブ140 mg投与期間に発現）であった。

表 21　重篤な有害事象（J-ISS-2：安全性解析対象集団）

	AMG 334		
System Organ Class Preferred Term	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All serious treatment-emergent adverse events	19 (4.6) / 512.8 [3.7]	10 (3.7) / 334.0 [3.0]	29 (6.2) / 846.8 [3.4]
耳および迷路障害	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.4 [0.3]	1 (0.2) / 872.2 [0.1]
頭位性回転性めまい	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.4 [0.3]	1 (0.2) / 872.2 [0.1]
眼障害	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.8 [0.3]	1 (0.2) / 871.6 [0.1]
眼瞼下垂	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.8 [0.3]	1 (0.2) / 871.6 [0.1]
胃腸障害	4 (1.0) / 525.2 [0.8]	0 (0.0) / 343.8 [0.0]	4 (0.9) / 869.0 [0.5]
出血性腸憩室	1 (0.2) / 527.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
腸炎	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
大腸ポリープ	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
痔核	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.5 [0.1]
感染症および寄生虫症	2 (0.5) / 526.9 [0.4]	3 (1.1) / 341.0 [0.9]	5 (1.1) / 867.9 [0.6]
ウイルス性髄膜炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.5 [0.3]	1 (0.2) / 871.4 [0.1]
咽頭炎	1 (0.2) / 527.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
扁桃炎	1 (0.2) / 527.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
マイコバクテリア感染	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.7 [0.3]	1 (0.2) / 871.5 [0.1]
憩室炎	1 (0.2) / 528.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.0 [0.1]
胃腸炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.3 [0.1]
腸結核	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.4 [0.1]
傷害、中毒および処置合併症	6 (1.4) / 523.9 [1.1]	1 (0.4) / 342.5 [0.3]	7 (1.5) / 866.4 [0.8]
歯牙破折	1 (0.2) / 527.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]
手骨折	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.5 [0.3]	1 (0.2) / 871.3 [0.1]
鎖骨骨折	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
筋断裂	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
腱断裂	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
軟骨損傷	1 (0.2) / 528.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.1 [0.1]
半月板損傷	1 (0.2) / 528.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.2 [0.1]
術後イレウス	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]

表 21　重篤な有害事象（J-ISS-2：安全性解析対象集団）（続き）

System Organ Class Preferred Term	AMG 334 70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	AMG 334 Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
代謝および栄養障害	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
脱水	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
筋骨格系および結合組織障害	2 (0.5) / 527.8 [0.4]	2 (0.7) / 341.3 [0.6]	4 (0.9) / 869.1 [0.5]
軟骨疾患	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.2 [0.3]	1 (0.2) / 871.1 [0.1]
骨壊死	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.9 [0.3]	1 (0.2) / 871.8 [0.1]
四肢拘縮	1 (0.2) / 528.1 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.9 [0.1]
全身性エリテマトーデス	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
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 (1.0) / 525.5 [0.8]	0 (0.0) / 343.8 [0.0]	4 (0.9) / 869.3 [0.5]
大腸腺腫	1 (0.2) / 527.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
子宮平滑筋腫	1 (0.2) / 527.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.3 [0.1]
乳癌	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
乳管内増殖性病変	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
神経系障害	1 (0.2) / 527.9 [0.2]	2 (0.7) / 342.8 [0.6]	3 (0.6) / 870.7 [0.3]
脊髄症	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
頭蓋内動脈瘤	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.0 [0.3]	1 (0.2) / 871.8 [0.1]
頭痛	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.7 [0.3]	1 (0.2) / 872.5 [0.1]
精神障害	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.1 [0.3]	1 (0.2) / 871.9 [0.1]
うつ病	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.1 [0.3]	1 (0.2) / 871.9 [0.1]
生殖系および乳房障害	1 (0.2) / 527.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]
子宮頚部上皮異形成	1 (0.2) / 527.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1

[redacted]

2.1.5　その他の重要な有害事象

本項では国内併合解析の結果を示す。

2.1.5.1　治験薬の投与中止に至った有害事象

20120309試験で認められた治験薬の投与中止に至った有害事象を発現した被験者一覧を表 付録-18に示す。20170609試験では治験薬の投与中止に至った有害事象は認められなかった。

1. 二重盲検プラセボ対照期

Pool J-ISS-1に認められた治験薬の投与中止に至った有害事象を表 22に示す。

治験薬の投与中止に至った有害事象の発現割合はエレヌマブ70 mg群で0.8%（2/265例）であり、プラセボ群［0.4%（1/267例）］と比較して同程度であった。その他のエレヌマブの投与群では治験薬の投与中止に至った有害事象は認められなかった。

エレヌマブを投与された被験者で計2例に認められた治験薬の投与中止に至った有害事象は、エレヌマブ70 mg群で発現した全身性エリテマトーデス（2.1.2.2項参照）及びそう痒性皮疹であった。そう痒性皮疹は4[redacted]歳の女性でDay 5に発現し、重症度はグレード2で非重篤であったが、治験薬との関連ありと判断された。当該被験者の抗エレヌマブ結合抗体は陰性であった。

表 22　治験薬の投与中止に至った有害事象（J-ISS-1：安全性解析対象集団）

		AMG 334			
System Organ Class Preferred Term	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
Number of subjects reporting treatment-emergent adverse events leading to withdrawal of investigational product	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
筋骨格系および結合組織障害	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
全身性エリテマトーデス	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
神経系障害	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
片頭痛	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚および皮下組織障害	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
そう痒性皮疹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1

[redacted]

2. 全投与期

Pool J-ISS-2に認められた治験薬の投与中止に至った有害事象を表 23に示す。

治験薬の投与中止に至った有害事象の発現頻度はエレヌマブ70 mg投与期間で1.1例／100人年であり、Pool J-ISS-1のエレヌマブ70 mg群（1.7例／100人年、表 付録-3）と同程度であった。140 mg投与期間の治験薬の投与中止に至った有害事象の発現頻度は0.6例／100人年であった。

エレヌマブを投与された被験者で計8例に認められた治験薬の投与中止に至った有害事象は、いずれの事象も各1例のみの発現であり、一定の傾向は認められなかった。このうち、重症度がグレード3以上の事象は全身性エリテマトーデス、乳癌、乳管内増殖性病変及び片頭痛（いずれもエレヌマブ70 mg投与期間に発現）であった。紅斑性皮疹は4[redacted]歳の女性でDay 279のエレヌマブ140 mg投与期間に発現した。重症度はグレード2であり、治験薬との関連ありと判断された。当該被験者の抗エレヌ

マブ結合抗体は陰性であった。その他、治験薬との関連ありと判断された治験薬の投与中止に至った事象は全身性エリテマトーデス、乳癌、甲状腺機能亢進症及びそう痒性皮疹であった。

表 23　治験薬の投与中止に至った有害事象（J-ISS-2：安全性解析対象集団）

	AMG 334		
System Organ Class Preferred Term	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent adverse events leading to withdrawal of investigational product	6 (1.4) / 527.4 [1.1]	2 (0.7) / 343.2 [0.6]	8 (1.7) / 870.6 [0.9]
内分泌障害	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
甲状腺機能亢進症	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
筋骨格系および結合組織障害	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
全身性エリテマトーデス	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
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 (0.5) / 528.3 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 872.1 [0.2]
乳癌	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
乳管内増殖性病変	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
神経系障害	1 (0.2) / 528.8 [0.2]	1 (0.4) / 343.5 [0.3]	2 (0.4) / 872.3 [0.2]
緊張性頭痛	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.3 [0.1]
片頭痛	1 (0.2) / 528.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.6 [0.1]
皮膚および皮下組織障害	1 (0.2) / 528.5 [0.2]	1 (0.4) / 343.5 [0.3]	2 (0.4) / 872.1 [0.2]
紅斑性皮疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.4 [0.1]
そう痒性皮疹	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1



2.1.5.2　機器関連の有害事象

1.　二重盲検プラセボ対照期

Pool J-ISS-1に認められた機器関連の有害事象を表 24に示す。

機器関連の有害事象はエレヌマブ70 mg群の1例（0.4%）に認められた円形脱毛症のみであった。本事象の重症度はグレード1で、非重篤であり、治験薬の投与中止に至らなかった。

表 24　機器関連の有害事象（J-ISS-1：安全性解析対象集団）

System Organ Class Preferred Term	Placebo (N = 267) n (%)	AMG 334 28 mg QM (N = 66) n (%)	AMG 334 70 mg QM (N = 265) n (%)	AMG 334 140 mg QM (N = 137) n (%)	AMG 334 Overall (N = 468) n (%)
Number of subjects reporting device-related treatment-emergent adverse events	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
皮膚および皮下組織障害	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
円形脱毛症	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1

[redacted]

2.　全投与期

Pool J-ISS-2に認められた機器関連の有害事象を表 25に示す。

機器関連の有害事象の発現頻度はエレヌマブ70 mg投与期間で0.6例／100人年、140 mg投与期間で2.4例／100人年であった。

エレヌマブを投与された被験者（計10例）に認められた機器関連の有害事象のうち、2例以上に発現した事象は注射部位反応（3例：エレヌマブ70 mg投与期間2例、140 mg投与期間2例）及び注射部位内出血（2例：いずれも140 mg投与期間）であった。報告された機器関連の有害事象はいずれもグレード2以下であり、重篤又は治験薬の投与中止に至った事象は認められなかった。

表 25　機器関連の有害事象（J-ISS-2：安全性解析対象集団）

System Organ Class Preferred Term	AMG 334 70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	AMG 334 Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All device-related treatment-emergent adverse events	3 (0.7) / 525.7 [0.6]	8 (3.0) / 333.2 [2.4]	10 (2.1) / 858.9 [1.2]
胃腸障害	1 (0.2) / 527.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.0 [0.1]
悪心	1 (0.2) / 527.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.0 [0.1]
一般・全身障害および投与部位の状態	2 (0.5) / 527.4 [0.4]	7 (2.6) / 334.5 [2.1]	8 (1.7) / 861.9 [0.9]
注射部位反応	2 (0.5) / 527.4 [0.4]	2 (0.7) / 341.3 [0.6]	3 (0.6) / 868.7 [0.3]
注射部位内出血	0 (0.0) / 528.8 [0.0]	2 (0.7) / 341.1 [0.6]	2 (0.4) / 869.9 [0.2]
注射部位出血	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.4 [0.3]	1 (0.2) / 871.2 [0.1]
注射部位紅斑	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.5 [0.3]	1 (0.2) / 871.3 [0.1]
異常感	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.6 [0.3]	1 (0.2) / 871.4 [0.1]
注射部位そう痒感	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.7 [0.3]	1 (0.2) / 871.5 [0.1]
注射部位疼痛	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.8 [0.3]	1 (0.2) / 871.6 [0.1]
注射部位腫脹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.1 [0.3]	1 (0.2) / 872.0 [0.1]
皮膚および皮下組織障害	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.5 [0.3]	1 (0.2) / 871.4 [0.1]
皮下出血	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.5 [0.3]	1 (0.2) / 871.4 [0.1]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1



2.1.6　器官別又は症候群別有害事象の解析

本項では1.1.1.1.1項に定めた注目すべき有害事象について、国内併合解析の結果を示す。

2.1.6.1　免疫系障害

他の高分子薬と同様に、エレヌマブを投与すると免疫介在性過敏症等の全身反応が起こる可能性が考えられる。また、海外では重篤な過敏症反応が市販後に報告されている（モジュール1.6　6項参照）。そのため、免疫系障害SOC及び皮膚および皮下組織障害SOC、並びに過敏症SMQ及びアナフィラキシー反応SMQによる検索式を用いて、過敏症及びアナフィラキシー反応に関連する事象を特定した。

また本項では、エレヌマブの免疫原性として、抗エレヌマブ抗体の発現状況とその発現が影響すると考えられる有害事象（主に過敏症及び注射部位反応等）との関連を評価した。

2.1.6.1.1 免疫系障害SOC

1. 二重盲検プラセボ対照期

Pool J-ISS-1において、免疫系障害SOCに該当する有害事象はエレヌマブ70 mg群の1例に認められた節足動物刺傷アレルギーのみであった（表 付録-4）。本事象はグレード2、非重篤で、治験薬との関連なしと判断された。

2. 全投与期

Pool J-ISS-2において、免疫系障害SOCに該当する有害事象の発現頻度はエレヌマブ70 mg投与期間で1.9例／100人年であり、Pool J-ISS-1のエレヌマブ70 mg群（0.8例／100人年、表 付録-5）と同程度であった。140 mg投与期間の本SOCに該当する有害事象の発現頻度は1.5例／100人年であった（表 付録-7）。

エレヌマブ70 mg投与期間に100人年あたり1例以上の発現頻度で認められた事象は、季節性アレルギー（エレヌマブ70 mg投与期間1.5例／100人年、140 mg投与期間0.9例／100人年）のみであった。本SOCに該当する有害事象はいずれも重症度がグレード2以下であり、重篤又は治験薬の投与中止に至った事象は認められなかった。

2.1.6.1.2 皮膚および皮下組織障害SOC

1. 二重盲検プラセボ対照期

Pool J-ISS-1において、皮膚および皮下組織障害SOCに該当する有害事象の発現割合はエレヌマブ70 mg群で8.3%（22/265例）であり、プラセボ群［4.1%（11/267例）］と比較して高く、その他のエレヌマブ群でもプラセボ群に比較して発現割合が高かった［28 mg群7.6%（5/66例）、140 mg群7.3%（10/137例）］（表 付録-4）。

エレヌマブ70 mg群で1%以上の被験者に認められた事象は湿疹（エレヌマブ70 mg群1.9%、プラセボ群0.7%、以下同順）及び蕁麻疹（1.1%、0.4%）であった。本SOCに該当する有害事象の重症度は、エレヌマブ70 mg群の合計2例に認められたグレード3の薬疹及び特発性蕁麻疹を除き、いずれもグレード2以下であった。薬疹及び特発性蕁麻疹は非重篤で、治験薬の投与中止には至らず、治験薬との関連なしと判断された。重篤な事象は認められず、治験薬の投与中止に至った事象はエレヌマブ70 mg群の1例に認められたそう痒性皮疹（2.1.5.1項参照）のみであった。

2. 全投与期

Pool J-ISS-2において、皮膚および皮下組織障害SOCに該当する有害事象の発現頻度はエレヌマブ70 mg投与期間で12.7例／100人年であり、Pool J-ISS-1のエレヌマブ70 mg群（18.8例／100人年、表 付録-5）に比較し低かった。140 mg投与期間の本SOCに該当する有害事象の発現頻度は13.9例／100人年であった（表 付録-7）。

エレヌマブ70 mg投与期間に100人年あたり1例以上の発現頻度で認められた事象は湿疹（エレヌマブ70 mg投与期間2.7例／100人年、140 mg投与期間3.3例／100人年、以下同順）、蕁麻疹（1.7例／100人年、1.8例／100人年）、及びざ瘡（1.3例／100人年、1.2例／100人年）であった。本SOCに該当する有害事象はいずれも重症度がグレード2以下であり、重篤な事象は報告されなかった。治験薬

の投与中止に至った事象は、70 mg投与期間及び140 mg投与期間に各1例に認められたそう痒性皮疹及び紅斑性皮疹であった（2.1.5.1項参照）。

2.1.6.1.3 過敏症SMQ

1. 二重盲検プラセボ対照期

Pool J-ISS-1に認められた過敏症SMQに該当する有害事象の概要を表 26に、本SMQに該当するPT別の有害事象を表 付録-19に示す。

本SMQに該当する有害事象の発現割合はエレヌマブ70 mg群で8.3%（22/265例）であり、プラセボ群［2.2%（6/267例）］と比較して高く、その他のエレヌマブ群でもプラセボ群に比較して発現割合が高かった［28 mg群7.6%（5/66例）、140 mg群7.3%（10/137例）］。

エレヌマブ70 mg群で1%以上の被験者に認められた事象は湿疹（エレヌマブ70 mg群1.9%、プラセボ群0.7%、以下同順）、及び蕁麻疹（1.1%、0.4%）であった。本SMQに該当する有害事象の重症度は、エレヌマブ70 mg群の合計2例に認められたグレード3の薬疹及び特発性蕁麻疹を除き、いずれもグレード2以下であった。重篤な事象は認められず、治験薬の投与中止に至った事象はエレヌマブ70 mg群の1例に認められたそう痒性皮疹（2.1.5.1項参照）のみであった。

表 26 過敏症SMQに該当する有害事象の概要（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
All treatment-emergent hypersensitivity event of interest	6 (2.2)	5 (7.6)	22 (8.3)	10 (7.3)	37 (7.9)
Grade ≥ 2	5 (1.9)	4 (6.1)	18 (6.8)	9 (6.6)	31 (6.6)
Grade ≥ 3	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
Grade ≥ 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Based on hypersensitivity standard MedDRA query (SMQ; narrow)

[redacted]

2. 全投与期

Pool J-ISS-2に認められた過敏症SMQに該当する有害事象を表 27に、本SMQに該当するPT別の有害事象を表 付録-20に示す。

本SMQに該当する有害事象の発現頻度はエレヌマブ70 mg投与期間で11.1例／100人年、140 mg投与期間で13.3例／100人年であった。

エレヌマブ70 mg投与期間に100人年あたり1例以上の発現頻度で認められた事象は湿疹（エレヌマブ70 mg投与期間2.7例／100人年、140 mg投与期間3.3例／100人年、以下同順）、アレルギー性鼻炎（2.5例／100人年、0.9例／100人年）、蕁麻疹（1.7例／100人年、1.8例／100人年）、及びアレルギー性結膜炎（1.1例／100人年、1.5例／100人年）であった。本SMQに該当する有害事象はいずれも重症度がグレード2以下であり、重篤な事象は報告されなかった。治験薬の投与中止に至った事象は70 mg投与期間及び140 mg投与期間に各1例に認められたそう痒性皮疹及び紅斑性皮疹であった（2.1.5.1項参照）。

表 27　過敏症SMQに該当する有害事象の概要（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent hypersensitivity event of interest	53 (12.8) / 475.8 [11.1]	41 (15.2) / 307.6 [13.3]	92 (19.6) / 772.5 [11.9]
Grade ≥ 2	42 (10.1) / 489.1 [8.6]	31 (11.5) / 314.6 [9.9]	71 (15.1) / 795.6 [8.9]
Grade ≥ 3	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Grade ≥ 4	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Serious adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Leading to discontinuation of investigational product	1 (0.2) / 528.5 [0.2]	1 (0.4) / 343.5 [0.3]	2 (0.4) / 872.1 [0.2]
Fatal adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Treatment-related treatment-emergent adverse events	4 (1.0) / 524.6 [0.8]	3 (1.1) / 341.9 [0.9]	7 (1.5) / 864.9 [0.8]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Grading categories determined using CTCAE version 4.03
Based on hypersensitivity standard MedDRA query (SMQ; narrow)



2.1.6.1.4　アナフィラキシー反応SMQ

1.　二重盲検プラセボ対照期

Pool J-ISS-1に認められたアナフィラキシー反応SMQに該当する有害事象の概要を表 28に、本SMQに該当するPT別の有害事象を表 付録-21に示す。

本SMQに該当する有害事象の発現割合はエレヌマブ70 mg群で4.2%（11/265例）であり、プラセボ群［4.5%（12/267例）］と同程度で、その他のエレヌマブ群とも同程度であった［28 mg群4.5%（3/66例）、140 mg群2.2%（3/137例）］。

エレヌマブ70 mg群で0.5%以上の被験者に認められた事象は蕁麻疹（エレヌマブ70 mg群1.1%、プラセボ群0.4%、以下同順）、咳嗽（0.8%、1.9%）、発疹（0.8%、0.0%）、丘疹状蕁麻疹（0.8%、0.0%）であった。本SMQに該当する有害事象の重症度はいずれもグレード2以下であり、重篤な事

象は報告されなかった。治験薬の投与中止に至った事象はエレヌマブ70 mg群の1例に認められたそう痒性皮疹（2.1.5.1項参照）のみであり、本事象は治験薬との関連ありと判断された。

表 28　アナフィラキシー反応SMQに該当する有害事象の概要
（J-ISS-1：安全性解析対象集団）

	Placebo (N = 267) n (%)	AMG 334 28 mg QM (N = 66) n (%)	AMG 334 70 mg QM (N = 265) n (%)	AMG 334 140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
All treatment-emergent anaphylactic reaction event of interest	12 (4.5)	3 (4.5)	11 (4.2)	3 (2.2)	17 (3.6)
Grade ≥ 2	11 (4.1)	2 (3.0)	9 (3.4)	2 (1.5)	13 (2.8)
Grade ≥ 3	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)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Based on anaphylactic reaction standard MedDRA query (SMQ; narrow and broad)

[redacted]

2.　全投与期

Pool J-ISS-2に認められたアナフィラキシー反応SMQに該当する有害事象の概要を表 29に、本SMQに該当するPT別の有害事象を表 付録-22に示す。

本SMQに該当する有害事象の発現頻度はエレヌマブ70 mg投与期間で8.3例／100人年、140 mg投与期間で5.8例／100人年であった。

エレヌマブ70 mg投与期間に100人年あたり1例以上の発現頻度で認められた事象は蕁麻疹（エレヌマブ70 mg投与期間1.7例／100人年、140 mg投与期間1.8例／100人年、以下同順）、咳嗽（1.7例／100人年、1.2例／100人年）、及び喘息（1.3例／100人年、0.9例／100人年）であった。本SMQに該当する有害事象はいずれも重症度がグレード2以下であり、重篤な事象は報告されなかった。治験薬の投与中止に至った事象は70 mg投与期間及び140 mg投与期間に各1例に認められたそう痒性皮疹及び紅斑性皮疹であった（2.1.5.1項参照）。

表 29　アナフィラキシー反応SMQに該当する有害事象の概要
（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent anaphylactic reaction event of interest	41 (9.9) / 493.2 [8.3]	19 (7.1) / 328.6 [5.8]	57 (12.1) / 814.4 [7.0]
Grade ≥ 2	26 (6.3) / 505.9 [5.1]	9 (3.3) / 334.7 [2.7]	34 (7.2) / 834.2 [4.1]
Grade ≥ 3	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Grade ≥ 4	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Serious adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Leading to discontinuation of investigational product	1 (0.2) / 528.5 [0.2]	1 (0.4) / 343.5 [0.3]	2 (0.4) / 872.1 [0.2]
Fatal adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Treatment-related treatment-emergent adverse events	4 (1.0) / 524.6 [0.8]	1 (0.4) / 343.5 [0.3]	5 (1.1) / 868.1 [0.6]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Grading categories determined using CTCAE version 4.03
Based on anaphylactic reaction standard MedDRA query (SMQ; narrow and broad)

[redacted]

2.1.6.1.5　免疫原性

本項は20120309試験及び20170609試験の各試験のデータセットに基づく結果を示す。

20120309試験

本試験では、エレヌマブ投与後、被験者の3.2%（15/471例）で抗エレヌマブ結合抗体が陽性であった。ベースライン時に結合抗体が陽性の被験者は認められなかった。この15例のうち11例では、最終評価時点の結合抗体の結果は陰性であった。いずれの被験者でも中和抗体は認められなかった。（モジュール2.7.2　4.2.1項参照）。

結合抗体検査で陽性が認められた15例のうち、5例が過敏症関連の有害事象（アレルギー性結膜炎2例、蕁麻疹1例、季節性アレルギー1例、アレルギー性そう痒症1例、動物アレルギー1例）、2例が注射部位反応関連の有害事象（注射部位紅斑、注射部位そう痒感、注射部位腫脹、注射部位疼痛、各1例）を発現した。これらの重症度はすべてグレード2以下であり、治験薬との関連ありと判断された事象は、同一被験者に発現した注射部位紅斑及び注射部位そう痒感のみであった。重篤又は治験薬の投与中止に至った有害事象は認められなかった（モジュール5.3.5.1-1.2　Listing 16-2.7）。

20170609試験

本試験では、エレヌマブ投与後、被験者の5.4%（7/129例）で抗エレヌマブ結合抗体が陽性であった。また1例（0.8%）はベースライン時の結合抗体の結果が陽性であった（モジュール

2.7.2　4.2.1項参照）。この8例のうち3例では、二重盲検投与期の最終評価（24週）時点の結合抗体の結果は陰性であった。いずれの被験者でも中和抗体は認められなかった（モジュール5.3.5.1-2　Listing 16-2.8.1）。

結合抗体検査で陽性が認められた8例のうち、過敏症関連の有害事象を発現した被験者は認められず、注射部位反応関連の有害事象では1例が注射部位紅斑を発現した。本事象は治験薬との因果関係ありと判断されたが、重症度はグレード1で、非重篤であり、治験薬の投与中止に至らなかった（モジュール5.3.5.1-2　Listing 16-2.7.2）。

以上より、抗エレヌマブ結合抗体が陽性であった被験者で、エレヌマブが免疫反応を誘発する可能性を示唆する所見は認められなかった。

2.1.6.2　一般・全身障害および投与部位の状態

他の生物学的製剤の皮下投与と同様に、エレヌマブを投与すると発赤、圧痛／疼痛、挫傷、熱感、腫脹、そう痒症、感染等の注射部位反応が引き起こされる可能性がある。そのため、一般・全身障害および投与部位の状態SOC、並びに注射部位反応AMQによる検索式を用いて、注射部位反応に関連する事象を特定した。

2.1.6.2.1　一般・全身障害および投与部位の状態SOC

1.　二重盲検プラセボ対照期

Pool J-ISS-1において、一般・全身障害および投与部位の状態SOCに該当する有害事象の発現割合はエレヌマブ70 mg群で7.5%（20/265例）であり、プラセボ群［3.7%（10/267例）］と比較して高く、その他のエレヌマブ群でもプラセボ群に比較して発現割合が高かった［28 mg群6.1%（4/66例）、140 mg群6.6%（9/137例）］（表 付録-4）。

エレヌマブ70 mg群で0.5%以上の被験者に認められた事象は注射部位紅斑（エレヌマブ70 mg群0.8%、プラセボ群0.0%、以下同順）、注射部位腫脹（0.8%、0.4%）、注射部位出血（0.8%、0.4%）、注射部位反応（0.8%、0.0%）、悪寒（0.8%、0.0%）、及び異常感（0.8%、0.0%）であり、注射部位に関連する事象が多かった。本SOCに該当する有害事象は、いずれもグレード2以下であり、重篤又は治験薬の投与中止に至った事象は認められなかった。

2.　全投与期

Pool J-ISS-2において、一般・全身障害および投与部位の状態SOCに該当する有害事象の発現頻度はエレヌマブ70 mg投与期間で7.5例／100人年であり、Pool J-ISS-1のエレヌマブ70 mg群（17.2例／100人年、表 付録-5）に比較し低かった。140 mg投与期間の本SOCに該当する有害事象の発現頻度は8.7例／100人年であった（表 付録-7）。

エレヌマブ70 mg投与期間に100人年あたり0.5例以上の発現頻度で認められた事象は注射部位紅斑（エレヌマブ70 mg投与期間0.8例／100人年、140 mg投与期間2.4例／100人年、以下同順）、注射部位反応（0.8例／100人年、1.2例／100人年）、発熱（0.8例／100人年、0.3例／100人年）、注射部位

出血（0.6例／100人年、0.9例／100人年）、及び末梢性浮腫（0.6例／100人年、0.0例／100人年）であり、二重盲検プラセボ対照期と同様、注射部位に関連する事象が多かった。本SOCに該当する有害事象はいずれもグレード2以下であり、重篤又は治験薬の投与中止に至った事象は認められなかった。

2.1.6.2.2 注射部位反応AMQ

1. 二重盲検プラセボ対照期

Pool J-ISS-1に認められた注射部位反応AMQに該当する有害事象の概要を表 30に、本AMQに該当するPT別の有害事象を表 付録-23に示す。

本AMQに該当する有害事象の発現割合はエレヌマブ70 mg群で4.2%（11/265例）であり、プラセボ群［1.5%（4/267例）］と比較して高く、その他のエレヌマブ群でもプラセボ群に比較して発現割合が高かった［28 mg群4.5%（3/66例）、140 mg群4.4%（6/137例）］。

エレヌマブ70 mg群で0.5%以上の被験者に認められた事象は注射部位紅斑（エレヌマブ70 mg群0.8%、プラセボ群0.0%、以下同順）、注射部位腫脹（0.8%、0.4%）、注射部位出血（0.8%、0.4%）、及び注射部位反応（0.8%、0.0%）であった。本AMQに該当する有害事象は、いずれもグレード2以下であり、重篤又は治験薬の投与中止に至った事象は認められなかった。

表 30 注射部位反応AMQに該当する有害事象の概要
（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
All treatment-emergent injection site reaction event of interest	4 (1.5)	3 (4.5)	11 (4.2)	6 (4.4)	20 (4.3)
Grade ≥ 2	1 (0.4)	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	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	2 (0.7)	1 (1.5)	6 (2.3)	4 (2.9)	11 (2.4)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Based on injection site reaction Amgen MedDRA query (AMQ; narrow)

[redacted]

2. 全投与期

Pool J-ISS-2に認められた注射部位反応AMQに該当する有害事象の概要を表 31に、本AMQに該当するPT別の有害事象を表 付録-24に示す。

本AMQに該当する有害事象の発現頻度はエレヌマブ70 mg投与期間で3.5例／100人年、140 mg投与期間で6.3例／100人年であった。

エレヌマブ70 mg投与期間に100人年あたり0.5例以上の発現頻度で認められた事象は注射部位紅斑（エレヌマブ70 mg投与期間0.8例／100人年、140 mg投与期間2.4例／100人年、以下同順）、注射部位反応（0.8例／100人年、1.2例／100人年）、及び注射部位出血（0.6例／100人年、0.9例／100人年）であった。本SOCに該当する有害事象はいずれもグレード2以下であり、重篤又は治験薬の投与中止に至った事象は認められなかった。

表 31　注射部位反応AMQに該当する有害事象の概要
（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent injection site reaction event of interest	18 (4.3) / 511.2 [3.5]	20 (7.4) / 317.6 [6.3]	36 (7.7) / 817.5 [4.4]
Grade ≥ 2	2 (0.5) / 527.5 [0.4]	2 (0.7) / 341.1 [0.6]	3 (0.6) / 868.7 [0.3]
Grade ≥ 3	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Grade ≥ 4	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Serious adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Leading to discontinuation of investigational product	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Fatal adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Treatment-related treatment-emergent adverse events	10 (2.4) / 516.8 [1.9]	13 (4.8) / 327.1 [4.0]	21 (4.5) / 840.5 [2.5]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Grading categories determined using CTCAE version 4.03
Based on injection site reaction Amgen MedDRA query (AMQ; narrow)

[redacted]

2.1.6.3　胃腸障害

非臨床のデータではCGRPは哺乳類において胃保護作用を有し、CGRPの阻害は胃腸の炎症あるいは潰瘍のリスクを増加させる可能性があると考えられている（Evangelista, 2009、Tache et al, 1984、Saeki et al, 2000）。また、CGRPは胃腸内の内臓の痛覚、血流、炎症、運動及び結腸への分泌における役割が知られており（Bhargava et al, 2013、Yoshikawa et al, 2011、Keates et al, 1998）、CGRPの阻害は一部の患者に便秘を引き起こす可能性がある。海外では重篤な合併症を伴う便秘が市販後に報告されている（モジュール1.6　6項参照）。そのため、胃腸障害SOC及び便秘AMQよる検索式を用いて、胃腸障害及び便秘関連事象を特定した。

2.1.6.3.1 胃腸障害SOC

1. 二重盲検プラセボ対照期

Pool J-ISS-1において、胃腸障害SOCに該当する有害事象の発現割合はエレヌマブ70 mg群で22.3%（59/265例）であり、プラセボ群［12.4%（33/267例）］と比較して高かった。その他のエレヌマブ群では発現割合はプラセボ群と同程度であった［28 mg群13.6%（9/66例）、140 mg群14.6%（20/137例）］（表 付録-4）。

エレヌマブ70 mg群で2%以上の被験者に認められた事象は便秘（エレヌマブ70 mg群4.9%、プラセボ群1.5%、以下同順）、齲歯（4.2%、1.9%）、上腹部痛（2.6%、0.7%）、及び口内炎（2.3%、1.1%）であった。これらの事象の発現割合はいずれもエレヌマブ70 mg群でプラセボ群に比較して高く、便秘においては140 mg群でもプラセボ群に比較して高かった（5.1%）。便秘を除き、エレヌマブの投与群間で発現割合に明らかな違いが認められた事象はなかった。本SOCに該当する有害事象のうち、重症度がグレード3以上の事象はエレヌマブ70 mg群の1例に認められた齲歯のみであり、本事象は治験薬との関連なしと判断された。重篤又は治験薬の投与中止に至った事象は認められなかった。

2. 全投与期

Pool J-ISS-2おいて、胃腸障害SOCに該当する有害事象の発現頻度はエレヌマブ70 mg投与期間で33.7例／100人年であり、Pool J-ISS-1のエレヌマブ70 mg群（55.7例／100人年、表 付録-5）に比較して低かった。140 mg投与期間の本SOCに該当する有害事象の発現頻度は26.5例／100人年であった（表 付録-7）。

エレヌマブ70 mg投与期間に100人年あたり2例以上の発現頻度で認められた事象は齲歯（エレヌマブ70 mg投与期間4.7例／100人年、140 mg投与期間3.3例／100人年、以下同順）、便秘（4.2例／100人年、3.6例／100人年）、上腹部痛（4.7例／100人年、1.8例／100人年）、胃炎（2.5例／100人年、3.0例／100人年）、下痢（2.3例／100人年、1.5例／100人年）、及び口内炎（2.3例／100人年、1.2例／100人年）であった。本SOCに該当する有害事象は、大部分の重症度がグレード2以下であった。グレード3以上の事象は齲歯、出血性腸憩室、腸炎及び痔核（各1例、いずれも70 mg投与期間で発現）であり、齲歯を除き重篤と判定された。また、その他、重篤な有害事象として大腸ポリープ（グレード2）が認められた。これらのグレード3以上又は重篤な事象のうち、治験薬と関連ありと判断されたのは出血性腸憩室のみであった。出血性腸憩室は4[redacted]歳男性でDay 257に発現し、治験薬の投与を中止することなく6日後に回復した。本SOCに該当する有害事象のうち、治験薬の投与中止に至った事象は認められなかった。

2.1.6.3.2 便秘AMQ

1. 二重盲検プラセボ対照期

Pool J-ISS-1に認められた便秘AMQに該当する有害事象の概要を表 32に、本AMQに該当するPT別の有害事象を表 付録-25に示す。また、曝露期間で調整した発現頻度を算出した本AMQに該当する有害事象の概要及びPT別の有害事象を表 付録-26及び表 付録-27に示す。

本AMQに該当する有害事象（便秘関連事象）の発現割合はエレヌマブ70 mg群で5.3%（14/265例）であり、プラセボ群［1.5%（4/267例）］と比較して高かった。エレヌマブの投与群間では28 mg群［0.0%（0/66例）］に比較して70 mg群及び140 mg群［5.8%（8/137例）］で発現割合が高かった。

エレヌマブ70 mg群で認められた便秘関連事象は、便秘（エレヌマブ70 mg群4.9%、140 mg群5.1%、プラセボ群1.5%、以下同順）及び腹部膨満（0.4%、0.7%、0%）であった。便秘関連事象はいずれもグレード2以下であり、重篤又は治験薬の投与中止に至った事象は認められなかった。

表 32　便秘AMQに該当する有害事象の概要（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
All treatment-emergent constipation event of interest	4 (1.5)	0 (0.0)	14 (5.3)	8 (5.8)	22 (4.7)
Grade ≥ 2	2 (0.7)	0 (0.0)	3 (1.1)	2 (1.5)	5 (1.1)
Grade ≥ 3	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)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	1 (0.4)	0 (0.0)	4 (1.5)	5 (3.6)	9 (1.9)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Based on constipation Amgen MedDRA query (AMQ; narrow and broad)

[redacted]

2.　全投与期

Pool J-ISS-2に認められた便秘AMQに該当する有害事象の概要を表 33に、便秘AMQに該当するPT別の有害事象を表 付録-28に示す。

便秘関連事象の発現頻度はエレヌマブ70 mg投与期間で5.0例／100人年であり、Pool J-ISS-1のエレヌマブ70 mg群（12.0例/100人年、表 付録-26）と比較して低かった。140 mg投与期間の便秘関連事象の発現頻度は3.9例／100人年であった。

エレヌマブ70 mg投与期間に認められた便秘関連事象は、便秘（70 mg投与期間4.2例／100人年、140 mg投与期間3.6例／100人年、以下同順）、腹部膨満（0.4例／100人年、0.3例／100人年）、鼓腸（0.2例／100人年、0.0例／100人年）、及び術後イレウス（0.2例／100人年、0.0例／100人年）であった。

術後イレウス以外の便秘関連事象の重症度はグレード2以下で、非重篤であった。術後イレウスは医師より術後癒着性イレウスと報告され、重症度がグレード3、及び重篤と判定されたが、治験薬との関連なしと判断され、治験薬の投与中止には至らなかった。治験薬の投与中止に至った便秘関連事象はなかった。

表 33　便秘AMQに該当する有害事象の概要（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent constipation event of interest	25 (6.0) / 499.8 [5.0]	13 (4.8) / 332.7 [3.9]	37 (7.9) / 817.6 [4.5]
Grade ≥ 2	10 (2.4) / 515.3 [1.9]	6 (2.2) / 339.7 [1.8]	16 (3.4) / 854.1 [1.9]
Grade ≥ 3	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
Grade ≥ 4	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Serious adverse events	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
Leading to discontinuation of investigational product	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Fatal adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Treatment-related treatment-emergent adverse events	7 (1.7) / 523.2 [1.3]	5 (1.9) / 341.0 [1.5]	11 (2.3) / 852.5 [1.3]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Grading categories determined using CTCAE version 4.03
Based on constipation Amgen MedDRA query (AMQ; narrow and broad)

[redacted]

2.1.6.4　心臓、脳血管及び血管障害

CGRPは血管拡張作用があり、痛覚伝達の修飾物質としての役割もある。CGRP受容体の阻害は、特に冠動脈疾患による虚血状態である場合に、代償性血管拡張の阻害により理論的には心血管系にリスクをもたらす可能性がある。エレヌマブが心血管及びその他の血管に及ぼす潜在的な影響について検討するため、心臓障害SOC、並びに虚血性中枢神経系血管障害SMQ、虚血性心疾患SMQ、末梢動脈疾患AMQ及び高血圧SMQよる検索式を用いて、心臓、脳血管及び血管障害に関連する事象を特定した。

2.1.6.4.1　心臓障害SOC

1.　二重盲検プラセボ対照期

Pool J-ISS-1において、心臓障害SOCに該当する有害事象はエレヌマブ70 mg群及びプラセボ群ではいずれも1例（各0.4%）のみに認められ、その内訳は動悸及びプリンツメタル狭心症であった（表 付録-4）。その他のエレヌマブ群では、本SOCに該当する有害事象は140 mg群の4例（2.9%）に認められ、その内訳は動悸2例、心房細動1例、心室性期外収縮1例であった。

エレヌマブを投与された被験者で計5例に認められた本SOCに該当する有害事象は、いずれもグレード1であり、重篤又は治験薬の投与中止に至った事象はなく、エレヌマブ140 mg群の1例で発現した動悸（2件）のみを除き、治験薬との関連なしと判断された。

2. 全投与期

Pool J-ISS-2において、心臓障害SOCに該当する有害事象の発現頻度はエレヌマブ70 mg投与期間で0.8例／100人年であり、Pool J-ISS-1のエレヌマブ70 mg群（0.8例／100人年、表 付録-5）と同程度であった。140 mg投与期間の本SOCに該当する有害事象の発現頻度は3.0例／100人年であった（表 付録-7）。

エレヌマブを投与された被験者で計14例に認められた本SOCに該当する有害事象のうち、2例以上に発現した事象は動悸（6例：70 mg投与期間2例、140 mg投与期間4例）、狭心症（2例：70 mg投与期間1例、140 mg投与期間1例）であった。いずれの本SOCに該当する事象も重症度はグレード2以下であり、重篤又は治験薬の投与中止に至った事象は認められず、二重盲検プラセボ対照期に発現した動悸2件（140 mg投与期間）のみを除き、治験薬との関連なしと判断された。

2.1.6.4.2 虚血性中枢神経系血管障害SMQ

全投与期間を通して、虚血性中枢神経系血管障害SMQに該当する有害事象は認められなかった（表 付録-29及び表 付録-30）。

2.1.6.4.3 虚血性心疾患SMQ

1. 二重盲検プラセボ対照期

Pool J-ISS-1において、虚血性心疾患SMQに該当する有害事象を発現した被験者はプラセボ群の2例（0.7%）のみであった（プリンツメタル狭心症及び心電図T波逆転）（表 付録-31及び表 付録-32）。エレヌマブ群で本SMQに該当する有害事象を発現した被験者は認められなかった。

2. 全投与期

Pool J-ISS-2において、虚血性心疾患SMQに該当する有害事象の発現頻度はエレヌマブ70 mg投与期間で0.4例/100人年、140 mg投与期間で0.3例/100人年であった（表 付録-33）。

エレヌマブを投与された被験者で計3例に認められた本SMQに該当する有害事象は、狭心症（2例：エレヌマブ70 mg投与期間及び140 mg投与期間で各1例）及び血中クレアチニンホスホキナーゼ増加（1例：エレヌマブ70 mg投与期間）であった（表 付録-34）。いずれの事象も重症度はグレード2以下であり、非重篤で治験薬の投与中止に至らなかった。また、いずれの事象も治験薬との関連なしと判断された。

2.1.6.4.4 末梢動脈疾患AMQ

1. 二重盲検プラセボ対照期

Pool J-ISS-1において、末梢動脈疾患AMQに該当する有害事象は認められなかった（表 付録-35）。

2. 全投与期

Pool J-ISS-2において、末梢動脈疾患SMQに該当する有害事象を発現した被験者はエレヌマブ70 mg投与期間の2例（0.4例／100人年）のみであった（表 付録-36）。発現した事象は末梢血管障害及びレイノー現象であり、いずれの事象も重症度はグレード2以下、非重篤で治験薬の投与中止に至らなかった。また、両事象とも治験薬との関連なしと判断された（表 付録-37）。

2.1.6.4.5 高血圧SMQ

1. 二重盲検プラセボ対照期

Pool J-ISS-1に認められた高血圧SMQに該当する有害事象の概要を表 34に、本SMQに該当するPT別の有害事象を表 付録-38に示す。

本SMQに該当する有害事象はエレヌマブ70 mg群及びプラセボ群では各1例（0.4%）のみに認められ、いずれの事象も高血圧であった。その他のエレヌマブ群では本SMQに該当する有害事象は認められなかった。

エレヌマブ70 mgで発現した高血圧の重症度はグレード2であり、非重篤で治験薬の投与中止に至らず、治験薬との関連なしと判断された。

表 34 高血圧SMQに該当する有害事象の概要
（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
All treatment-emergent hypertension event of interest	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Grade ≥ 2	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Grade ≥ 3	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)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Based on hypertension standardized MedDRA query (SMQ; narrow and broad)

[redacted]

2. 全投与期

Pool J-ISS-2に認められた高血圧SMQに該当する有害事象の概要を表 35に、高血圧SMQに該当するPT別の有害事象を表 付録-39に示す。

本SMQに該当する有害事象の発現頻度はエレヌマブ70 mg投与期間で1.5例／100人年であり、Pool J-ISS-1のエレヌマブ70 mg群（0.8例／100人年、表 付録-5）と同程度であった。140 mg投与期間の本SMQに該当する有害事象の発現頻度は0.9例／100人年であった。

本SMQに該当する有害事象はすべて高血圧であり、エレヌマブ70 mg投与期間に認められた1例（グレード3）を除いて、すべてグレード2以下、非重篤で、治験薬の投与中止に至った事象は認められなかった。グレード3の高血圧は4[redacted]歳女性でDay 223に発現し、非重篤で治験薬の投与中止には至らず、治験薬との関連はありと判断された。

表 35 高血圧SMQに該当する有害事象の概要（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent hypertension event of interest	8 (1.9) / 523.4 [1.5]	3 (1.1) / 342.3 [0.9]	11 (2.3) / 863.9 [1.3]
Grade ≥ 2	7 (1.7) / 523.4 [1.3]	3 (1.1) / 342.3 [0.9]	10 (2.1) / 864.0 [1.2]
Grade ≥ 3	1 (0.2) / 527.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]
Grade ≥ 4	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Serious adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Leading to discontinuation of investigational product	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Fatal adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Treatment-related treatment-emergent adverse events	3 (0.7) / 526.3 [0.6]	0 (0.0) / 343.8 [0.0]	3 (0.6) / 870.1 [0.3]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Grading categories determined using CTCAE version 4.03
Based on hypertension standardized MedDRA query (SMQ; narrow and broad)

[redacted]

2.1.6.5 その他

エレヌマブの安全性プロファイルを検討する上で重要と考えられる下記のSOCについて、二重盲検プラセボ対照期及び全投与期に発現した有害事象を評価した（表 付録-4及び表 付録-7）。

- 精神障害
- 肝胆道系障害
- 神経系障害
- 良性、悪性および詳細不明の新生物

- 筋骨格系および結合組織障害

プラセボ群に比較して発現割合に明らかな違いが認められたSOCはなく、長期投与で発現頻度が顕著に増加した又は新たな事象が発現したSOCは認められず（表 付録-5）、臨床的に重要な安全性所見は確認されなかった。

2.2 個別有害事象の文章による説明

20120309試験及び20170609試験で認められた重篤な有害事象の叙述はモジュール2.7.6　付録1に示す。

3. 臨床検査値の評価

本項では1.1.1.3項に定めた臨床検査値項目について、国内併合解析の結果を示す。

3.1 血液学

Pool J-ISS-1における好中球絶対数、赤血球数、ヘモグロビン量、平均赤血球容積、平均赤血球ヘモグロビン量、平均赤血球ヘモグロビン濃度、ヘマトクリット値、血小板数及び白血球数の要約統計量のベースラインからの推移をモジュール5.3.5.3-1.2　Table 14-7.101.1～9に示す。

これらの項目について、二重盲検プラセボ対照期のいずれの時点においてもエレヌマブ70 mg群とプラセボ群で明らかな違いは認められず、臨床的に問題となる変化はなかった。また、エレヌマブの投与群間でも明らかな違いは認められなかった。

3.2 肝機能

Pool J-ISS-1及びPool J-ISS-2におけるALT、AST、総ビリルビン及びALPの、CTCAEグレードのベースラインに対するシフトテーブルをモジュール5.3.5.3-1.2　Table 14-7.102.1～4及びTable 14-7.202.1～4に示す。

これらの肝機能項目において、ベースラインはすべての被験者でグレード0又は1であった。二重盲検プラセボ対照期及び全投与期では、ほとんどの被験者でグレードの変化は認められなかった。

Pool J-ISS-1において、肝機能値がベースラインから3グレード以上悪化した被験者はエレヌマブ140 mg群の1例のみであり、ALT及びASTがそれぞれベースラインのグレード0から3へ悪化した。本被験者は4[redacted]歳の女性で、Day 83（Week 12）に原発性胆汁性胆管炎（非重篤及びグレード2）を発現し、ALT及びASTが高値（グレード3）となり、エレヌマブの投与を中断した。Week 36にはALT及びASTはグレード0に回復し、Week 40には投与を再開し、その後肝機能値に異常は認められなかった。本事象は治験薬との関連なしと判断され、これらの肝機能値上昇は有害事象としては報告されなかった。肝機能値がベースラインから2グレード悪化した被験者は、ALTでエレヌマブ70 mg群の2例（0.8%）、ASTで70 mg群の1例（0.4%）、総ビリルビンで28 mg群の1例（1.5%）及び140 mg群の1例（0.7%）であった。プラセボ群では肝機能値がベースラインから2グレード以上悪化した被験者は認められなかった。

Pool J-ISS-2において、肝機能値がベースラインから3グレード以上悪化した被験者は、上記の二重盲検プラセボ対照期にALT及びASTが3グレード悪化した1例のみであった。肝機能値がベースラインから2グレード悪化した被験者はALTで4例（0.9%）、ASTで3例（0.6%）、総ビリルビンで1例（0.6%）であった。

また、薬物性肝障害の可能性はHy's lawの基準（1.1.1.3項参照）に該当する被験者を特定することにより評価した。二重盲検プラセボ対照期及び全投与期で本基準に該当する被験者は認められなかった（表 付録-40及び表 付録-41）。

3.3 腎機能

Pool J-ISS-1におけるクレアチニン、BUN、総蛋白及びアルブミンの要約統計量のベースラインからの推移をモジュール5.3.5.3-1.2　Table 14-7.101.10～13に示す。

これらの項目について、二重盲検プラセボ対照期のいずれの時点においてもエレヌマブ70 mg群とプラセボ群で明らかな違いは認められず、臨床的に問題となる変化は認められなかった。また、エレヌマブの投与群間でも明らかな違いは認められなかった。

3.4 代謝及び筋

Pool J-ISS-1における糖、ナトリウム、カリウム、クロール、重炭酸及びカルシウムの要約統計量のベースラインからの推移をモジュール5.3.5.3-1.2　Table 14-7.101.14～19に示す。

これらの項目について、二重盲検プラセボ対照期のいずれの時点においてもエレヌマブ70 mg群とプラセボ群で明らかな違いは認められず、臨床的に問題となる変化は認められなかった。また、エレヌマブの投与群間でも明らかな違いは認められなかった。

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

本項では、バイタルサインは国内併合解析、心電図及びC-SSRSは20120309試験及び20170609試験の各試験のデータセットに基づく結果を示す。

4.1 バイタルサイン

Pool J-ISS-1における収縮期／拡張期血圧及び心拍数の要約統計量のベースラインからの推移をモジュール5.3.5.3-1.2　Table 14-8.101.1～3に示す。これらのバイタルサインについて、二重盲検プラセボ対照期のいずれの時点においてもエレヌマブ70 mg群とプラセボ群で明らかな違いは認められず、臨床的に問題となる変化は認められなかった。また、エレヌマブの投与群間でも明らかな違いは認められなかった。

Pool J-ISS-1における24週時のベースラインからのカテゴリー別（1.1.1.4項参照）の血圧及び心拍数の変化を表 36及び表 37に、来院ごとのベースラインからのカテゴリー別の血圧及び心拍数の変化をモジュール5.3.5.3-1.2　Table 14-8.102.1及びTable 14-8.103.1に示す。24週時の血圧及び心拍数のいずれのカテゴリーでも、該当する被験者の割合はエレヌマブ70 mg群とプラセボ群で同程度であった。

表 36　24週時のベースラインからのカテゴリー別の血圧の変化（J-ISS-1：安全性解析対象集団）

		AMG 334			
Visit	Placebo (N = 267) n / N1 (%)	28 mg QM (N = 66) n / N1 (%)	70 mg QM (N = 265) n / N1 (%)	140 mg QM (N = 137) n / N1 (%)	Overall (N = 468) n / N1 (%)
Week 24					
Number of subjects with blood pressure results - N1	262	65	258	134	457
Increase from baseline ≥ 10 mmHg in DBP with DBP > 90 mmHg	6 / 262 (2.3)	2 / 65 (3.1)	3 / 258 (1.2)	3 / 134 (2.2)	8 / 457 (1.8)
Increase from baseline ≥ 10 mmHg in DBP with DBP ≤ 90 mmHg	28 / 262 (10.7)	6 / 65 (9.2)	21 / 258 (8.1)	8 / 134 (6.0)	35 / 457 (7.7)
Increase from baseline ≥ 20 mmHg in SBP with SBP > 140 mmHg	1 / 262 (0.4)	1 / 65 (1.5)	2 / 258 (0.8)	2 / 134 (1.5)	5 / 457 (1.1)
Increase from baseline ≥ 20 mmHg in SBP with SBP ≤ 140 mmHg	1 / 262 (0.4)	2 / 65 (3.1)	2 / 258 (0.8)	3 / 134 (2.2)	7 / 457 (1.5)

N = Number of subjects in the analysis set
N1 = Number of subjects with observed data
n = Number of subjects meeting criterion
% = n / N1 * 100
DBP = Diastolic blood pressure
SBP = Systolic blood pressure

[redacted]

表 37　24週時のベースラインからのカテゴリー別の心拍数の変化
（J-ISS-1：安全性解析対象集団）

		AMG 334			
Visit	Placebo (N = 267) n / N1 (%)	28 mg QM (N = 66) n / N1 (%)	70 mg QM (N = 265) n / N1 (%)	140 mg QM (N = 137) n / N1 (%)	Overall (N = 468) n / N1 (%)
Week 24					
Number of subjects with HR results - N1	262	65	258	134	457
Increase from baseline ≥ 15 in HR or HR ≥ 120 bpm	13 / 262 (5.0)	5 / 65 (7.7)	8 / 258 (3.1)	4 / 134 (3.0)	17 / 457 (3.7)
Decrease from baseline ≤ -15 in HR or HR ≤ 50 bpm	13 / 262 (5.0)	1 / 65 (1.5)	22 / 258 (8.5)	14 / 134 (10.4)	37 / 457 (8.1)

N = Number of subjects in the analysis set
N1 = Number of subjects with observed data
n = Number of subjects meeting criterion
% = n / N1 * 100
HR = Heart rate

[redacted]

4.2　心電図

20120309試験

二重盲検プラセボ対照期に認められた心電図異常のほとんどの発現割合は、いずれの投与群でも2%未満であった。エレヌマブ70 mg群で2%以上に報告された心電図異常（ベースライン時に正常で、ベースライン後に異常と診断、以下同様）は、異常－T波平低化［エレヌマブ28 mg群1.7%（1/60例）、70 mg群4.1%（5/122例）、140 mg群1.6%（2/125例）、プラセボ群2.5%（3/119例）］、及び調律異常－異所性上室調律［エレヌマブ28 mg群0.0%（0/60例）、70 mg群2.5%（3/122例）、140 mg群1.6%（2/125例）、プラセボ群0.8%（1/119例）］であった。これらの異常に投与群間で違いは認められなかった（モジュール5.3.5.1-1.1　Table 14-8.9.1）。

非盲検投与期においても、心電図異常のほとんどの発現割合は2%未満であった。エレヌマブ70 mg又は140 mgを投与された459例のうち2%以上に報告された心電図異常は、異常－T波逆転3.8%、異常伝導－第一度房室ブロック2.6%、及び異常－T波平低化2.4%であった（モジュール5.3.5.1-1.2　Table 14-8.9.1）。このうち、エレヌマブを140 mgへ増量した116例で、増量後に2%以上に報告された心電図異常は、異常－T波逆転（2.9%）のみであった（モジュール5.3.5.1-1.2　Table 14-8.9.2）。

20170609試験

心電図検査において、ベースライン時に正常で、ベースライン後に臨床的に問題となる異常を認めた被験者はいなかった。ベースライン時に正常で、ベースライン後に臨床的に問題ではないが異常を認めた被験者の割合はエレヌマブ70 mg群で5.8%（7/120例）であり、プラセボ群（4.2%、5/119例）と同程度であった。

ベースライン時に臨床的に問題ではないが異常を認めた被験者は、エレヌマブ70 mg群で9例及びプラセボ群で12例であった。これらのうち、ベースライン後に正常であった被験者はそれぞれ5例（55.6%）及び6例（50.0%）、臨床的に問題ではないが異常を認めた被験者はそれぞれ4例（44.4%）及び6例（50.0%）であった（モジュール5.3.5.1-1.2　Table 14-8.8.1）。

以上より、エレヌマブ群とプラセボ群で心電図異常の発現割合に明らかな違いは認められなかった。

4.3 コロンビア自殺企図評価尺度

20120309試験

ベースライン時では、エレヌマブ70 mg群の135例中1例（0.7%）で自殺念慮が認められた（重症度1：死んでしまいたいという願望）。二重盲検投与期では、エレヌマブ70 mg群の2例（1.5%）で自殺念慮が認められた［重症度2（積極的な自殺念慮－具体性なし）：1例、重症度3（積極的な自殺念慮－実行する意思はなし）：1例（いずれの被験者もベースライン時は重症度0）］。その他の投与群では自殺念慮又は自殺行動が認められた被験者はいなかった（モジュール5.3.5.1-1.1　Table 14-8.8.1）。

非盲検投与期では、459例中2例（0.4%）に自殺念慮が認められた［重症度1（死んでしまいたいという願望）：1例（非盲検投与期開始前の重症度0）、重症度3：1例（非盲検投与期開始前の重症度3）］（モジュール5.3.5.1-1.2　Table 14-8.8.1）。

20170609試験

ベースライン時に自殺念慮又は自殺行動が認められた被験者はいなかった。二重盲検投与期では、プラセボ群の131例中1例（0.8%）で自殺念慮が認められた［重症度2（ベースライン時の重症度0）］。エレヌマブ70 mg群では自殺念慮又は自殺行動が認められた被験者はいなかった（モジュール5.3.5.1-2　Table 14-8.4.1）。

以上より、自殺念慮又は自殺行動のリスクがプラセボ群に比較してエレヌマブ群で明らかに高い傾向は認められなかった。

5. 特別な患者集団及び状況下における安全性

本項では1.1.1.1.2項に定めた部分集団について、国内併合解析におけるPool J-ISS-1の結果を以下に示す。Pool J-ISS-2の結果はモジュール5.3.5.3-1.2　Table 14-6.221.1～13及びTable 14-6.223.1～13に示す。

5.1 内因性要因

5.1.1 性別

Pool J-ISS-1では、男性はエレヌマブ70 mg群で39例、プラセボ群で33例、女性はエレヌマブ70 mg群で226例、プラセボ群で234例であった。すべての有害事象、グレード3以上の有害事象、重篤な有害事象及び治験薬の投与中止に至った有害事象の発現割合は、男女別のいずれの集団においても、エレヌマブ70 mg群とプラセボ群で同程度であった。また、報告された個々の有害事象のエレヌマブ70 mg群とプラセボ群における発現割合は、男女のいずれの集団においても、全体集団のエレヌマブ70 mg群とプラセボ群の発現割合（表 15）とおおむね同程度であった（表 38及び表 39）。

表 38　有害事象の要約：男性（J-ISS-1：安全性解析対象集団）

	Placebo (N = 33) n (%)	AMG 334 28 mg QM (N = 11) n (%)	AMG 334 70 mg QM (N = 39) n (%)	AMG 334 140 mg QM (N = 25) n (%)	AMG 334 Overall (N = 75) n (%)
All treatment-emergent adverse events	22 (66.7)	6 (54.5)	24 (61.5)	14 (56.0)	44 (58.7)
Grade ≥ 2	11 (33.3)	4 (36.4)	17 (43.6)	11 (44.0)	32 (42.7)
Grade ≥ 3	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	1 (1.3)
Grade ≥ 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	0 (0.0)	0 (0.0)	3 (7.7)	1 (4.0)	4 (5.3)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	10 (30.3)	2 (18.2)	6 (15.4)	7 (28.0)	15 (20.0)
背部痛	1 (3.0)	1 (9.1)	3 (7.7)	0 (0.0)	4 (5.3)
便秘	0 (0.0)	0 (0.0)	2 (5.1)	1 (4.0)	3 (4.0)
齲歯	0 (0.0)	1 (9.1)	3 (7.7)	0 (0.0)	4 (5.3)
咽頭炎	0 (0.0)	0 (0.0)	2 (5.1)	1 (4.0)	3 (4.0)
上腹部痛	1 (3.0)	0 (0.0)	1 (2.6)	0 (0.0)	1 (1.3)
胃腸炎	2 (6.1)	0 (0.0)	0 (0.0)	1 (4.0)	1 (1.3)
口内炎	1 (3.0)	0 (0.0)	1 (2.6)	0 (0.0)	1 (1.3)
筋骨格硬直	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

[redacted]

表 39　有害事象の要約：女性（J-ISS-1：安全性解析対象集団）

	Placebo (N = 234) n (%)	AMG 334 28 mg QM (N = 55) n (%)	AMG 334 70 mg QM (N = 226) n (%)	AMG 334 140 mg QM (N = 112) n (%)	AMG 334 Overall (N = 393) n (%)
All treatment-emergent adverse events	149 (63.7)	34 (61.8)	157 (69.5)	84 (75.0)	275 (70.0)
Grade ≥ 2	118 (50.4)	29 (52.7)	122 (54.0)	54 (48.2)	205 (52.2)
Grade ≥ 3	6 (2.6)	1 (1.8)	6 (2.7)	0 (0.0)	7 (1.8)
Grade ≥ 4	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Serious adverse events	6 (2.6)	1 (1.8)	3 (1.3)	1 (0.9)	5 (1.3)
Leading to discontinuation of investigational product	1 (0.4)	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.5)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	11 (4.7)	5 (9.1)	25 (11.1)	12 (10.7)	42 (10.7)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	68 (29.1)	20 (36.4)	68 (30.1)	38 (33.9)	126 (32.1)
背部痛	7 (3.0)	2 (3.6)	11 (4.9)	1 (0.9)	14 (3.6)
便秘	4 (1.7)	0 (0.0)	11 (4.9)	6 (5.4)	17 (4.3)
齲歯	5 (2.1)	1 (1.8)	8 (3.5)	2 (1.8)	11 (2.8)
咽頭炎	7 (3.0)	3 (5.5)	8 (3.5)	2 (1.8)	13 (3.3)
上腹部痛	1 (0.4)	1 (1.8)	6 (2.7)	2 (1.8)	9 (2.3)
胃腸炎	6 (2.6)	2 (3.6)	7 (3.1)	4 (3.6)	13 (3.3)
口内炎	2 (0.9)	2 (3.6)	5 (2.2)	1 (0.9)	8 (2.0)
筋骨格硬直	3 (1.3)	1 (1.8)	6 (2.7)	1 (0.9)	8 (2.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

[redacted]

5.1.2　年齢

Pool J-ISS-1において、すべての被験者における年齢の中央値は45.0歳であった（1.3.1項参照）。年齢が中央値未満の被験者はエレヌマブ70 mg群で135例、プラセボ群で126例、中央値以上の被験者はエレヌマブ70 mg群で130例、プラセボ群で141例であった。すべての有害事象、グレード3以上の有害事象、重篤な有害事象及び治験薬の投与中止に至った有害事象の発現割合は、年齢別（中央値未満、以上）のいずれの集団においても、エレヌマブ70 mg群とプラセボ群でおおむね同程度であった。また、報告された個々の有害事象のエレヌマブ70 mg群とプラセボ群における発現割合は、年齢別のいずれの集団においても、全体集団のエレヌマブ70 mg群とプラセボ群の発現割合（表 15）とおおむね同程度であった（表 40及び表 41）。

表 40　有害事象の要約：年齢中央値未満（J-ISS-1：安全性解析対象集団）

	Placebo (N = 126) n (%)	AMG 334 28 mg QM (N = 38) n (%)	AMG 334 70 mg QM (N = 135) n (%)	AMG 334 140 mg QM (N = 61) n (%)	AMG 334 Overall (N = 234) n (%)
All treatment-emergent adverse events	77 (61.1)	23 (60.5)	88 (65.2)	43 (70.5)	154 (65.8)
Grade ≥ 2	58 (46.0)	20 (52.6)	68 (50.4)	32 (52.5)	120 (51.3)
Grade ≥ 3	1 (0.8)	1 (2.6)	4 (3.0)	0 (0.0)	5 (2.1)
Grade ≥ 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	1 (0.8)	1 (2.6)	1 (0.7)	1 (1.6)	3 (1.3)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.4)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	4 (3.2)	2 (5.3)	18 (13.3)	4 (6.6)	24 (10.3)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	40 (31.7)	15 (39.5)	32 (23.7)	23 (37.7)	70 (29.9)
背部痛	2 (1.6)	1 (2.6)	6 (4.4)	0 (0.0)	7 (3.0)
便秘	0 (0.0)	0 (0.0)	5 (3.7)	3 (4.9)	8 (3.4)
齲歯	1 (0.8)	1 (2.6)	6 (4.4)	1 (1.6)	8 (3.4)
咽頭炎	4 (3.2)	1 (2.6)	6 (4.4)	1 (1.6)	8 (3.4)
上腹部痛	1 (0.8)	0 (0.0)	5 (3.7)	1 (1.6)	6 (2.6)
胃腸炎	4 (3.2)	1 (2.6)	3 (2.2)	4 (6.6)	8 (3.4)
口内炎	2 (1.6)	2 (5.3)	2 (1.5)	1 (1.6)	5 (2.1)
筋骨格硬直	2 (1.6)	1 (2.6)	2 (1.5)	1 (1.6)	4 (1.7)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

[redacted]

表 41　有害事象の要約：年齢中央値以上（J-ISS-1：安全性解析対象集団）

	Placebo (N = 141) n (%)	AMG 334 28 mg QM (N = 28) n (%)	AMG 334 70 mg QM (N = 130) n (%)	AMG 334 140 mg QM (N = 76) n (%)	AMG 334 Overall (N = 234) n (%)
All treatment-emergent adverse events	94 (66.7)	17 (60.7)	93 (71.5)	55 (72.4)	165 (70.5)
Grade ≥ 2	71 (50.4)	13 (46.4)	71 (54.6)	33 (43.4)	117 (50.0)
Grade ≥ 3	5 (3.5)	0 (0.0)	3 (2.3)	0 (0.0)	3 (1.3)
Grade ≥ 4	1 (0.7)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Serious adverse events	5 (3.5)	0 (0.0)	2 (1.5)	0 (0.0)	2 (0.9)
Leading to discontinuation of investigational product	1 (0.7)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	7 (5.0)	3 (10.7)	10 (7.7)	9 (11.8)	22 (9.4)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	38 (27.0)	7 (25.0)	42 (32.3)	22 (28.9)	71 (30.3)
背部痛	6 (4.3)	2 (7.1)	8 (6.2)	1 (1.3)	11 (4.7)
便秘	4 (2.8)	0 (0.0)	8 (6.2)	4 (5.3)	12 (5.1)
齲歯	4 (2.8)	1 (3.6)	5 (3.8)	1 (1.3)	7 (3.0)
咽頭炎	3 (2.1)	2 (7.1)	4 (3.1)	2 (2.6)	8 (3.4)
上腹部痛	1 (0.7)	1 (3.6)	2 (1.5)	1 (1.3)	4 (1.7)
胃腸炎	4 (2.8)	1 (3.6)	4 (3.1)	1 (1.3)	6 (2.6)
口内炎	1 (0.7)	0 (0.0)	4 (3.1)	0 (0.0)	4 (1.7)
筋骨格硬直	1 (0.7)	0 (0.0)	4 (3.1)	0 (0.0)	4 (1.7)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

[redacted]

5.1.3　体重

Pool J-ISS-1において、すべての被験者における体重の中央値は54.40 kgであった（1.3.1項参照）。体重が中央値未満の被験者はエレヌマブ70 mg群で134例、プラセボ群で140例、中央値以上の被験者はエレヌマブ70 mg群で131例、プラセボ群で127例であった。すべての有害事象の発現割合は中央値未満の被験者において、エレヌマブ70 mg群（67.2%）でプラセボ群（57.9%）に比較して高い傾向がみられたものの、グレード3以上の有害事象、重篤な有害事象及び治験薬の投与中止に至った有害事象の発現割合については体重別のいずれの集団においても、エレヌマブ70 mg群とプラセボ群で同程度であった。また、報告された個々の有害事象のエレヌマブ70 mg群とプラセボ群における発現割合は、体重別のいずれの集団においても、全体集団のエレヌマブ70 mg群とプラセボ群の発現割合（表 15）とおおむね同程度であった（表 42及び表 43）。

表 42　有害事象の要約：体重中央値未満（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (N = 140) n (%)	28 mg QM (N = 31) n (%)	70 mg QM (N = 134) n (%)	140 mg QM (N = 58) n (%)	Overall (N = 223) n (%)
All treatment-emergent adverse events	81 (57.9)	18 (58.1)	90 (67.2)	47 (81.0)	155 (69.5)
Grade ≥ 2	66 (47.1)	14 (45.2)	69 (51.5)	32 (55.2)	115 (51.6)
Grade ≥ 3	2 (1.4)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.4)
Grade ≥ 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	2 (1.4)	0 (0.0)	0 (0.0)	1 (1.7)	1 (0.4)
Leading to discontinuation of investigational product	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.4)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	6 (4.3)	3 (9.7)	14 (10.4)	7 (12.1)	24 (10.8)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	31 (22.1)	12 (38.7)	40 (29.9)	20 (34.5)	72 (32.3)
背部痛	5 (3.6)	0 (0.0)	8 (6.0)	1 (1.7)	9 (4.0)
便秘	3 (2.1)	0 (0.0)	7 (5.2)	3 (5.2)	10 (4.5)
齲歯	3 (2.1)	0 (0.0)	6 (4.5)	1 (1.7)	7 (3.1)
咽頭炎	5 (3.6)	2 (6.5)	6 (4.5)	2 (3.4)	10 (4.5)
上腹部痛	1 (0.7)	0 (0.0)	4 (3.0)	2 (3.4)	6 (2.7)
胃腸炎	4 (2.9)	1 (3.2)	3 (2.2)	2 (3.4)	6 (2.7)
口内炎	1 (0.7)	1 (3.2)	4 (3.0)	1 (1.7)	6 (2.7)
筋骨格硬直	2 (1.4)	0 (0.0)	3 (2.2)	0 (0.0)	3 (1.3)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

[redacted]

表 43　有害事象の要約：体重中央値以上（J-ISS-1：安全性解析対象集団）

	Placebo (N = 127) n (%)	AMG 334 28 mg QM (N = 35) n (%)	AMG 334 70 mg QM (N = 131) n (%)	AMG 334 140 mg QM (N = 79) n (%)	AMG 334 Overall (N = 245) n (%)
All treatment-emergent adverse events	90 (70.9)	22 (62.9)	91 (69.5)	51 (64.6)	164 (66.9)
Grade ≥ 2	63 (49.6)	19 (54.3)	70 (53.4)	33 (41.8)	122 (49.8)
Grade ≥ 3	4 (3.1)	1 (2.9)	6 (4.6)	0 (0.0)	7 (2.9)
Grade ≥ 4	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Serious adverse events	4 (3.1)	1 (2.9)	3 (2.3)	0 (0.0)	4 (1.6)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	5 (3.9)	2 (5.7)	14 (10.7)	6 (7.6)	22 (9.0)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	47 (37.0)	10 (28.6)	34 (26.0)	25 (31.6)	69 (28.2)
背部痛	3 (2.4)	3 (8.6)	6 (4.6)	0 (0.0)	9 (3.7)
便秘	1 (0.8)	0 (0.0)	6 (4.6)	4 (5.1)	10 (4.1)
齲歯	2 (1.6)	2 (5.7)	5 (3.8)	1 (1.3)	8 (3.3)
咽頭炎	2 (1.6)	1 (2.9)	4 (3.1)	1 (1.3)	6 (2.4)
上腹部痛	1 (0.8)	1 (2.9)	3 (2.3)	0 (0.0)	4 (1.6)
胃腸炎	4 (3.1)	1 (2.9)	4 (3.1)	3 (3.8)	8 (3.3)
口内炎	2 (1.6)	1 (2.9)	2 (1.5)	0 (0.0)	3 (1.2)
筋骨格硬直	1 (0.8)	1 (2.9)	3 (2.3)	1 (1.3)	5 (2.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

[redacted]

5.1.4　反復性片頭痛及び慢性片頭痛被験者

Pool J-ISS-1では、EM被験者はエレヌマブ70 mg群で213例、プラセボ群で217例、CM被験者はエレヌマブ70 mg群で52例、プラセボ群で50例であった。すべての有害事象の発現割合はCM被験者において、エレヌマブ70 mg群（71.2%）でプラセボ群（58.0%）に比較して高かったものの、グレード3以上の有害事象、重篤な有害事象及び治験薬の投与中止に至った有害事象の発現割合については、EM又はCM被験者別のいずれの集団においてもエレヌマブ70 mg群とプラセボ群で同程度であった。

報告された個々の有害事象では、CM被験者のエレヌマブ70 mg群でプラセボ群と比較して筋骨格硬直の発現割合が高く（それぞれ7.7%及び2.0%、以下同順）、全体集団（2.3%及び1.1%）とは異なる傾向がみられたものの、当該部分集団の被験者数は少なく、エレヌマブ70 mg群のCM被験者4例で発現した筋骨格硬直は、いずれもグレード2以下であり、非重篤で治験薬の投与中止に至らず、治験薬との関連なしと判断された。その他の有害事象ではエレヌマブ70 mg群とプラセボ群における発

現割合は、EM又はCM被験者別のいずれの集団においても、全体集団のエレヌマブ70 mg群とプラセボ群の発現割合（表 15）とおおむね同程度であった（表 44及び表 45）。

表 44　有害事象の要約：EM患者（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (N = 217) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 213) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 416) n (%)
All treatment-emergent adverse events	142 (65.4)	40 (60.6)	144 (67.6)	98 (71.5)	282 (67.8)
Grade ≥ 2	105 (48.4)	33 (50.0)	108 (50.7)	65 (47.4)	206 (49.5)
Grade ≥ 3	5 (2.3)	1 (1.5)	6 (2.8)	0 (0.0)	7 (1.7)
Grade ≥ 4	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Serious adverse events	5 (2.3)	1 (1.5)	3 (1.4)	1 (0.7)	5 (1.2)
Leading to discontinuation of investigational product	1 (0.5)	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.5)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	8 (3.7)	5 (7.6)	24 (11.3)	13 (9.5)	42 (10.1)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	66 (30.4)	22 (33.3)	59 (27.7)	45 (32.8)	126 (30.3)
背部痛	6 (2.8)	3 (4.5)	10 (4.7)	1 (0.7)	14 (3.4)
便秘	4 (1.8)	0 (0.0)	10 (4.7)	7 (5.1)	17 (4.1)
齲歯	5 (2.3)	2 (3.0)	9 (4.2)	2 (1.5)	13 (3.1)
咽頭炎	6 (2.8)	3 (4.5)	8 (3.8)	3 (2.2)	14 (3.4)
上腹部痛	1 (0.5)	1 (1.5)	6 (2.8)	2 (1.5)	9 (2.2)
胃腸炎	7 (3.2)	2 (3.0)	4 (1.9)	5 (3.6)	11 (2.6)
口内炎	2 (0.9)	2 (3.0)	4 (1.9)	1 (0.7)	7 (1.7)
筋骨格硬直	2 (0.9)	1 (1.5)	2 (0.9)	1 (0.7)	4 (1.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Summary of migraine criteria is based on actual data collected instead of randomization stratification.
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

[redacted]

表 45　有害事象の要約：CM患者（J-ISS-1：安全性解析対象集団）

	Placebo (N = 50) n (%)	AMG 334 28 mg QM (N = 0) n (%)	AMG 334 70 mg QM (N = 52) n (%)	AMG 334 140 mg QM (N = 0) n (%)	AMG 334 Overall (N = 52) n (%)
All treatment-emergent adverse events	29 (58.0)	0 (-)	37 (71.2)	0 (-)	37 (71.2)
Grade ≥ 2	24 (48.0)	0 (-)	31 (59.6)	0 (-)	31 (59.6)
Grade ≥ 3	1 (2.0)	0 (-)	1 (1.9)	0 (-)	1 (1.9)
Grade ≥ 4	0 (0.0)	0 (-)	0 (0.0)	0 (-)	0 (0.0)
Serious adverse events	1 (2.0)	0 (-)	0 (0.0)	0 (-)	0 (0.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (-)	0 (0.0)	0 (-)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (-)	0 (0.0)	0 (-)	0 (0.0)
Treatment-related treatment-emergent adverse events	3 (6.0)	0 (-)	4 (7.7)	0 (-)	4 (7.7)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	12 (24.0)	0 (-)	15 (28.8)	0 (-)	15 (28.8)
背部痛	2 (4.0)	0 (-)	4 (7.7)	0 (-)	4 (7.7)
便秘	0 (0.0)	0 (-)	3 (5.8)	0 (-)	3 (5.8)
齲歯	0 (0.0)	0 (-)	2 (3.8)	0 (-)	2 (3.8)
咽頭炎	1 (2.0)	0 (-)	2 (3.8)	0 (-)	2 (3.8)
上腹部痛	1 (2.0)	0 (-)	1 (1.9)	0 (-)	1 (1.9)
胃腸炎	1 (2.0)	0 (-)	3 (5.8)	0 (-)	3 (5.8)
口内炎	1 (2.0)	0 (-)	2 (3.8)	0 (-)	2 (3.8)
筋骨格硬直	1 (2.0)	0 (-)	4 (7.7)	0 (-)	4 (7.7)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Summary of migraine criteria is based on actual data collected instead of randomization stratification.
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

[redacted]

5.1.5　心血管リスク

Pool J-ISS-1では、ベースライン時の心血管リスク因子なしの被験者はエレヌマブ70 mg群で115例、プラセボ群で124例、リスク因子が1つのみの被験者はエレヌマブ70 mg群で108例、プラセボ群で103例、2つ以上の被験者はエレヌマブ70 mg群で42例、プラセボ群で40例であった。すべての有害事象、重篤な有害事象及び治験薬の投与中止に至った有害事象の発現割合は、心血管リスク因子数別のいずれの集団においても、エレヌマブ70 mg群とプラセボ群でおおむね同程度であった。グレード3以上の有害事象の発現割合はリスク因子が1つのみの被験者において、エレヌマブ70 mg群（3.7%）でプラセボ群（0.0%）に比較して高い傾向がみられたものの、2つ以上の被験者においてはエレヌマブ70 mg群（0.0%）でプラセボ群（5.0%）に比較して発現割合は高くなかった。

心臓障害SOCの発現割合は、心血管リスク因子なしの被験者ではエレヌマブ70 mg群0.0%、プラセボ群0.0%、リスク因子が1つのみの被験者ではエレヌマブ70 mg群0.0%、プラセボ群1.0%、2つ以

上の被験者ではエレヌマブ70 mg群2.4%（1例）、プラセボ群0.0%であり、リスク因子数が増加しても、エレヌマブ70 mg群で心臓障害関連の事象の発現割合が増加する傾向は認められなかった。その他の個々の有害事象ではエレヌマブ70 mg群とプラセボ群における発現割合は、心血管リスク因子数別のいずれの集団においても、全体集団のエレヌマブ70 mg群とプラセボ群の発現割合（表 15）とおおむね同程度であった（表 46、表 47及び表 48）。

表 46　有害事象の要約：ベースライン時の心血管リスク因子なし（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (N = 124) n (%)	28 mg QM (N = 25) n (%)	70 mg QM (N = 115) n (%)	140 mg QM (N = 46) n (%)	Overall (N = 186) n (%)
All treatment-emergent adverse events	77 (62.1)	18 (72.0)	75 (65.2)	37 (80.4)	130 (69.9)
Grade ≥ 2	58 (46.8)	14 (56.0)	62 (53.9)	25 (54.3)	101 (54.3)
Grade ≥ 3	4 (3.2)	1 (4.0)	3 (2.6)	0 (0.0)	4 (2.2)
Grade ≥ 4	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	3 (2.4)	1 (4.0)	1 (0.9)	0 (0.0)	2 (1.1)
Leading to discontinuation of investigational product	1 (0.8)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	5 (4.0)	4 (16.0)	11 (9.6)	4 (8.7)	19 (10.2)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	41 (33.1)	8 (32.0)	28 (24.3)	18 (39.1)	54 (29.0)
背部痛	2 (1.6)	2 (8.0)	5 (4.3)	1 (2.2)	8 (4.3)
便秘	3 (2.4)	0 (0.0)	3 (2.6)	3 (6.5)	6 (3.2)
齲歯	2 (1.6)	0 (0.0)	4 (3.5)	1 (2.2)	5 (2.7)
咽頭炎	3 (2.4)	1 (4.0)	5 (4.3)	1 (2.2)	7 (3.8)
上腹部痛	1 (0.8)	0 (0.0)	4 (3.5)	2 (4.3)	6 (3.2)
胃腸炎	5 (4.0)	0 (0.0)	3 (2.6)	2 (4.3)	5 (2.7)
口内炎	1 (0.8)	2 (8.0)	3 (2.6)	1 (2.2)	6 (3.2)
筋骨格硬直	2 (1.6)	0 (0.0)	1 (0.9)	1 (2.2)	2 (1.1)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Baseline cardiovascular risk factors include: diabetes mellitus, hypertension and / or high blood pressure, history of smoking, history of dyslipidemia / high cholesterol level / high lipid levels, BMI > 30, coronary artery disease and cerebrovascular and peripheral artery disease.
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

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表 47　有害事象の要約：ベースライン時の心血管リスク因子数1つのみ
（J-ISS-1：安全性解析対象集団）

	Placebo (N = 103) n (%)	AMG 334 28 mg QM (N = 31) n (%)	AMG 334 70 mg QM (N = 108) n (%)	AMG 334 140 mg QM (N = 63) n (%)	Overall (N = 202) n (%)
All treatment-emergent adverse events	70 (68.0)	17 (54.8)	81 (75.0)	44 (69.8)	142 (70.3)
Grade ≥ 2	52 (50.5)	15 (48.4)	57 (52.8)	28 (44.4)	100 (49.5)
Grade ≥ 3	0 (0.0)	0 (0.0)	4 (3.7)	0 (0.0)	4 (2.0)
Grade ≥ 4	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Serious adverse events	1 (1.0)	0 (0.0)	2 (1.9)	0 (0.0)	2 (1.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	3 (2.9)	1 (3.2)	14 (13.0)	5 (7.9)	20 (9.9)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	30 (29.1)	11 (35.5)	34 (31.5)	23 (36.5)	68 (33.7)
背部痛	6 (5.8)	0 (0.0)	5 (4.6)	0 (0.0)	5 (2.5)
便秘	0 (0.0)	0 (0.0)	8 (7.4)	3 (4.8)	11 (5.4)
齲歯	2 (1.9)	1 (3.2)	5 (4.6)	0 (0.0)	6 (3.0)
咽頭炎	3 (2.9)	2 (6.5)	3 (2.8)	0 (0.0)	5 (2.5)
上腹部痛	1 (1.0)	1 (3.2)	2 (1.9)	0 (0.0)	3 (1.5)
胃腸炎	2 (1.9)	2 (6.5)	3 (2.8)	1 (1.6)	6 (3.0)
口内炎	2 (1.9)	0 (0.0)	3 (2.8)	0 (0.0)	3 (1.5)
筋骨格硬直	1 (1.0)	1 (3.2)	3 (2.8)	0 (0.0)	4 (2.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Baseline cardiovascular risk factors include: diabetes mellitus, hypertension and / or high blood pressure, history of smoking, history of dyslipidemia / high cholesterol level / high lipid levels, BMI > 30, coronary artery disease and cerebrovascular and peripheral artery disease.
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

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表 48　有害事象の要約：ベースライン時の心血管リスク因子数2つ以上
（J-ISS-1：安全性解析対象集団）

	Placebo (N = 40) n (%)	AMG 334 28 mg QM (N = 10) n (%)	AMG 334 70 mg QM (N = 42) n (%)	AMG 334 140 mg QM (N = 28) n (%)	AMG 334 Overall (N = 80) n (%)
All treatment-emergent adverse events	24 (60.0)	5 (50.0)	25 (59.5)	17 (60.7)	47 (58.8)
Grade ≥ 2	19 (47.5)	4 (40.0)	20 (47.6)	12 (42.9)	36 (45.0)
Grade ≥ 3	2 (5.0)	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)
Serious adverse events	2 (5.0)	0 (0.0)	0 (0.0)	1 (3.6)	1 (1.3)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	3 (7.5)	0 (0.0)	3 (7.1)	4 (14.3)	7 (8.8)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	7 (17.5)	3 (30.0)	12 (28.6)	4 (14.3)	19 (23.8)
背部痛	0 (0.0)	1 (10.0)	4 (9.5)	0 (0.0)	5 (6.3)
便秘	1 (2.5)	0 (0.0)	2 (4.8)	1 (3.6)	3 (3.8)
齲歯	1 (2.5)	1 (10.0)	2 (4.8)	1 (3.6)	4 (5.0)
咽頭炎	1 (2.5)	0 (0.0)	2 (4.8)	2 (7.1)	4 (5.0)
上腹部痛	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (1.3)
胃腸炎	1 (2.5)	0 (0.0)	1 (2.4)	2 (7.1)	3 (3.8)
口内炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
筋骨格硬直	0 (0.0)	0 (0.0)	2 (4.8)	0 (0.0)	2 (2.5)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Baseline cardiovascular risk factors include: diabetes mellitus, hypertension and / or high blood pressure, history of smoking, history of dyslipidemia / high cholesterol level / high lipid levels, BMI > 30, coronary artery disease and cerebrovascular and peripheral artery disease.
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

[redacted]

5.1.6　腎機能障害

Pool J-ISS-1では、ベースライン時に腎機能障害を有する（定義は1.1.1.1.2項参照）被験者はエレヌマブ70 mg群で27例、プラセボ群で26例、腎機能障害が無い被験者はエレヌマブ70 mg群で238例、プラセボ群で241例であった。腎機能障害を有する被験者は少数であったものの、すべての有害事象、グレード3以上の有害事象、重篤な有害事象及び治験薬の投与中止に至った有害事象の発現割合は、腎機能障害有無別のいずれの集団においても、エレヌマブ70 mg群とプラセボ群で同程度であった。また、報告された個々の有害事象のエレヌマブ70 mg群とプラセボ群における発現割合は、腎機能障害有無別のいずれの集団においても、全体集団のエレヌマブ70 mg群とプラセボ群の発現割合（表 15）とおおむね同程度であった（表 49及び表 50）。

表 49　有害事象の要約：ベースライン時の腎機能障害有（J-ISS-1：安全性解析対象集団）

	Placebo (N = 26) n (%)	AMG 334 28 mg QM (N = 3) n (%)	AMG 334 70 mg QM (N = 27) n (%)	AMG 334 140 mg QM (N = 10) n (%)	AMG 334 Overall (N = 40) n (%)
All treatment-emergent adverse events	20 (76.9)	1 (33.3)	20 (74.1)	8 (80.0)	29 (72.5)
Grade ≥ 2	15 (57.7)	1 (33.3)	13 (48.1)	3 (30.0)	17 (42.5)
Grade ≥ 3	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)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	1 (3.8)	0 (0.0)	1 (3.7)	2 (20.0)	3 (7.5)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	9 (34.6)	0 (0.0)	8 (29.6)	2 (20.0)	10 (25.0)
背部痛	3 (11.5)	0 (0.0)	1 (3.7)	0 (0.0)	1 (2.5)
便秘	1 (3.8)	0 (0.0)	1 (3.7)	1 (10.0)	2 (5.0)
齲歯	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
咽頭炎	0 (0.0)	1 (33.3)	2 (7.4)	0 (0.0)	3 (7.5)
上腹部痛	1 (3.8)	0 (0.0)	1 (3.7)	0 (0.0)	1 (2.5)
胃腸炎	0 (0.0)	0 (0.0)	1 (3.7)	1 (10.0)	2 (5.0)
口内炎	1 (3.8)	0 (0.0)	1 (3.7)	0 (0.0)	1 (2.5)
筋骨格硬直	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (2.5)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

[redacted]

表 50　有害事象の要約：ベースライン時の腎機能障害無（J-ISS-1：安全性解析対象集団）

	Placebo (N = 241) n (%)	AMG 334 28 mg QM (N = 63) n (%)	AMG 334 70 mg QM (N = 238) n (%)	AMG 334 140 mg QM (N = 127) n (%)	AMG 334 Overall (N = 428) n (%)
All treatment-emergent adverse events	151 (62.7)	39 (61.9)	161 (67.6)	90 (70.9)	290 (67.8)
Grade ≥ 2	114 (47.3)	32 (50.8)	126 (52.9)	62 (48.8)	220 (51.4)
Grade ≥ 3	6 (2.5)	1 (1.6)	7 (2.9)	0 (0.0)	8 (1.9)
Grade ≥ 4	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Serious adverse events	6 (2.5)	1 (1.6)	3 (1.3)	1 (0.8)	5 (1.2)
Leading to discontinuation of investigational product	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.5)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	10 (4.1)	5 (7.9)	27 (11.3)	11 (8.7)	43 (10.0)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	69 (28.6)	22 (34.9)	66 (27.7)	43 (33.9)	131 (30.6)
背部痛	5 (2.1)	3 (4.8)	13 (5.5)	1 (0.8)	17 (4.0)
便秘	3 (1.2)	0 (0.0)	12 (5.0)	6 (4.7)	18 (4.2)
齲歯	5 (2.1)	2 (3.2)	11 (4.6)	2 (1.6)	15 (3.5)
咽頭炎	7 (2.9)	2 (3.2)	8 (3.4)	3 (2.4)	13 (3.0)
上腹部痛	1 (0.4)	1 (1.6)	6 (2.5)	2 (1.6)	9 (2.1)
胃腸炎	8 (3.3)	2 (3.2)	6 (2.5)	4 (3.1)	12 (2.8)
口内炎	2 (0.8)	2 (3.2)	5 (2.1)	1 (0.8)	8 (1.9)
筋骨格硬直	3 (1.2)	1 (1.6)	5 (2.1)	1 (0.8)	7 (1.6)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

[redacted]

5.2　外因性要因

5.2.1　片頭痛予防薬の治療不成功歴

Pool J-ISS-1では、片頭痛予防薬の治療不成功歴を有する被験者はエレヌマブ70 mg群で102例、プラセボ群で102例、治療不成功歴が無い（使用なしも含む）被験者はエレヌマブ70 mg群で163例、プラセボ群で165例であった。すべての有害事象の発現割合は治療不成功歴を有する被験者において、エレヌマブ70 mg群（72.5%）でプラセボ群（61.8%）に比較して高かったものの、グレード3以上の有害事象、重篤な有害事象及び治験薬の投与中止に至った有害事象の発現割合については、片頭痛予防薬の治療不成功歴有無別のいずれの集団においても、エレヌマブ70 mg群とプラセボ群で同程度であった。また、報告された個々の有害事象のエレヌマブ70 mg群とプラセボ群における発現割合は、片頭痛予防薬の治療不成功歴有無別のいずれの集団においても、全体集団のエレヌマブ70 mg群とプラセボ群の発現割合（表 15）とおおむね同程度であった（表 51及び表 52）。

表 51　有害事象の要約：片頭痛予防薬の治療不成功歴有（J-ISS-1：安全性解析対象集団）

	Placebo (N = 102) n (%)	AMG 334 28 mg QM (N = 20) n (%)	AMG 334 70 mg QM (N = 102) n (%)	AMG 334 140 mg QM (N = 54) n (%)	AMG 334 Overall (N = 176) n (%)
All treatment-emergent adverse events	63 (61.8)	13 (65.0)	74 (72.5)	38 (70.4)	125 (71.0)
Grade ≥ 2	51 (50.0)	11 (55.0)	57 (55.9)	24 (44.4)	92 (52.3)
Grade ≥ 3	2 (2.0)	1 (5.0)	4 (3.9)	0 (0.0)	5 (2.8)
Grade ≥ 4	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.6)
Serious adverse events	2 (2.0)	1 (5.0)	2 (2.0)	0 (0.0)	3 (1.7)
Leading to discontinuation of investigational product	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.6)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	5 (4.9)	0 (0.0)	12 (11.8)	4 (7.4)	16 (9.1)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	30 (29.4)	8 (40.0)	28 (27.5)	19 (35.2)	55 (31.3)
背部痛	4 (3.9)	0 (0.0)	6 (5.9)	0 (0.0)	6 (3.4)
便秘	3 (2.9)	0 (0.0)	6 (5.9)	1 (1.9)	7 (4.0)
齲歯	3 (2.9)	1 (5.0)	3 (2.9)	0 (0.0)	4 (2.3)
咽頭炎	3 (2.9)	1 (5.0)	3 (2.9)	2 (3.7)	6 (3.4)
上腹部痛	1 (1.0)	1 (5.0)	1 (1.0)	0 (0.0)	2 (1.1)
胃腸炎	4 (3.9)	1 (5.0)	5 (4.9)	1 (1.9)	7 (4.0)
口内炎	2 (2.0)	0 (0.0)	2 (2.0)	0 (0.0)	2 (1.1)
筋骨格硬直	1 (1.0)	0 (0.0)	4 (3.9)	0 (0.0)	4 (2.3)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

[redacted]

表 52　有害事象の要約：片頭痛予防薬の治療不成功歴無（J-ISS-1：安全性解析対象集団）

	Placebo (N = 165) n (%)	AMG 334 28 mg QM (N = 46) n (%)	AMG 334 70 mg QM (N = 163) n (%)	AMG 334 140 mg QM (N = 83) n (%)	AMG 334 Overall (N = 292) n (%)
All treatment-emergent adverse events	108 (65.5)	27 (58.7)	107 (65.6)	60 (72.3)	194 (66.4)
Grade ≥ 2	78 (47.3)	22 (47.8)	82 (50.3)	41 (49.4)	145 (49.7)
Grade ≥ 3	4 (2.4)	0 (0.0)	3 (1.8)	0 (0.0)	3 (1.0)
Grade ≥ 4	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	4 (2.4)	0 (0.0)	1 (0.6)	1 (1.2)	2 (0.7)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	6 (3.6)	5 (10.9)	16 (9.8)	9 (10.8)	30 (10.3)
Most commonly ≥ 2% reported preferred terms in the erenumab 70 mg group in overall population					
上咽頭炎	48 (29.1)	14 (30.4)	46 (28.2)	26 (31.3)	86 (29.5)
背部痛	4 (2.4)	3 (6.5)	8 (4.9)	1 (1.2)	12 (4.1)
便秘	1 (0.6)	0 (0.0)	7 (4.3)	6 (7.2)	13 (4.5)
齲歯	2 (1.2)	1 (2.2)	8 (4.9)	2 (2.4)	11 (3.8)
咽頭炎	4 (2.4)	2 (4.3)	7 (4.3)	1 (1.2)	10 (3.4)
上腹部痛	1 (0.6)	0 (0.0)	6 (3.7)	2 (2.4)	8 (2.7)
胃腸炎	4 (2.4)	1 (2.2)	2 (1.2)	4 (4.8)	7 (2.4)
口内炎	1 (0.6)	2 (4.3)	4 (2.5)	1 (1.2)	7 (2.4)
筋骨格硬直	2 (1.2)	1 (2.2)	2 (1.2)	1 (1.2)	4 (1.4)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Coded using MedDRA version 22.1

[redacted]

5.2.2　在宅での臨床使用

20120309試験では、在宅での臨床使用（CHU）サブスタディとして、非盲検投与期に被験者がエレヌマブ140 mgを、70 mg/mLペン型プレフィルド自己注射器（AI/Pen）を2回又は140 mg/mL AI/Penを1回のいずれかを使用して、在宅で自己投与が可能であるかを評価した。被験者のサブスタディへの参加は任意であった。本サブスタディには合計49例が登録され、70 mg/mL AI/Pen 2回の自己投与に24例が、140 mg/mL AI/Pen 1回の自己投与に25例が無作為化に割り付けられた。被験者はDay 1に治験実施医療機関の監視下でエレヌマブを自己投与し、Day 29及びDay 57に自宅等で自己投与を行うこととした。

すべての被験者（49/49例）がDay 29及びDay 57の両時点で、割り付けられた方法での自己投与により、エレヌマブ140 mgを全量投与した。

本サブスタディで報告された有害事象の概要を表 53に示す。有害事象は70 mg/mL AI/Penを2回自己投与した被験者で45.8%、140 mg/mL AI/Penを1回自己投与した被験者で56.0%に発現した。発現した有害事象はすべてグレード2以下であった。70 mg/mL AI/Penを2回自己投与した被験者に、重篤な

有害事象としてマイコバクテリア感染が1件報告された。本事象の重症度はグレード2であり、治験薬との関連はあるが、医療機器との関連はなしと判断された。なお、治験薬の投与中止に至った有害事象は認められなかった。機器関連の有害事象は70 mg/mL AI/Penを2回自己投与した被験者では2例（注射部位出血及び皮下出血、各1例）、140 mg/mL AI/Penを1回自己投与した被験者では1例（注射部位反応が2件）に発現した。1件の注射部位反応（グレード2）を除くすべての事象は、重症度がグレード1であった。

全体として、在宅での自己投与による安全性に明らかな懸念は認められなかった。

表 53　有害事象の概要（20120309試験：CHUサブスタディ解析対象集団）

	AMG 334 2 X 70 mg/mL AI/Pen (N = 24) n (%)	AMG 334 1 X 140 mg/mL AI/Pen (N = 25) n (%)	Total (N = 49) n (%)
All treatment-emergent adverse events	11 (45.8)	14 (56.0)	25 (51.0)
Grade ≥ 2	9 (37.5)	9 (36.0)	18 (36.7)
Grade ≥ 3	0 (0.0)	0 (0.0)	0 (0.0)
Grade ≥ 4	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	1 (4.2)	0 (0.0)	1 (2.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)
Adverse device effects	2 (8.3)	1 (4.0)	3 (6.1)

CHU = Clinical home use
N = Number of subjects in the CHU substudy safety analysis set
n = Number of subjects reporting at least one occurrence of an adverse event that occurred on or after the first dose of CHU investigational product (IP) and up to and including end date of CHU substudy
% = n / N * 100
Treatment emergent AEs leading to discontinuation of IP are TEAEs leading to complete discontinuation of AMG 334 regardless of CHU IP or parent study IP.
Grading categories determined using CTCAE version 4.03.

[redacted]

5.3　薬物相互作用

エレヌマブはモノクローナル抗体でありサイトカイン調節物質ではないため、併用する低分子薬との間に薬物相互作用は予測されない。エレヌマブの薬力学又は薬物動態的相互作用の可能性を検討するため、2つの試験が実施された。

20140255試験は、血圧上昇がスマトリプタンの静脈内投与の既知のリスクであることと、エレヌマブによりCGRPの血管拡張作用を抑制することを踏まえ、併用により相加作用又は相乗作用が生じる可能性を検討した。その結果、スマトリプタンを単独で投与した被験者とスマトリプタンとエレヌマブを併用投与した被験者の間に、血圧への作用を含む安全性に臨床的に意味のある差は認められず、またエレヌマブはスマトリプタンの薬物動態に影響を与えなかった（モジュール2.7.6　7項）。

片頭痛患者の大半は妊娠可能年齢の女性と予測されることから、20150334試験ではエレヌマブと一般的に使用される経口避妊薬（エストロゲン及びプロゲスチン配合）を併用したときの薬物相互

作用を検討した。エレヌマブは経口避妊薬の有効成分の薬物動態に影響を与えなかった（モジュール2.7.6　8項）。

5.4　妊娠及び授乳時の使用

妊娠及び授乳時のエレヌマブの使用を検討した臨床試験は実施していない。

動物での生殖試験において、サルに器官形成期から分娩までエレヌマブを投与したところ、ヒトでの最大推奨用量である月に1回140 mgで投与したときの17倍までの曝露量では、出生児及び授乳期のサルの成長に影響はみられなかった。測定可能なエレヌマブの血清中濃度が出生児に認められたことから、エレヌマブが他の免疫グロブリン抗体と同様に胎盤関門を通過することが確認された。カニクイザルを用いた拡充型出生前及び出生後発生毒性試験では、母体毒性は認められず、胎児若しくは出生児の死亡、又は出生後6カ月までの成長及び発達に影響はないことが示された（モジュール2.6.6　1項）。エレヌマブの授乳又は乳汁産生への影響について検討したデータはない。

20120309試験及び20170609試験並びに海外試験では、妊娠中又は授乳中の女性は試験から除外されたため、臨床試験から得られた妊娠に関する情報は限られている。20[redacted]年[redacted]月[redacted]日時点で、国内及び海外臨床試験、並びに海外で報告された臨床試験以外の情報より合計243例が妊娠前又は妊娠中にエレヌマブに曝露された。なお、比較対照による臨床試験でエレヌマブを投与されていなかったことが判明した被験者は集計に含めていない。また、エレヌマブに曝露された母親から授乳された乳児は7例であった（モジュール5.3.6）。以下に、国内及び海外臨床試験、並びに海外で報告された臨床試験以外の情報からの妊娠及び転帰、並びに授乳に関する報告を示す。

5.4.1　妊娠時の使用

5.4.1.1　臨床試験

エレヌマブ又は盲検下の治験薬に曝露された妊娠に関する出生転帰を表 54に示す。国内及び海外臨床試験において、2019年11月16日時点で合計44例が妊娠前又は妊娠中にエレヌマブ又は盲検下の治験薬に曝露された。

母性曝露は38件、父性曝露は7件であった。このうち自然流産は4件であった。1件目は8年前に子宮内膜アブレーションの施行歴があり、生命保続可能性のない胎児の妊娠であった。2件目は4[redacted]歳の高齢妊娠であり、3件目は自然流産の前日に母親が他界したことからストレスと関連があると考えられた。4件目は情報不足のため、評価できなかった。

表 54　臨床試験でエレヌマブ又は盲検下の治験薬に曝露された妊娠に関する出生転帰（20[redacted]年[redacted]月[redacted]日から20[redacted]年[redacted]月[redacted]日までの累積）

Birth Outcomes	Maternal Exposures	Paternal Exposures
Term without complication	7	0
Live birth, normal	3	3
Full term delivery NOS	2[a]	0
Delivered NOS	0	1
Preterm birth without complications	1	1
Preterm birth NOS	1	0
Elective termination NOS	5	0
Spontaneous abortion NOS	4	0
Lost to follow-up	11	2
Unknown[b]	4	0
Total	38[a]	7

NOS = not otherwise specified

[a] Includes 1 case with twin outcome.

[b] Follow-up is pending or delivery is anticipated after the reporting period.

国内の20120309試験及び20170609試験では、20[redacted]年[redacted]月[redacted]日時点で4例（母性曝露が3例、父性曝露が1例）が妊娠前又は妊娠中にエレヌマブに曝露された。以下に4例の詳細を示す。

- 3[redacted]歳（登録時）の女性で、二重盲検投与期にプラセボ、非盲検投与期にエレヌマブ70 mg及び140 mgが投与された。エレヌマブの最終投与日はDay 669であった。Day 772にグレード2、非重篤の切迫流産が発現した。本事象は治験薬との関連なしと判断された。
- 4[redacted]歳の女性で、二重盲検投与期にエレヌマブ28 mg、非盲検投与期にエレヌマブ70 mgが投与された。エレヌマブの最終投与日はDay 670であった。Day 784に安全性追跡調査の血液検査にて妊娠陽性であることが判明した。Day 826に妊娠11週の検診にて胎児が8週の大きさで死亡していたことが判明し、稽留流産と診断された。本事象は治験薬との関連があるかもしれないと判断された。
- パートナーが本試験に参加した3[redacted]歳の女性で、妊娠し、出産した（妊娠／出産日不明）。パートナーは二重盲検投与期にプラセボ、非盲検投与期にエレヌマブ140 mgが投与された。出生児に合併症、医学的問題又は先天異常は認められていない。
- 3[redacted]歳の女性で、二重盲検投与期にエレヌマブ70 mgを受け、妊娠した（妊娠日不明）。エレヌマブの最終投与日はDay 223であった。本被験者はエレヌマブの投与を中止した。出生転帰は不明である。

5.4.1.2　臨床試験以外

海外で報告された臨床試験以外でエレヌマブに曝露された妊娠に関する出生転帰を表 55に示す。20[redacted]年[redacted]月[redacted]日時点で合計199例が妊娠前又は妊娠中にエレヌマブに曝露された。

母性曝露は200件で、父性曝露の報告はなかった。これらのうち、先天異常を伴った自然流産が1件、4[redacted]歳の高齢妊娠患者で発現した。

当該患者は不妊の病歴があり、2回の卵細胞質内精子注入法を不特定時期に受けていた。受胎前の最後の月経期間は報告されていない。エレヌマブは妊娠3週と6日での投与を最後に、妊娠のため中止された。併用薬としてQlaira（吉草酸エストラジオール及びジエノゲスト）及びイブプロフェンを服薬していたが、受胎の1週間前はQlairaの服薬を再開していなかった。妊娠6週と1日目、超音波検

査で胎児の心臓の活動を確認できなかったため、自然流産と診断された。妊娠10週で堕胎手術を行い、遺伝子診断により胎児の遊離15トリソミーが流産の原因になったと示された。当該患者は潜在性甲状腺機能低下症であるとも診断された。

その他自然流産は21件報告され、これらのうちリスク因子を有していたのは、高齢妊娠5件、不明の理由による治療的堕胎歴あり1件、先天異常のリスクのある併用薬の摂取2件、受胎困難の病歴、並びに流産及び早産の家族歴があり、多くの併用薬を摂取及び合併症あり1件、病歴及び産科歴は不明だが、経口避妊薬を服薬しているにも関わらずエレヌマブを開始してから自然流産を2回経験1例（2件）であった。その他の自然流産については十分な情報は得られていない。

表 55　臨床試験以外でエレヌマブに曝露された妊娠に関する出生転帰
（20[redacted]年[redacted]月[redacted]日から20[redacted]年[redacted]月[redacted]日までの累積）

Birth Outcomes	Maternal Exposures	Paternal Exposures
Delivered NOS	3	0
Live birth NOS	2	0
Live birth, normal	1	0
Preterm birth with complications	1	0
Preterm birth NOS	1	0
Spontaneous abortion NOS	21	0
Spontaneous abortion with congenital anomaly	1	0
Lost to follow-up	101[a]	0
Unknown[b]	69[a]	0
Total	200[a]	0

NOS = not otherwise specified

[a] Includes 1 case with twin outcome.

[b] Follow-up is pending or delivery is anticipated after the reporting period.

5.4.2　授乳時の使用

国内及び海外臨床試験において、20[redacted]年[redacted]月[redacted]日時点でエレヌマブに曝露された母親から授乳された乳児はいなかった。国内20120309試験及び20170609試験では、20[redacted]年[redacted]月[redacted]日時点でエレヌマブに曝露された母親から授乳された乳児の報告はなかった。

海外で報告された臨床試験以外で、エレヌマブに曝露された母親から授乳された乳児は7例であった。これらのうち6例では有害事象は報告されていない。1例の乳児において、重篤な有害事象として乳児の栄養摂取不良（医師記載用語：ミルクを飲むのを拒む）が発現した。エレヌマブの曝露期間及び本事象の転帰は不明であった。

以上より、報告された妊娠及び授乳の例数では、妊娠及び授乳に対するエレヌマブの影響について結論を導き出すには不十分であるが、これまでの報告に基づくと、安全性についての懸念事項は認められていない。

5.5　過量投与

20120309試験及び20170609試験において過量投与は報告されなかった。なお、20170609試験では、自殺又は自傷を意図したと考えられる企図的過量投与でない限り、過量投与は有害事象又は重

篤な有害事象として報告されなかった。20120309試験では、過量投与の報告に関して治験実施計画書において特定の規定は定めていなかった。

海外試験においても過量投与が報告された被験者はいなかった。臨床試験で投与されたエレヌマブの最高用量は、20101268試験（第I相）で健康被験者に投与した280 mgの単回皮下投与（Day 1）に続いて、210 mgの2回皮下投与（Day 29及び57）を実施した混合レジメンであった。この用量において、重篤な有害事象又は用量制限毒性は認められなかった（モジュール2.7.6　6項）。

5.6　薬物乱用

エレヌマブの作用機序や、中枢神経系において影響のある曝露量に達しないことを踏まえると、エレヌマブに乱用又は依存の可能性は想定されない（Boado et al, 2010; Pardridge, 2007）。他の抗体と同様、エレヌマブの一部は血液脳関門を通過する可能性があるが、中枢での濃度は血中濃度の0.3%以下と低く、中枢への影響は低いと考えられる（St Amour et al, 2013; Watts and Dennis, 2013; Poduslo et al, 1994; Triguero et al, 1989; Jones and Shusta, 2007; Frank et al, 2011; Yu and Watts, 2013）。カニクイザルの脳脊髄液中のエレヌマブ濃度は血清中濃度の0.1%未満であった。動物を使った試験では、テレメトリー装着カニクイザルの試験、反復投与毒性試験、又は140 mgの4週に1回投与での定常状態時のヒトでのC_{max}の38倍、88倍及び3.4倍までの曝露による試験において、神経行動学的作用は認められていない（モジュール2.4　5.7.4項）。エレヌマブに薬物乱用又は誤用の可能性があることを示すエビデンスはなく、観察された例もないことから、依存性に関する非臨床試験は実施していない。加えて、薬効薬理及び副次的薬理を含む文献から総合的に判断すると、CGRPとその受容体に鎮静、多幸症、知覚及びその他の認知のゆがみ、幻覚並びに気分変化等の乱用のおそれにつながるとみなされる正の向精神作用はないとされる。

20120309試験及び20170609試験において、薬物乱用及び薬物乱用を示唆する有害事象は報告されなかった。また、海外試験においても、報告された有害事象の性質及び頻度から乱用の可能性を示唆する所見は認められなかった。

5.7　離脱症状及び反跳現象

離脱症状及び反跳現象を検討した臨床試験は実施していない。20120309試験及び20170609試験において、離脱症状又は反跳現象、及びこれらを示唆する有害事象は報告されなかった。また、海外試験においてもこれらを示唆する所見は認めらなかった。

5.8　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

エレヌマブは自動車運転若しくは機械操作能力に影響、又は精神機能に障害を及ぼす可能性はないと考えられる。非臨床試験では中枢神経系、協調又は眼に関連する有害作用は認められなかった（5.6項参照）。20120309試験及び20170609試験において、自動車運転若しくは機械操作能力に影響、又は精神機能に障害を及ぼす可能性のある神経学的又は精神学的事象は報告されなかった。また、海外試験においてもこれらを示唆する所見は認めらなかった。

6. 市販後データ

エレヌマブは米国、欧州連合（EU）及びその他の多くの国で成人の片頭痛予防薬として承認されており、承認用法・用量は70 mg又は140 mgの月1回投与である。

Amgen社はNovartis社とエレヌマブを共同開発し、Amgen社が米国及び日本での、Novartis社がEU及びその他の国での製造販売権を有している。Amgen社はグローバル安全性データベースの所有者であり、定期的ベネフィット・リスク評価報告（PBRER）/定期的安全性最新報告（PSUR）には両社からの情報が統合されている。

Amgen社とNovartis社での推定曝露量及び情報量の計算には異なる手法が用いられており、それぞれを別々に示す。エレヌマブの国際誕生日（2018年5月17日）から20[redacted]年[redacted]月[redacted]日（PBRER/PSUR No.3）までの市販後におけるエレヌマブの推定曝露量は、Amgen社の販売地域で203605人年であり、Novartis社の販売地域で22478人年である（モジュール5.3.6）。

20[redacted]年[redacted]月[redacted]日現在、Amgen社が受領した医学的に確認された又は未確認の副作用の自発報告は累積で計29220件である。このうち2278件が重篤な副作用であり、26942件が非重篤な副作用であった。また、20[redacted]年[redacted]月[redacted]日の時点でAmgen社が非介入市販後試験及びその他の非自発的な情報源から受領した重篤な副作用は累積で計2287件である。

自発報告及び非介入試験／非自発的な情報源から得られた重篤な副作用情報（それぞれ2278件及び2287件、以下同順）のうち、比較的高い頻度で報告された副作用の器官別大分類は神経系障害（485件及び515件）、胃腸障害（289件及び288件）、一般・全身障害および投与部位の状態（246件及び250件）、精神障害（215件及び162件）であった。自発報告及び非介入試験／非自発的な情報源からの重篤な副作用報告は、エレヌマブの既知の安全性プロファイルと一致しているか、原疾患に特徴的なものであった。

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8. 付録

8.1 SMQ又はAMQを構成する検索用語

SMQ and AMQ Search Terms (MedDRA ver.22.1)

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Acquired C1 inhibitor deficiency	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Acute respiratory failure	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Allergic oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Anaphylactic reaction	22.1	Narrow
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Anaphylactic shock	22.1	Narrow
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Anaphylactic transfusion reaction	22.1	Narrow
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Anaphylactoid reaction	22.1	Narrow
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Anaphylactoid shock	22.1	Narrow
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Angioedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Asthma	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Blood pressure decreased	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Blood pressure diastolic decreased	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Blood pressure systolic decreased	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Bronchial oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Bronchospasm	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Cardiac arrest	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Cardio-respiratory arrest	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Cardio-respiratory distress	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Cardiovascular insufficiency	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Chest discomfort	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Choking	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Choking sensation	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Circulatory collapse	22.1	Narrow
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Circumoral oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Circumoral swelling	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Cough	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Cyanosis	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Dialysis membrane reaction	22.1	Narrow
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Diastolic hypotension	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Dyspnoea	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Erythema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Eye oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Eye pruritus	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Eye swelling	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Eyelid oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Face oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Flushing	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Hereditary angioedema with C1 esterase inhibitor deficiency	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Hyperventilation	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Hypotension	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Injection site urticaria	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Irregular breathing	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Kounis syndrome	22.1	Narrow
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Laryngeal dyspnoea	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Laryngeal oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Laryngospasm	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Laryngotracheal oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Lip oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Lip swelling	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Mouth swelling	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Nasal obstruction	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Nodular rash	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Ocular hyperaemia	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Oedema blister	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Oedema mouth	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Oropharyngeal oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Oropharyngeal spasm	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Oropharyngeal swelling	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Periorbital oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Periorbital swelling	22.1	Broad

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Pharyngeal oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Pharyngeal swelling	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Procedural shock	22.1	Narrow
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Pruritus	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Pruritus allergic	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Rash	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Rash erythematous	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Rash pruritic	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Respiratory arrest	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Respiratory distress	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Respiratory failure	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Reversible airways obstruction	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Sensation of foreign body	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Shock	22.1	Narrow
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Shock symptom	22.1	Narrow
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Skin swelling	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Sneezing	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Stridor	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Swelling	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Swelling face	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Swelling of eyelid	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Swollen tongue	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Tachypnoea	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Throat tightness	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Tongue oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Tracheal obstruction	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Tracheal oedema	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Type I hypersensitivity	22.1	Narrow
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Upper airway obstruction	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Urticaria	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Urticaria papular	22.1	Broad
Anaphylactic reaction	Anaphylactic reaction (SMQ)	Wheezing	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Abdominal distension	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Abnormal faeces	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Anal stenosis	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Anorectal discomfort	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Anorectal stenosis	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Autonomic failure syndrome	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Barium impaction	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Bowel movement irregularity	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Change of bowel habit	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Colonic lavage	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Constipation	22.1	Narrow
Constipation - erenumab	Constipation - erenumab (EOI)	Defaecation disorder	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Diabetic gastroparesis	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Distal intestinal obstruction syndrome	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Enteric neuropathy	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Faecal disimpaction	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Faecal volume decreased	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Faecal vomiting	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Faecalith	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Faecaloma	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Faeces hard	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Fixed bowel loop	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Flatulence	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Gallstone ileus	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Gastrointestinal hypomotility	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Gastrointestinal motility disorder	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Gastrointestinal obstruction	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Gastrointestinal pain	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Gastrointestinal sounds abnormal	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Hollow visceral myopathy	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Ileus	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Ileus paralytic	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Ileus spastic	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Infrequent bowel movements	22.1	Narrow
Constipation - erenumab	Constipation - erenumab (EOI)	Intestinal dilatation	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Intestinal neuronal dysplasia	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Intestinal obstruction	22.1	Broad

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Constipation - erenumab	Constipation - erenumab (EOI)	Intestinal pseudo-obstruction	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Intestinal stenosis	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Large intestinal obstruction	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Large intestinal obstruction reduction	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Large intestinal stenosis	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Laxative supportive care	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Mechanical ileus	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Necrotising colitis	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Neonatal intestinal dilatation	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Obstructive defaecation	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Post procedural constipation	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Postoperative ileus	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Rectal obstruction	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Rectal stenosis	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Subileus	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Volvulus	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Volvulus of small bowel	22.1	Broad
Constipation - erenumab	Constipation - erenumab (EOI)	Volvulus repair	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Acquired C1 inhibitor deficiency	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Acute generalised exanthematous pustulosis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Acute respiratory failure	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Administration related reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Administration site dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Administration site eczema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Administration site hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Administration site photosensitivity reaction	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Administration site rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Administration site recall reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Administration site urticaria	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Administration site vasculitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Airway remodelling	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Allergic bronchitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic colitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic cough	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic cystitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic eosinophilia	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic gastroenteritis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic hepatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic keratitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic otitis externa	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic otitis media	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic pharyngitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic reaction to excipient	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic respiratory disease	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic respiratory symptom	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic sinusitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic stomatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergic transfusion reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergy alert test positive	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergy test positive	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergy to chemicals	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Allergy to fermented products	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Allergy to immunoglobulin therapy	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergy to surgical sutures	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Allergy to vaccine	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Alpha tumour necrosis factor increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Alveolitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Anal eczema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Anaphylactic reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Anaphylactic shock	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Anaphylactic transfusion reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Anaphylactoid reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Anaphylactoid shock	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Anaphylaxis treatment	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Angioedema	22.1	Narrow

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Hypersensitivity	Hypersensitivity (SMQ)	Anti-insulin antibody increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Anti-insulin antibody positive	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Anti-insulin receptor antibody increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Anti-insulin receptor antibody positive	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Anti-neutrophil cytoplasmic antibody positive vasculitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Antiallergic therapy	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Antibody test abnormal	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Antibody test positive	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Antiendomysial antibody positive	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Application site dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Application site eczema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Application site hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Application site photosensitivity reaction	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Application site rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Application site recall reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Application site urticaria	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Application site vasculitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Arthritis allergic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Aspirin-exacerbated respiratory disease	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Asthma	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Asthma late onset	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Asthma-chronic obstructive pulmonary disease overlap syndrome	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Asthmatic crisis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Atopic cough	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Atopy	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Auricular swelling	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Blepharitis allergic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Blister	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Blister rupture	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Blood immunoglobulin A abnormal	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Blood immunoglobulin A increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Blood immunoglobulin D increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Blood immunoglobulin E abnormal	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Blood immunoglobulin E increased	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Blood immunoglobulin G abnormal	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Blood immunoglobulin G increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Blood immunoglobulin M abnormal	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Blood immunoglobulin M increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Bromoderma	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Bronchial hyperreactivity	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Bronchial oedema	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Bronchospasm	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Bullous impetigo	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Caffeine allergy	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Capillaritis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Catheter site dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Catheter site eczema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Catheter site hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Catheter site rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Catheter site urticaria	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Catheter site vasculitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Charcot-Leyden crystals	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Cheilitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Childhood asthma	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Choking	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Choking sensation	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Chronic eosinophilic rhinosinusitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Chronic hyperplastic eosinophilic sinusitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Circulatory collapse	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Circumoral oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Circumoral swelling	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Complement factor C1 decreased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Complement factor C2 decreased	22.1	Broad

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Hypersensitivity	Hypersensitivity (SMQ)	Complement factor C3 decreased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Complement factor C4 decreased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Complement factor decreased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Conjunctival oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Conjunctivitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Conjunctivitis allergic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Contact stomatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Contrast media allergy	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Contrast media reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Corneal exfoliation	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Corneal oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Cutaneous vasculitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Cytokine release syndrome	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Cytokine storm	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Dennie-Morgan fold	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Dermatitis acneiform	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Dermatitis allergic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Dermatitis atopic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Dermatitis bullous	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Dermatitis contact	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Dermatitis exfoliative	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Dermatitis exfoliative generalised	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Dermatitis herpetiformis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Dermatitis infected	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Dermatitis psoriasiform	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Device allergy	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Dialysis membrane reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Distributive shock	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Documented hypersensitivity to administered product	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Drug eruption	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Drug hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Drug provocation test	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Drug reaction with eosinophilia and systemic symptoms	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Ear swelling	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Eczema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Eczema infantile	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Eczema nummular	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Eczema vaccinatum	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Eczema vesicular	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Eczema weeping	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Encephalitis allergic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Encephalopathy allergic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Eosinophil count abnormal	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Eosinophil count increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Eosinophil percentage abnormal	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Eosinophil percentage increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Eosinophilia	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Eosinophilia myalgia syndrome	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Eosinophilic bronchitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Eosinophilic granulomatosis with polyangiitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Eosinophilic oesophagitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Eosinophilic pneumonia	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Eosinophilic pneumonia acute	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Eosinophilic pneumonia chronic	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Epidermal necrosis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Epidermolysis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Epidermolysis bullosa	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Epiglottic oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Erythema	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Erythema multiforme	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Erythema nodosum	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Exfoliative rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Eye allergy	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Eye oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Eye swelling	22.1	Narrow

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Hypersensitivity	Hypersensitivity (SMQ)	Eyelid oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Face oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Fixed eruption	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Flushing	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Gastrointestinal oedema	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Generalised oedema	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Genital rash	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Genital swelling	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Giant papillary conjunctivitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Gingival oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Gingival swelling	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Gleich's syndrome	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	HLA marker study positive	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Haemolytic transfusion reaction	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Haemorrhagic urticaria	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Hand dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Henoch-Schonlein purpura	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Henoch-Schonlein purpura nephritis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Heparin-induced thrombocytopenia	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Hereditary angioedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Hereditary angioedema with C1 esterase inhibitor deficiency	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Human anti-hamster antibody increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Human anti-hamster antibody positive	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Hypersensitivity myocarditis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Hypersensitivity pneumonitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Hypersensitivity vasculitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Idiopathic urticaria	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Immediate post-injection reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Immune complex level increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Immune thrombocytopenic purpura	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Immune tolerance induction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Immunoglobulins abnormal	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Immunoglobulins increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Immunology test abnormal	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Implant site dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Implant site hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Implant site photosensitivity	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Implant site rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Implant site urticaria	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Incision site dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Incision site rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Infusion related hypersensitivity reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Infusion related reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Infusion site dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Infusion site eczema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Infusion site hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Infusion site photosensitivity reaction	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Infusion site rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Infusion site recall reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Infusion site urticaria	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Infusion site vasculitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Injection related reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Injection site dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Injection site eczema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Injection site hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Injection site panniculitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Injection site photosensitivity reaction	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Injection site rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Injection site recall reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Injection site urticaria	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Injection site vasculitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Instillation site hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Instillation site rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Instillation site urticaria	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Interstitial granulomatous dermatitis	22.1	Narrow

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Hypersensitivity	Hypersensitivity (SMQ)	Interstitial lung disease	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Intestinal angioedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Iodine allergy	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Kaposi's varicelliform eruption	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Kounis syndrome	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Laryngeal dyspnoea	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Laryngeal obstruction	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Laryngeal oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Laryngitis allergic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Laryngospasm	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Laryngotracheal oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Leukotriene increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Limbal swelling	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Lip exfoliation	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Lip oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Lip swelling	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Localised oedema	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Macrophage inflammatory protein 1-alpha increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Mast cell degranulation present	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Mechanical urticaria	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Medical device site dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Medical device site eczema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Medical device site hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Medical device site photosensitivity reaction	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Medical device site rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Medical device site recall reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Medical device site urticaria	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Mesenteric panniculitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Monocyte chemotactic protein-2 increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Mouth swelling	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Mouth ulceration	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Mucocutaneous rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Mucocutaneous ulceration	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Mucosa vesicle	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Mucosal erosion	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Mucosal exfoliation	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Mucosal necrosis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Mucosal ulceration	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Multiple allergies	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Nasal crease	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Necrotising panniculitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Nephritis allergic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Neurodermatitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Neutralising antibodies positive	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Nikolsky's sign	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Nodular rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Non-neutralising antibodies positive	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Noninfective conjunctivitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Occupational asthma	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Occupational dermatitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Oculomucocutaneous syndrome	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Oculorespiratory syndrome	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Oedema mouth	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Oedema mucosal	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Oral allergy syndrome	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Oral mucosal exfoliation	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Orbital oedema	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Oropharyngeal blistering	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Oropharyngeal oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Oropharyngeal spasm	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Oropharyngeal swelling	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Palatal oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Palatal swelling	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Palisaded neutrophilic granulomatous dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Palpable purpura	22.1	Narrow

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Hypersensitivity	Hypersensitivity (SMQ)	Panniculitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Pathergy reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Penile exfoliation	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Penile oedema	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Penile rash	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Penile swelling	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Perineal rash	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Perioral dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Periorbital oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Periorbital swelling	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Perivascular dermatitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Pharyngeal oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Pharyngeal swelling	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Photosensitivity reaction	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Pneumonitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Procedural shock	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Prurigo	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Pruritus	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Pruritus allergic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Pulmonary eosinophilia	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Radioallergosorbent test positive	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash erythematous	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash follicular	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash macular	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash maculo-papular	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash maculovesicular	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash morbilliform	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash neonatal	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash papulosquamous	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash pruritic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash pustular	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash rubelliform	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash scarlatiniform	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rash vesicular	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Reaction to azo-dyes	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Reaction to colouring	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Reaction to excipient	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Reaction to food additive	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Reaction to preservatives	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Reactive airways dysfunction syndrome	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Red man syndrome	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Respiratory arrest	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Respiratory distress	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Respiratory failure	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Respiratory tract oedema	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Reversible airways obstruction	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Rhinitis allergic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Rhinitis perennial	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	SJS-TEN overlap	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Scleral oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Scleritis allergic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Scrotal eczema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Scrotal exfoliation	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Scrotal oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Scrotal swelling	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Seasonal allergy	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Septal panniculitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Serum sickness	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Serum sickness-like reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Shock	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Shock symptom	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Skin erosion	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Skin exfoliation	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Skin necrosis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Skin oedema	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Skin reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Skin swelling	22.1	Broad

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Hypersensitivity	Hypersensitivity (SMQ)	Skin test positive	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Sneezing	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Solar urticaria	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Solvent sensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Status asthmaticus	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Stevens-Johnson syndrome	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Stoma site hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Stoma site rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Stomatitis	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Streptokinase antibody increased	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Stridor	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Suffocation feeling	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Swelling face	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Swelling of eyelid	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Swollen tongue	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Symmetrical drug-related intertriginous and flexural exanthema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Therapeutic product cross-reactivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Throat tightness	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Tongue exfoliation	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Tongue oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Toxic epidermal necrolysis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Toxic skin eruption	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Tracheal obstruction	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Tracheal oedema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Tracheostomy	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Transplantation associated food allergy	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Type I hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Type II hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Type III immune complex mediated reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Type IV hypersensitivity reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Upper airway obstruction	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Urticaria	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Urticaria cholinergic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Urticaria chronic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Urticaria contact	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Urticaria papular	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Urticaria physical	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Urticaria pigmentosa	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Urticaria vesiculosa	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Urticarial dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Urticarial vasculitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vaccination site dermatitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vaccination site eczema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vaccination site exfoliation	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vaccination site hypersensitivity	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vaccination site photosensitivity reaction	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Vaccination site rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vaccination site recall reaction	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vaccination site urticaria	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vaccination site vasculitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vaccination site vesicles	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vaginal exfoliation	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vaginal oedema	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Vaginal ulceration	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vasculitic rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vernal keratoconjunctivitis	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vessel puncture site rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vessel puncture site vesicles	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Visceral oedema	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Vulval eczema	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vulval oedema	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Vulval ulceration	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vulvovaginal rash	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Vulvovaginal swelling	22.1	Broad
Hypersensitivity	Hypersensitivity (SMQ)	Vulvovaginal ulceration	22.1	Narrow

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Hypersensitivity	Hypersensitivity (SMQ)	Vulvovaginitis allergic	22.1	Narrow
Hypersensitivity	Hypersensitivity (SMQ)	Wheezing	22.1	Broad
Hypertension	Hypertension (SMQ)	Accelerated hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Aldosterone urine abnormal	22.1	Broad
Hypertension	Hypertension (SMQ)	Aldosterone urine increased	22.1	Broad
Hypertension	Hypertension (SMQ)	Angiotensin I increased	22.1	Broad
Hypertension	Hypertension (SMQ)	Angiotensin II increased	22.1	Broad
Hypertension	Hypertension (SMQ)	Angiotensin II receptor type 1 antibody positive	22.1	Broad
Hypertension	Hypertension (SMQ)	Angiotensin converting enzyme increased	22.1	Broad
Hypertension	Hypertension (SMQ)	Blood aldosterone abnormal	22.1	Broad
Hypertension	Hypertension (SMQ)	Blood aldosterone increased	22.1	Broad
Hypertension	Hypertension (SMQ)	Blood catecholamines abnormal	22.1	Broad
Hypertension	Hypertension (SMQ)	Blood catecholamines increased	22.1	Broad
Hypertension	Hypertension (SMQ)	Blood pressure abnormal	22.1	Broad
Hypertension	Hypertension (SMQ)	Blood pressure ambulatory abnormal	22.1	Broad
Hypertension	Hypertension (SMQ)	Blood pressure ambulatory increased	22.1	Narrow
Hypertension	Hypertension (SMQ)	Blood pressure diastolic abnormal	22.1	Broad
Hypertension	Hypertension (SMQ)	Blood pressure diastolic increased	22.1	Narrow
Hypertension	Hypertension (SMQ)	Blood pressure fluctuation	22.1	Broad
Hypertension	Hypertension (SMQ)	Blood pressure inadequately controlled	22.1	Narrow
Hypertension	Hypertension (SMQ)	Blood pressure increased	22.1	Narrow
Hypertension	Hypertension (SMQ)	Blood pressure management	22.1	Narrow
Hypertension	Hypertension (SMQ)	Blood pressure orthostatic abnormal	22.1	Broad
Hypertension	Hypertension (SMQ)	Blood pressure orthostatic increased	22.1	Narrow
Hypertension	Hypertension (SMQ)	Blood pressure systolic abnormal	22.1	Broad
Hypertension	Hypertension (SMQ)	Blood pressure systolic increased	22.1	Narrow
Hypertension	Hypertension (SMQ)	Cardiometabolic syndrome	22.1	Narrow
Hypertension	Hypertension (SMQ)	Catecholamine crisis	22.1	Narrow
Hypertension	Hypertension (SMQ)	Catecholamines urine abnormal	22.1	Broad
Hypertension	Hypertension (SMQ)	Catecholamines urine increased	22.1	Broad
Hypertension	Hypertension (SMQ)	Diastolic hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Diuretic therapy	22.1	Broad
Hypertension	Hypertension (SMQ)	Eclampsia	22.1	Narrow
Hypertension	Hypertension (SMQ)	Ectopic aldosterone secretion	22.1	Broad
Hypertension	Hypertension (SMQ)	Ectopic renin secretion	22.1	Broad
Hypertension	Hypertension (SMQ)	Endocrine hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Epinephrine abnormal	22.1	Broad
Hypertension	Hypertension (SMQ)	Epinephrine increased	22.1	Broad
Hypertension	Hypertension (SMQ)	Essential hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Gestational hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	HELLP syndrome	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hyperaldosteronism	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hypertension neonatal	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hypertensive angiopathy	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hypertensive cardiomegaly	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hypertensive cardiomyopathy	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hypertensive cerebrovascular disease	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hypertensive crisis	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hypertensive emergency	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hypertensive encephalopathy	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hypertensive end-organ damage	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hypertensive heart disease	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hypertensive nephropathy	22.1	Narrow
Hypertension	Hypertension (SMQ)	Hypertensive urgency	22.1	Narrow
Hypertension	Hypertension (SMQ)	Labile blood pressure	22.1	Broad
Hypertension	Hypertension (SMQ)	Labile hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Malignant hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Malignant hypertensive heart disease	22.1	Narrow
Hypertension	Hypertension (SMQ)	Malignant renal hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Maternal hypertension affecting foetus	22.1	Narrow
Hypertension	Hypertension (SMQ)	Mean arterial pressure increased	22.1	Narrow
Hypertension	Hypertension (SMQ)	Metanephrine urine abnormal	22.1	Broad
Hypertension	Hypertension (SMQ)	Metanephrine urine increased	22.1	Broad
Hypertension	Hypertension (SMQ)	Neurogenic hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Non-dipping	22.1	Broad

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Hypertension	Hypertension (SMQ)	Norepinephrine abnormal	22.1	Broad
Hypertension	Hypertension (SMQ)	Norepinephrine increased	22.1	Broad
Hypertension	Hypertension (SMQ)	Normetanephrine urine increased	22.1	Broad
Hypertension	Hypertension (SMQ)	Orthostatic hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Page kidney	22.1	Narrow
Hypertension	Hypertension (SMQ)	Postoperative hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Pre-eclampsia	22.1	Narrow
Hypertension	Hypertension (SMQ)	Prehypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Procedural hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Pseudoaldosteronism	22.1	Broad
Hypertension	Hypertension (SMQ)	Renal hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Renal sympathetic nerve ablation	22.1	Narrow
Hypertension	Hypertension (SMQ)	Renin abnormal	22.1	Broad
Hypertension	Hypertension (SMQ)	Renin increased	22.1	Broad
Hypertension	Hypertension (SMQ)	Renin-angiotensin system inhibition	22.1	Broad
Hypertension	Hypertension (SMQ)	Renovascular hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Retinopathy hypertensive	22.1	Narrow
Hypertension	Hypertension (SMQ)	Secondary aldosteronism	22.1	Narrow
Hypertension	Hypertension (SMQ)	Secondary hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Supine hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Systolic hypertension	22.1	Narrow
Hypertension	Hypertension (SMQ)	Tyramine reaction	22.1	Broad
Hypertension	Hypertension (SMQ)	Withdrawal hypertension	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site abscess	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site abscess sterile	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site anaesthesia	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site atrophy	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site bruise	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site calcification	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site cellulitis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site coldness	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site cyst	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site dermatitis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site discharge	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site discolouration	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site discomfort	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site dryness	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site dysaesthesia	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site eczema	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site erosion	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site erythema	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site exfoliation	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site extravasation	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site fibrosis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site granuloma	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site haematoma	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site haemorrhage	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site hyperaesthesia	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site hypersensitivity	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site hypertrichosis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site hypertrophy	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site hypoaesthesia	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site indentation	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site induration	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site infection	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site inflammation	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site injury	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site irritation	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site ischaemia	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site joint discomfort	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site joint effusion	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site joint erythema	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site joint inflammation	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site joint movement impairment	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site joint pain	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site joint warmth	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site laceration	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site lymphadenopathy	22.1	Narrow

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Injection site reactions	Injection site reactions (EOI)	Administration site macule	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site mass	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site movement impairment	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site necrosis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site nerve damage	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site nodule	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site odour	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site oedema	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site pain	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site pallor	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site papule	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site paraesthesia	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site phlebitis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site photosensitivity reaction	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site plaque	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site pruritus	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site pustule	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site rash	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site reaction	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site recall reaction	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site scab	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site scar	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site streaking	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site swelling	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site thrombosis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site ulcer	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site urticaria	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site vasculitis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Administration site vesicles	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Embolia cutis medicamentosa	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injected limb mobility decreased	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection related reaction	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Injection site abscess	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site abscess sterile	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site alopecia	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Injection site anaesthesia	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site atrophy	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site bruising	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site calcification	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site cellulitis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site coldness	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site cyst	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site deformation	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site dermatitis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site discharge	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site discolouration	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site discomfort	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site dryness	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site dysaesthesia	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site eczema	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site erosion	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site erythema	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site exfoliation	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site extravasation	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site fibrosis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site granuloma	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Injection site haematoma	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site haemorrhage	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site hyperaesthesia	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site hypersensitivity	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site hypertrichosis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site hypertrophy	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site hypoaesthesia	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site indentation	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site induration	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site infection	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site inflammation	22.1	Narrow

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Injection site reactions	Injection site reactions (EOI)	Injection site injury	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site irritation	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site ischaemia	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site joint discomfort	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site joint effusion	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site joint erythema	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site joint infection	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site joint inflammation	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site joint movement impairment	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site joint pain	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site joint swelling	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site joint warmth	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site laceration	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site lymphadenopathy	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site macule	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site mass	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site movement impairment	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site necrosis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site nerve damage	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site nodule	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site oedema	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site pain	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site pallor	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site papule	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site paraesthesia	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site phlebitis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site photosensitivity reaction	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site plaque	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site pruritus	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site pustule	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site rash	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site reaction	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site recall reaction	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site scab	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site scar	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site streaking	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site swelling	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site telangiectasia	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site thrombosis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site ulcer	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site urticaria	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site vasculitis	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site vesicles	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Injection site warmth	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Malabsorption from injection site	22.1	Narrow
Injection site reactions	Injection site reactions (EOI)	Puncture site abscess	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Puncture site bruise	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Puncture site discharge	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Puncture site erythema	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Puncture site haematoma	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Puncture site haemorrhage	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Puncture site hernia	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Puncture site hypoaesthesia	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Puncture site induration	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Puncture site infection	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Puncture site oedema	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Puncture site pain	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Puncture site reaction	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Puncture site swelling	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Systemic leakage	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site anaesthesia	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site bruise	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site cellulitis	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site discharge	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site erythema	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site haematoma	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site haemorrhage	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site hypoaesthesia	22.1	Broad

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site induration	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site infection	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site inflammation	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site pain	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site paraesthesia	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site pruritus	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site reaction	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site swelling	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site thrombosis	22.1	Broad
Injection site reactions	Injection site reactions (EOI)	Vessel puncture site vesicles	22.1	Broad
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Amaurosis fugax	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Basal ganglia infarction	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Basal ganglia stroke	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Basilar artery occlusion	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Basilar artery stenosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Basilar artery thrombosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Brachiocephalic arteriosclerosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Brachiocephalic artery occlusion	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Brachiocephalic artery stenosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Brain hypoxia	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Brain stem embolism	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Brain stem infarction	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Brain stem ischaemia	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Brain stem stroke	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Brain stem thrombosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Brain stent insertion	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	CADASIL	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	CARASIL syndrome	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Capsular warning syndrome	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid angioplasty	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid arterial embolus	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid arteriosclerosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid artery bypass	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid artery disease	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid artery insufficiency	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid artery occlusion	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid artery restenosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid artery stenosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid artery stent insertion	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid artery stent removal	22.1	Narrow

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid artery thrombosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid endarterectomy	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Carotid revascularisation	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebellar artery occlusion	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebellar artery thrombosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebellar embolism	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebellar infarction	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebellar ischaemia	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebellar stroke	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral arteriosclerosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral artery embolism	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral artery occlusion	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral artery restenosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral artery stenosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral artery stent insertion	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral artery thrombosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral gas embolism	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral infarction	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral infarction foetal	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral ischaemia	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral microembolism	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral revascularisation	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral septic infarct	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral small vessel ischaemic disease	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral thrombosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral vascular occlusion	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral vasoconstriction	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebral venous thrombosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebrovascular accident	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebrovascular disorder	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebrovascular insufficiency	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Cerebrovascular stenosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Delayed ischaemic neurological deficit	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Embolic cerebral infarction	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Embolic stroke	22.1	Narrow

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Foville syndrome	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Hypoxic-ischaemic encephalopathy	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Inner ear infarction	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Ischaemic cerebral infarction	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Ischaemic stroke	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Jugular vein embolism	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Lacunar infarction	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Lacunar stroke	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Lateral medullary syndrome	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Migrainous infarction	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Millard-Gubler syndrome	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Moyamoya disease	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Perinatal stroke	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Post cardiac arrest syndrome	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Post procedural stroke	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Precerebral arteriosclerosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Precerebral artery occlusion	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Reversible cerebral vasoconstriction syndrome	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Reversible ischaemic neurological deficit	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Spinal artery embolism	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Spinal artery thrombosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Spinal cord infarction	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Spinal cord ischaemia	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Spinal stroke	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Stroke in evolution	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Subclavian steal syndrome	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Thalamic infarction	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Thrombotic cerebral infarction	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Thrombotic stroke	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Transient ischaemic attack	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Vascular encephalopathy	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Vascular stent occlusion	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Vascular stent stenosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Vertebral artery occlusion	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Vertebral artery stenosis	22.1	Narrow

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Vertebral artery thrombosis	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Vertebrobasilar insufficiency	22.1	Narrow
Ischaemic central nervous system vascular conditions	Ischaemic central nervous system vascular conditions (SMQ)	Vertebrobasilar stroke	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Acute cardiac event	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Acute coronary syndrome	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Acute myocardial infarction	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Angina pectoris	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Angina unstable	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Anginal equivalent	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Arteriogram coronary abnormal	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Arteriosclerosis coronary artery	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Arteriospasm coronary	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Blood creatine phosphokinase MB abnormal	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Blood creatine phosphokinase MB increased	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Blood creatine phosphokinase abnormal	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Blood creatine phosphokinase increased	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Cardiac stress test abnormal	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Cardiac ventricular scarring	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Cardiopulmonary exercise test abnormal	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Cardiovascular event prophylaxis	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Computerised tomogram coronary artery abnormal	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary angioplasty	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary arterial stent insertion	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary artery bypass	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary artery compression	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary artery disease	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary artery dissection	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary artery embolism	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary artery insufficiency	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary artery occlusion	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary artery reocclusion	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary artery restenosis	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary artery stenosis	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary artery surgery	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary artery thrombosis	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary brachytherapy	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary bypass stenosis	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary bypass thrombosis	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary endarterectomy	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary no-reflow phenomenon	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary ostial stenosis	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary revascularisation	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary vascular graft occlusion	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Coronary vascular graft stenosis	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Diabetic coronary microangiopathy	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	ECG electrically inactive area	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	ECG signs of myocardial infarction	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	ECG signs of myocardial ischaemia	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Elastic vessel recoil complication	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Electrocardiogram PR segment depression	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Electrocardiogram Q wave abnormal	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Electrocardiogram ST segment abnormal	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Electrocardiogram ST segment depression	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Electrocardiogram ST segment elevation	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Electrocardiogram ST-T segment abnormal	22.1	Broad

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Electrocardiogram ST-T segment depression	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Electrocardiogram ST-T segment elevation	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Electrocardiogram T wave abnormal	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Electrocardiogram T wave inversion	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Electrocardiogram U wave inversion	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Exercise electrocardiogram abnormal	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Exercise test abnormal	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	External counterpulsation	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Haemorrhage coronary artery	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Infarction	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Ischaemic cardiomyopathy	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Ischaemic mitral regurgitation	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Kounis syndrome	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Microvascular coronary artery disease	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Myocardial hypoperfusion	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Myocardial hypoxia	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Myocardial infarction	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Myocardial ischaemia	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Myocardial necrosis	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Myocardial necrosis marker increased	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Myocardial reperfusion injury	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Myocardial stunning	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Papillary muscle infarction	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Percutaneous coronary intervention	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Periprocedural myocardial infarction	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Post angioplasty restenosis	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Post procedural myocardial infarction	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Postinfarction angina	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Prinzmetal angina	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Restenosis	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Scan myocardial perfusion abnormal	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Silent myocardial infarction	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Stress cardiomyopathy	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Stress echocardiogram abnormal	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Subclavian coronary steal syndrome	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Subendocardial ischaemia	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Troponin I increased	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Troponin T increased	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Troponin increased	22.1	Narrow
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Vascular graft occlusion	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Vascular stent occlusion	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Vascular stent stenosis	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Vascular stent thrombosis	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Wall motion score index abnormal	22.1	Broad
Ischaemic heart disease	Ischaemic heart disease (SMQ)	Wellens' syndrome	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Abdominal bruit	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Aneurysm repair	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Aneurysmectomy	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Angiogram abnormal	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Angiogram peripheral abnormal	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Angioplasty	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Ankle brachial index decreased	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Aortic arteriosclerosis	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Aortic bruit	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterectomy	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterectomy with graft replacement	22.1	Broad

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial aneurysm repair	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial bruit	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial bypass operation	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial catheterisation	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial catheterisation abnormal	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial compression therapy	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial graft	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial occlusive disease	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial repair	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial restenosis	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial stenosis	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial stent insertion	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial therapeutic procedure	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arterial thrombosis	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arteriogram abnormal	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arteriosclerosis	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arteriosclerosis Moenckeberg-type	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Arteriosclerotic gangrene	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Atherectomy	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Atheroembolism	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Atrophie blanche	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Biopsy artery abnormal	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Biopsy blood vessel abnormal	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Blood pressure difference of extremities	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Blue toe syndrome	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Brachial pulse abnormal	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Brachial pulse decreased	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Brachial pulse increased	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Brachiocephalic arteriosclerosis	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Brachiocephalic artery occlusion	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Brachiocephalic artery stenosis	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Cyanosis	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Directional Doppler flow tests abnormal	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Dry gangrene	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Endarterectomy	22.1	Narrow

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Epidermal necrosis	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Erythrocyanosis	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Extremity necrosis	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Femoral artery aneurysm	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Femoral artery dissection	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Femoral bruit	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Femoral pulse abnormal	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Femoral pulse decreased	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Femoral pulse increased	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Gangrene	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Hypoaesthesia	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Iliac artery disease	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Iliac artery occlusion	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Iliac artery rupture	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Iliac bruit	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Intermittent claudication	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Ischaemic limb pain	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Ischaemic neuropathy	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Ischaemic skin ulcer	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Livedo reticularis	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Muscle necrosis	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Nail necrosis	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Necrosis ischaemic	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Necrosis of artery	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Neuropathy peripheral	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Paraesthesia	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Pedal pulse abnormal	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Pedal pulse decreased	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral arterial occlusive disease	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral arterial reocclusion	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral artery aneurysm	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral artery aneurysm rupture	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral artery angioplasty	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral artery bypass	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral artery dissection	22.1	Narrow

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral artery occlusion	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral artery restenosis	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral artery stenosis	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral artery stent insertion	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral artery thrombosis	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral coldness	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral endarterectomy	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral ischaemia	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral pulse decreased	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral revascularisation	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Peripheral vascular disorder	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Poor peripheral circulation	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Popliteal pulse abnormal	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Popliteal pulse decreased	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Popliteal pulse increased	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Pulse abnormal	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Pulse pressure abnormal	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Pulse pressure decreased	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Pulse pressure increased	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Pulse volume decreased	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Radial pulse abnormal	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Radial pulse decreased	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Radial pulse increased	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Raynaud's phenomenon	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Skin necrosis	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Skin ulcer	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Skin ulcer excision	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Soft tissue necrosis	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Subclavian artery aneurysm	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Subclavian artery occlusion	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Subclavian artery stenosis	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Subclavian artery thrombosis	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Temperature difference of extremities	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Thrombectomy	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Thromboangiitis obliterans	22.1	Narrow

EOI Standard Name	EOI Composition	MedDRA preferred term	MedDRA version of the EOI	EOI scope
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Thromboembolectomy	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Ultrasonic angiogram abnormal	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Ultrasound Doppler abnormal	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Vascular anastomosis	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Vascular graft	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Vascular operation	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Vascular shunt	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Vascular stent insertion	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Vascular stent removal	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Vascular stent stenosis	22.1	Broad
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Vasoconstriction	22.1	Narrow
Peripheral arterial disease (PAD)	Peripheral arterial disease (PAD) (EOI)	Wound necrosis	22.1	Broad

8.2 付録表

表 付録-1 全投与期の人口統計学的特性（J-ISS-2：安全性解析対象集団）

	AMG 334			
	70 mg QM only (N = 201)	140 mg QM only (N = 56)	70/140 mg QM (N = 213)	Combined (N = 470)
Sex - n (%)				
Male	30 (14.9)	8 (14.3)	36 (16.9)	74 (15.7)
Female	171 (85.1)	48 (85.7)	177 (83.1)	396 (84.3)
Age (years)				
n	201	56	213	470
Mean	43.4	44.7	44.4	44.0
SD	8.9	7.7	8.5	8.6
Median	43.0	45.0	45.0	45.0
Q1, Q3	38.0, 50.0	39.5, 49.0	40.0, 50.0	39.0, 50.0
Min, Max	22, 64	26, 61	20, 64	20, 64
Age group - n (%)				
< Median	109 (54.2)	25 (44.6)	100 (46.9)	234 (49.8)
≥ Median	92 (45.8)	31 (55.4)	113 (53.1)	236 (50.2)
Weight (kg)				
n	201	56	213	470
Mean	56.21	58.89	56.54	56.68
SD	10.86	13.18	9.93	10.77
Median	53.80	54.35	54.80	54.40
Q1, Q3	49.50, 61.40	49.80, 66.45	48.70, 62.00	49.10, 62.10
Min, Max	32.1, 102.0	40.1, 98.5	38.0, 99.7	32.1, 102.0
Weight group - n (%)				
< Median	105 (52.2)	28 (50.0)	100 (46.9)	233 (49.6)
≥ Median	96 (47.8)	28 (50.0)	113 (53.1)	237 (50.4)
Body mass index (BMI, kg/m^2)				
n	201	56	213	470
Mean	21.79	22.70	21.89	21.94
SD	3.34	4.48	3.36	3 51
Median	21.14	21.73	21.42	21.32
Q1, Q3	19.40, 23.62	19.63, 25.67	19.48, 23.77	19.46, 23.79
Min, Max	13.9, 36.0	16.1, 38.1	14.8, 36.1	13.9, 38.1

N = Number of subjects in the analysis set
n = Number of subjects with observed data
% = n / N * 100

[redacted]

[redacted]

表 付録-2　全投与期のベースライン時のその他の特性（J-ISS-2：安全性解析対象集団）

Factor Category	AMG 334 70 mg QM only (N = 201) n (%)	 140 mg QM only (N = 56) n (%)	 70/140 mg QM (N = 213) n (%)	 Combined (N = 470) n (%)
Renal impairment				
Yes	21 (10.4)	5 (8.9)	13 (6.1)	39 (8.3)
No	180 (89.6)	51 (91.1)	200 (93.9)	431 (91.7)
CKD stages				
eGFR ≥ 90 mL/min/1.73 m^2	37 (18.4)	7 (12.5)	26 (12.2)	70 (14.9)
eGFR ≥ 60 to < 90 mL/min/1.73 m^2	143 (71.1)	44 (78.6)	174 (81.7)	361 (76.8)
eGFR ≥ 30 to < 60 mL/min/1.73 m^2	21 (10.4)	5 (8.9)	13 (6.1)	39 (8.3)
eGFR ≥ 15 to < 30 mL/min/1.73 m^2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
eGFR < 15 mL/min/1.73 m^2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of baseline cardiovascular risk factors				
0	56 (27.9)	14 (25.0)	76 (35.7)	146 (31.1)
1	99 (49.3)	29 (51.8)	95 (44.6)	223 (47.4)
≥ 2	46 (22.9)	13 (23.2)	42 (19.7)	101 (21.5)
Treatment failure of migraine preventive medication				
Yes	58 (28.9)	26 (46.4)	76 (35.7)	160 (34.0)
No	143 (71.1)	30 (53.6)	137 (64.3)	310 (66.0)

N = Number of subjects in the analysis set
n = Number of subjects with observed data
% = n / N * 100
EM = Episodic migraine
CM = Chronic migraine
Renal impairment: eGRF < 60 mL/min/1.73 m^2
Baseline cardiovascular risk factors include: diabetes mellitus, hypertension and / or high blood pressure, history of smoking, history of dyslipidemia / high cholesterol level / high lipid levels, BMI > 30, coronary artery disease and cerebrovascular and peripheral artery disease.



表 付録-3　曝露期間で調整した発現頻度による有害事象の要約（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (Subj-yr = 122.6) (N = 267) n (%) / e [r]	28 mg QM (Subj-yr = 30.5) (N = 66) n (%) / e [r]	70 mg QM (Subj-yr = 121.8) (N = 265) n (%) / e [r]	140 mg QM (Subj-yr = 63.7) (N = 137) n (%) / e [r]	Overall (Subj-yr = 216.0) (N = 468) n (%) / e [r]
All treatment-emergent adverse events	171 (64.0) / 75.6 [226.2]	40 (60.6) / 18.9 [211.4]	181 (68.3) / 67.1 [269.8]	98 (71.5) / 34.2 [286.2]	319 (68.2) / 120.2 [265.3]
Grade ≥ 2	129 (48.3) / 87.8 [146.9]	33 (50.0) / 22.2 [148.7]	139 (52.5) / 83.6 [166.3]	65 (47.4) / 46.5 [139.8]	237 (50.6) / 152.3 [155.6]
Grade ≥ 3	6 (2.2) / 121.0 [5.0]	1 (1.5) / 30.4 [3.3]	7 (2.6) / 120.0 [5.8]	0 (0.0) / 63.7 [0.0]	8 (1.7) / 214.0 [3.7]
Grade ≥ 4	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
Serious adverse events	6 (2.2) / 121.0 [5.0]	1 (1.5) / 30.4 [3.3]	3 (1.1) / 121.0 [2.5]	1 (0.7) / 63.3 [1.6]	5 (1.1) / 214.7 [2.3]
Leading to discontinuation of investigational product	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.2 [1.7]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.4 [0.9]
Fatal adverse events	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0 0]	0 (0.0) / 216.0 [0.0]
Treatment-related treatment-emergent adverse events	11 (4.1) / 119.6 [9.2]	5 (7.6) / 28.8 [17.4]	28 (10.6) / 111.7 [25.1]	13 (9.5) / 58.9 [22.1]	46 (9.8) / 199.4 [23.1]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years during the double-blind treatment period (DBTP). Total time at risk is the time from first dose of investigational product(IP) through to onset of first event or the min (end of study date(EOS), last DBTP dose date + 112, first OLTP dose date -1) if no event for study 20120309.Total time at risk is the time from first dose of IP through to onset of first event or the min (EOS, first OLTP dose date -1) if no event for study 20170609.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Grading categories determined using CTCAE version 4.03



表 付録-4　SOC及びPT別のすべての有害事象（J-ISS-1：安全性解析対象集団）

System Organ Class Preferred Term	Placebo (N = 267) n (%)	AMG 334 28 mg QM (N = 66) n (%)	AMG 334 70 mg QM (N = 265) n (%)	AMG 334 140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
Number of subjects reporting treatment-emergent adverse events	171 (64.0)	40 (60.6)	181 (68.3)	98 (71.5)	319 (68.2)
血液およびリンパ系障害	0 (0.0)	0 (0.0)	2 (0.8)	3 (2.2)	5 (1.1)
貧血	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
鉄欠乏性貧血	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
リンパ節症	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
リンパ節炎	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
心臓障害	1 (0.4)	0 (0.0)	1 (0.4)	4 (2.9)	5 (1.1)
動悸	0 (0.0)	0 (0.0)	1 (0.4)	2 (1.5)	3 (0.6)
心房細動	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
心室性期外収縮	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
プリンツメタル狭心症	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
耳および迷路障害	5 (1.9)	1 (1.5)	7 (2.6)	4 (2.9)	12 (2.6)
頭位性回転性めまい	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.7)	3 (0.6)
回転性めまい	2 (0.7)	1 (1.5)	1 (0.4)	1 (0.7)	3 (0.6)
耳鳴	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.6)
突発性難聴	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	2 (0.4)
難聴	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
感音性難聴	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
耳痛	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
耳管狭窄	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
内耳障害	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
メニエール病	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
眼障害	6 (2.2)	2 (3.0)	5 (1.9)	5 (3.6)	12 (2.6)
角膜炎	2 (0.7)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
ドライアイ	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
アレルギー性結膜炎	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
眼瞼炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
硝子体浮遊物	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
眼痛	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
黄斑変性	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
霰粒腫	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
眼瞼湿疹	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
アレルギー性角膜炎	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
眼瞼痙攣	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
硝子体出血	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
胃腸障害	33 (12.4)	9 (13.6)	59 (22.3)	20 (14.6)	88 (18.8)
便秘	4 (1.5)	0 (0.0)	13 (4.9)	7 (5.1)	20 (4.3)
齲歯	5 (1.9)	2 (3.0)	11 (4.2)	2 (1.5)	15 (3.2)
上腹部痛	2 (0.7)	1 (1.5)	7 (2.6)	2 (1.5)	10 (2.1)
口内炎	3 (1.1)	2 (3.0)	6 (2.3)	1 (0.7)	9 (1.9)
胃炎	5 (1.9)	0 (0.0)	5 (1.9)	3 (2.2)	8 (1.7)
下痢	2 (0.7)	0 (0.0)	5 (1.9)	1 (0.7)	6 (1.3)
悪心	1 (0.4)	1 (1.5)	2 (0.8)	1 (0.7)	4 (0.9)
下腹部痛	0 (0.0)	1 (1.5)	2 (0.8)	1 (0.7)	4 (0.9)
腹痛	1 (0.4)	1 (1.5)	3 (1.1)	0 (0.0)	4 (0.9)
歯痛	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.6)
腹部不快感	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.6)
歯周病	1 (0.4)	0 (0.0)	0 (0.0)	2 (1.5)	2 (0.4)
腹部膨満	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
口角口唇炎	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
慢性胃炎	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
小腸炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
胃食道逆流性疾患	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
大腸炎	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
口内乾燥	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
排便困難	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
消化不良	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)

表 付録-4　SOC及びPT別のすべての有害事象（J-ISS-1：安全性解析対象集団）（続き）

System Organ Class Preferred Term	Placebo (N = 267) n (%)	AMG 334 28 mg QM (N = 66) n (%)	AMG 334 70 mg QM (N = 265) n (%)	AMG 334 140 mg QM (N = 137) n (%)	AMG 334 Overall (N = 468) n (%)
歯肉腫脹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
大腸ポリープ	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
食道炎	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
埋伏歯	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
食中毒	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
十二指腸潰瘍	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
痔核	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
腰ヘルニア	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
口腔内潰瘍形成	1 (0.4)	0 (0.0)	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	10 (3.7)	4 (6.1)	20 (7.5)	9 (6.6)	33 (7.1)
注射部位紅斑	0 (0.0)	0 (0.0)	2 (0.8)	3 (2.2)	5 (1.1)
注射部位腫脹	1 (0.4)	0 (0.0)	2 (0.8)	2 (1.5)	4 (0.9)
注射部位そう痒感	0 (0.0)	1 (1.5)	1 (0.4)	2 (1.5)	4 (0.9)
注射部位出血	1 (0.4)	0 (0.0)	2 (0.8)	1 (0.7)	3 (0.6)
注射部位反応	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.7)	3 (0.6)
インフルエンザ様疾患	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
倦怠感	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
悪寒	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
異常感	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
注射部位疼痛	2 (0.7)	2 (3.0)	0 (0.0)	0 (0.0)	2 (0.4)
注射部位知覚低下	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
注射部位発疹	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
末梢腫脹	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
発熱	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
投与部位疼痛	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
胸部不快感	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
注射部位内出血	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
末梢性浮腫	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
浮腫	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
無力症	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
疲労	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
温度変化不耐症	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
口渇	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
肝胆道系障害	1 (0.4)	1 (1.5)	1 (0.4)	1 (0.7)	3 (0.6)
原発性胆汁性胆管炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
脂肪肝	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
肝機能異常	1 (0.4)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
胆嚢ポリープ	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
免疫系障害	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
節足動物刺傷アレルギー	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
感染症および寄生虫症	110 (41.2)	28 (42.4)	102 (38.5)	61 (44.5)	191 (40.8)
上咽頭炎	78 (29.2)	22 (33.3)	74 (27.9)	45 (32.8)	141 (30.1)
咽頭炎	7 (2.6)	3 (4.5)	10 (3.8)	3 (2.2)	16 (3.4)
胃腸炎	8 (3.0)	2 (3.0)	7 (2.6)	5 (3.6)	14 (3.0)
膀胱炎	4 (1.5)	1 (1.5)	3 (1.1)	2 (1.5)	6 (1.3)
インフルエンザ	6 (2.2)	1 (1.5)	4 (1.5)	1 (0.7)	6 (1.3)
気管支炎	3 (1.1)	1 (1.5)	1 (0.4)	2 (1.5)	4 (0.9)
歯肉炎	0 (0.0)	2 (3.0)	2 (0.8)	0 (0.0)	4 (0.9)
上気道感染	3 (1.1)	0 (0.0)	2 (0.8)	1 (0.7)	3 (0.6)
ヘルペスウイルス感染	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.7)	3 (0.6)
結膜炎	1 (0.4)	1 (1.5)	1 (0.4)	1 (0.7)	3 (0.6)
足部白癬	1 (0.4)	2 (3.0)	0 (0.0)	1 (0.7)	3 (0.6)
口腔ヘルペス	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
毛包炎	1 (0.4)	1 (1.5)	0 (0.0)	1 (0.7)	2 (0.4)
副鼻腔炎	3 (1.1)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
帯状疱疹	2 (0.7)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
扁桃炎	1 (0.4)	1 (1.5)	1 (0.4)	0 (0.0)	2 (0.4)
中耳炎	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)

表 付録-4　SOC及びPT別のすべての有害事象（J-ISS-1：安全性解析対象集団）（続き）

System Organ Class Preferred Term	Placebo (N = 267) n (%)	AMG 334 28 mg QM (N = 66) n (%)	AMG 334 70 mg QM (N = 265) n (%)	AMG 334 140 mg QM (N = 137) n (%)	AMG 334 Overall (N = 468) n (%)
鼻炎	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
アデノウイルス結膜炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
ウイルス性腸炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
陰部ヘルペス	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
腸結核	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
外耳炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
歯周炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
マイコプラズマ性肺炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
細菌性結膜炎	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
感染性腸炎	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
ウイルス性胃腸炎	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
ヘリコバクター性胃炎	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
ヘリコバクター感染	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Ｅ型肝炎	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
単純ヘルペス	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
扁桃周囲膿瘍	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
レンサ球菌感染	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
皮下組織膿瘍	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
尿道炎	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
麦粒腫	2 (0.7)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
耳下腺炎	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
歯膿瘍	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
虫垂炎	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
爪の皮膚糸状菌症	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
蓄膿	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ノロウイルス性胃腸炎	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
膿疱	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ロタウイルス感染	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
尿路感染	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
傷害、中毒および処置合併症	12 (4.5)	3 (4.5)	14 (5.3)	8 (5.8)	25 (5.3)
肋骨骨折	2 (0.7)	1 (1.5)	1 (0.4)	1 (0.7)	3 (0.6)
挫傷	2 (0.7)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.6)
節足動物刺傷	1 (0.4)	1 (1.5)	2 (0.8)	0 (0.0)	3 (0.6)
節足動物咬傷	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
靭帯捻挫	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
創傷	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
手骨折	0 (0.0)	1 (1.5)	1 (0.4)	0 (0.0)	2 (0.4)
半月板損傷	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
脳振盪	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
靭帯損傷	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
肉離れ	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
処置による疼痛	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
脳挫傷	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
鎖骨骨折	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
角膜擦過傷	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
上顆炎	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
腓骨骨折	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
骨折	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
筋挫傷	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
頭蓋骨骨折	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
熱傷	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
皮膚擦過傷	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
動物咬傷	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
転倒	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
熱中症	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
関節損傷	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
臨床検査	3 (1.1)	2 (3.0)	6 (2.3)	3 (2.2)	11 (2.4)
体重減少	0 (0.0)	1 (1.5)	1 (0.4)	1 (0.7)	3 (0.6)
アラニンアミノトランスフェラーゼ増加	1 (0.4)	1 (1.5)	2 (0.8)	0 (0.0)	3 (0.6)
好中球数減少	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)

表 付録-4　SOC及びPT別のすべての有害事象（J-ISS-1：安全性解析対象集団）（続き）

System Organ Class Preferred Term	Placebo (N = 267) n (%)	AMG 334 28 mg QM (N = 66) n (%)	AMG 334 70 mg QM (N = 265) n (%)	AMG 334 140 mg QM (N = 137) n (%)	AMG 334 Overall (N = 468) n (%)
白血球数減少	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
血中ブドウ糖増加	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
アスパラギン酸アミノトランスフェラーゼ増加	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
便潜血	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
血中乳酸脱水素酵素増加	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
血中尿酸増加	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
心電図Ｔ波逆転	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
代謝および栄養障害	3 (1.1)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
高脂血症	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
食欲減退	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
高血糖	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
筋骨格系および結合組織障害	30 (11.2)	7 (10.6)	40 (15.1)	11 (8.0)	58 (12.4)
背部痛	8 (3.0)	3 (4.5)	14 (5.3)	1 (0.7)	18 (3.8)
筋骨格硬直	3 (1.1)	1 (1.5)	6 (2.3)	1 (0.7)	8 (1.7)
筋肉痛	1 (0.4)	0 (0.0)	4 (1.5)	1 (0.7)	5 (1.1)
頚部痛	3 (1.1)	1 (1.5)	1 (0.4)	2 (1.5)	4 (0.9)
変形性脊椎症	1 (0.4)	0 (0.0)	3 (1.1)	1 (0.7)	4 (0.9)
腱鞘炎	0 (0.0)	0 (0.0)	4 (1.5)	0 (0.0)	4 (0.9)
四肢痛	1 (0.4)	0 (0.0)	2 (0.8)	1 (0.7)	3 (0.6)
足底筋膜炎	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.6)
関節炎	1 (0.4)	1 (1.5)	2 (0.8)	0 (0.0)	3 (0.6)
椎間板突出	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
関節周囲炎	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
筋痙縮	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
筋骨格痛	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
筋膜炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
椎間板障害	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
関節痛	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
変形性関節症	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
四肢腫瘤	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
脛骨内側過労性症候群	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
全身性エリテマトーデス	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
骨粗鬆症	2 (0.7)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
筋肉疲労	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
脊椎靭帯骨化症	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
腱炎	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
関節雑音	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
筋骨格系胸痛	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
筋膜疼痛症候群	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
顎関節症候群	1 (0.4)	0 (0.0)	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）	3 (1.1)	0 (0.0)	1 (0.4)	2 (1.5)	3 (0.6)
子宮平滑筋腫	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	2 (0.4)
アクロコルドン	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
肝臓血管腫	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
卵巣腺腫	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
腎細胞癌	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
神経系障害	19 (7.1)	2 (3.0)	19 (7.2)	6 (4.4)	27 (5.8)
感覚鈍麻	2 (0.7)	1 (1.5)	3 (1.1)	1 (0.7)	5 (1.1)
傾眠	1 (0.4)	0 (0.0)	5 (1.9)	0 (0.0)	5 (1.1)
浮動性めまい	5 (1.9)	1 (1.5)	2 (0.8)	1 (0.7)	4 (0.9)
肋間神経痛	0 (0.0)	1 (1.5)	1 (0.4)	1 (0.7)	3 (0.6)
頭痛	5 (1.9)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
頚腕症候群	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
神経痛	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
後頭神経痛	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
失神寸前の状態	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
味覚不全	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)

表 付録-4　SOC及びPT別のすべての有害事象（J-ISS-1：安全性解析対象集団）（続き）

System Organ Class Preferred Term	Placebo (N = 267) n (%)	AMG 334 28 mg QM (N = 66) n (%)	AMG 334 70 mg QM (N = 265) n (%)	AMG 334 140 mg QM (N = 137) n (%)	AMG 334 Overall (N = 468) n (%)
錯感覚	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
くも膜下出血	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
片頭痛	4 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
頚髄神経根障害	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
坐骨神経痛	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
製品の問題	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
医療機器破損	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
精神障害	4 (1.5)	1 (1.5)	5 (1.9)	2 (1.5)	8 (1.7)
不眠症	2 (0.7)	1 (1.5)	3 (1.1)	1 (0.7)	5 (1.1)
急性ストレス反応	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
不安	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
抑うつ気分	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
不安障害	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
腎および尿路障害	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.7)	3 (0.6)
腎結石症	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
尿管結石症	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
生殖系および乳房障害	4 (1.5)	2 (3.0)	7 (2.6)	0 (0.0)	9 (1.9)
月経困難症	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
不正子宮出血	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
乳房障害	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
子宮頚管ポリープ	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
不規則月経	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
多嚢胞性卵巣	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
卵巣機能不全	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
排卵痛	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
性器出血	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
卵巣嚢胞	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
頻発月経	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
呼吸器、胸郭および縦隔障害	13 (4.9)	5 (7.6)	11 (4.2)	6 (4.4)	22 (4.7)
咳嗽	5 (1.9)	1 (1.5)	2 (0.8)	2 (1.5)	5 (1.1)
口腔咽頭痛	1 (0.4)	0 (0.0)	4 (1.5)	1 (0.7)	5 (1.1)
鼻漏	1 (0.4)	1 (1.5)	3 (1.1)	0 (0.0)	4 (0.9)
上気道の炎症	1 (0.4)	1 (1.5)	0 (0.0)	2 (1.5)	3 (0.6)
アレルギー性鼻炎	1 (0.4)	1 (1.5)	1 (0.4)	1 (0.7)	3 (0.6)
喘息	4 (1.5)	1 (1.5)	0 (0.0)	1 (0.7)	2 (0.4)
発声障害	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
喉頭肉芽腫	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
逆流性喉頭炎	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
アデノイド肥大	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
睡眠時無呼吸症候群	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
息詰まり	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
口腔咽頭不快感	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚および皮下組織障害	11 (4.1)	5 (7.6)	22 (8.3)	10 (7.3)	37 (7.9)
湿疹	2 (0.7)	0 (0.0)	5 (1.9)	2 (1.5)	7 (1.5)
接触皮膚炎	1 (0.4)	1 (1.5)	2 (0.8)	2 (1.5)	5 (1.1)
蕁麻疹	1 (0.4)	0 (0.0)	3 (1.1)	1 (0.7)	4 (0.9)
皮膚炎	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.7)	3 (0.6)
ざ瘡	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
皮脂欠乏性湿疹	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
脂漏性皮膚炎	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
アレルギー性皮膚炎	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.7)	2 (0.4)
発疹	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
丘疹状蕁麻疹	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
日光皮膚炎	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
円形脱毛症	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
皮脂欠乏症	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
薬疹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)

表 付録-4　SOC及びPT別のすべての有害事象（J-ISS-1：安全性解析対象集団）（続き）

		AMG 334			
System Organ Class Preferred Term	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
特発性蕁麻疹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
そう痒性皮疹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
皮下出血	1 (0.4)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
ざ瘡様皮膚炎	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
過角化	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
中毒性皮疹	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
水疱	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚乾燥	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
異汗性湿疹	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
紅斑	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
血管障害	3 (1.1)	1 (1.5)	2 (0.8)	1 (0.7)	4 (0.9)
静脈瘤	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
高血圧	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
起立性低血圧	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
内出血	1 (0.4)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1

[redacted]

表 付録-5　曝露期間で調整した発現頻度によるSOC及びPT別のすべての有害事象
（J-ISS-1：安全性解析対象集団）

System Organ Class Preferred Term	Placebo (Subj-yr = 122 6) (N = 267) n (%) / e [r]	AMG 334 28 mg QM (Subj-yr = 30.5) (N = 66) n (%) / e [r]	AMG 334 70 mg QM (Subj-yr = 121.8) (N = 265) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 63.7) (N = 137) n (%) / e [r]	AMG 334 Overall (Subj-yr = 216.0) (N = 468) n (%) / e [r]
All treatment-emergent adverse events	171 (64.0) / 75.6 [226.2]	40 (60 6) / 18.9 [211.4]	181 (68.3) / 67.1 [269.8]	98 (71.5) / 34.2 [286.2]	319 (68.2) / 120.2 [265.3]
血液およびリンパ系障害	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.6 [1.6]	3 (2.2) / 63.2 [4.7]	5 (1.1) / 215.2 [2.3]
貧血	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	1 (0.7) / 63.6 [1.6]	2 (0.4) / 215.7 [0.9]
鉄欠乏性貧血	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.4 [1.6]	1 (0.2) / 215.6 [0.5]
リンパ節症	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	1 (0.2) / 215.9 [0.5]
リンパ節炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
心臓障害	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	4 (2.9) / 62.6 [6.4]	5 (1.1) / 214.5 [2.3]
動悸	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	2 (1.5) / 63.0 [3.2]	3 (0.6) / 214.9 [1.4]
心房細動	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.5 [1.6]	1 (0.2) / 215.8 [0.5]
心室性期外収縮	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	1 (0.2) / 215.8 [0.5]
プリンツメタル狭心症	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
耳および迷路障害	5 (1.9) / 122.0 [4.1]	1 (1.5) / 30.2 [3.3]	7 (2.6) / 120.1 [5.8]	4 (2.9) / 63.0 [6.3]	12 (2.6) / 213.3 [5.6]
回転性めまい	2 (0.7) / 122.2 [1.6]	1 (1.5) / 30.2 [3.3]	1 (0.4) / 121.4 [0.8]	1 (0.7) / 63.6 [1.6]	3 (0.6) / 215.2 [1.4]
頭位性回転性めまい	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.2 [1.7]	1 (0.7) / 63.6 [1.6]	3 (0.6) / 215.3 [1.4]
耳鳴	1 (0.4) / 122.6 [0.8]	0 (0.0) / 30.5 [0.0]	3 (1.1) / 121.1 [2.5]	0 (0.0) / 63.7 [0.0]	3 (0.6) / 215.3 [1.4]
突発性難聴	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	2 (1.5) / 63.3 [3.2]	2 (0.4) / 215.6 [0.9]
耳痛	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
感音性難聴	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
難聴	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
耳管狭窄	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
メニエール病	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
内耳障害	1 (0.4) / 122.6 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
眼障害	6 (2.2) / 121.2 [5.0]	2 (3.0) / 29.8 [6.7]	5 (1.9) / 120.5 [4.1]	5 (3.6) / 63.2 [7.9]	12 (2.6) / 213.4 [5.6]
角膜炎	2 (0.7) / 121.9 [1.6]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	1 (0.7) / 63.5 [1.6]	2 (0.4) / 215.3 [0.9]
アレルギー性結膜炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	1 (0.7) / 63.7 [1.6]	2 (0.4) / 215.6 [0.9]
ドライアイ	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.8 [0.8]	1 (0.7) / 63.7 [1.6]	2 (0.4) / 216.0 [0.9]
眼瞼湿疹	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.1 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
黄斑変性	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
霰粒腫	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.2 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
眼瞼炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	1 (0.2) / 215.9 [0.5]
眼痛	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
硝子体浮遊物	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	1 (0.2) / 215.9 [0.5]
硝子体出血	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
アレルギー性角膜炎	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
眼瞼痙攣	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
胃腸障害	33 (12.4) / 115.2 [28.6]	9 (13.6) / 28.6 [31.5]	59 (22.3) / 105.9 [55.7]	20 (14.6) / 57.5 [34.8]	88 (18 8) / 192.0 [45.8]
便秘	4 (1.5) / 122.1 [3.3]	0 (0.0) / 30.5 [0.0]	13 (4.9) / 117.4 [11.1]	7 (5.1) / 61.2 [11.4]	20 (4.3) / 209.1 [9.6]
齲歯	5 (1.9) / 121.5 [4.1]	2 (3.0) / 30.1 [6.6]	11 (4.2) / 119.9 [9.2]	2 (1.5) / 63.3 [3.2]	15 (3.2) / 213.3 [7.0]
上腹部痛	2 (0.7) / 121.8 [1.6]	1 (1.5) / 30.3 [3.3]	7 (2.6) / 120.0 [5.8]	2 (1.5) / 62.9 [3.2]	10 (2.1) / 213.2 [4.7]
口内炎	3 (1.1) / 121.6 [2.5]	2 (3.0) / 30.0 [6.7]	6 (2.3) / 120.1 [5.0]	1 (0.7) / 63.3 [1.6]	9 (1.9) / 213.5 [4.2]
胃炎	5 (1.9) / 121.6 [4.1]	0 (0.0) / 30.5 [0.0]	5 (1.9) / 120.7 [4.1]	3 (2.2) / 63.0 [4.8]	8 (1.7) / 214.1 [3.7]
下痢	2 (0.7) / 122.1 [1.6]	0 (0.0) / 30.5 [0.0]	5 (1.9) / 121.0 [4.1]	1 (0.7) / 63.7 [1.6]	6 (1.3) / 215.2 [2.8]
下腹部痛	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.3 [3.3]	2 (0.8) / 120.9 [1.7]	1 (0.7) / 63.4 [1.6]	4 (0.9) / 214.6 [1.9]
悪心	1 (0.4) / 122.2 [0.8]	1 (1.5) / 30.4 [3.3]	2 (0.8) / 120.8 [1.7]	1 (0.7) / 63.3 [1.6]	4 (0.9) / 214.6 [1.9]
腹痛	1 (0.4) / 122.2 [0.8]	1 (1.5) / 30.2 [3.3]	3 (1.1) / 120.8 [2.5]	0 (0.0) / 63.7 [0.0]	4 (0.9) / 214.7 [1.9]
歯痛	1 (0.4) / 122.6 [0.8]	0 (0.0) / 30.5 [0.0]	3 (1.1) / 121.2 [2.5]	0 (0.0) / 63.7 [0.0]	3 (0.6) / 215.4 [1.4]
腹部不快感	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	3 (1.1) / 121.3 [2.5]	0 (0.0) / 63.7 [0.0]	3 (0.6) / 215.5 [1.4]
腹部膨満	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	1 (0.7) / 63.5 [1.6]	2 (0.4) / 215.4 [0.9]
歯周病	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	2 (1.5) / 63.2 [3.2]	2 (0.4) / 215.5 [0.9]
口角口唇炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	1 (0.7) / 63.4 [1.6]	2 (0.4) / 215.6 [0.9]
慢性胃炎	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.4 [1.6]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.6 [0.9]
口内乾燥	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.5 [0.5]

表 付録-5　曝露期間で調整した発現頻度によるSOC及びPT別のすべての有害事象（J-ISS-1：安全性解析対象集団）（続き）

System Organ Class Preferred Term	Placebo (Subj-yr = 122 6) (N = 267) n (%) / e [r]	AMG 334 28 mg QM (Subj-yr = 30.5) (N = 66) n (%) / e [r]	AMG 334 70 mg QM (Subj-yr = 121.8) (N = 265) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 63.7) (N = 137) n (%) / e [r]	AMG 334 Overall (Subj-yr = 216.0) (N = 468) n (%) / e [r]
排便困難	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
消化不良	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
大腸ポリープ	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
埋伏歯	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.3 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
小腸炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.5 [1.6]	1 (0.2) / 215.8 [0.5]
歯肉腫脹	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
胃食道逆流性疾患	2 (0.7) / 122.3 [1.6]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
大腸炎	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
食道炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
食中毒	2 (0.7) / 121.9 [1.6]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
痔核	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
口腔内潰瘍形成	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
腰ヘルニア	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
十二指腸潰瘍	1 (0.4) / 122.6 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
一般・全身障害および投与部位の状態	10 (3.7) / 120.1 [8.3]	4 (6.1) / 28.8 [13.9]	20 (7.5) / 116.1 [17.2]	9 (6.6) / 60.9 [14.8]	33 (7.1) / 205.8 [16.0]
注射部位紅斑	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.3 [1.6]	3 (2.2) / 63.0 [4.8]	5 (1.1) / 214.8 [2.3]
注射部位そう痒感	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.1 [3.3]	1 (0.4) / 121.3 [0.8]	2 (1.5) / 63.2 [3.2]	4 (0.9) / 214.6 [1.9]
注射部位腫脹	1 (0.4) / 122.1 [0.8]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.0 [1.7]	2 (1.5) / 63.1 [3.2]	4 (0.9) / 214.6 [1.9]
注射部位反応	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.2 [1.7]	1 (0.7) / 63.3 [1.6]	3 (0.6) / 214.9 [1.4]
注射部位出血	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.3 [1.6]	1 (0.7) / 63.6 [1.6]	3 (0.6) / 215.4 [1.4]
異常感	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 120.9 [1.7]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.1 [0.9]
注射部位疼痛	2 (0.7) / 121.9 [1.6]	2 (3.0) / 29.7 [6.7]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.1 [0.9]
インフルエンザ様疾患	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	1 (0.7) / 63.3 [1.6]	2 (0.4) / 215.2 [0.9]
倦怠感	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	1 (0.7) / 63.3 [1.6]	2 (0.4) / 215.5 [0.9]
悪寒	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.6 [1.6]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.8 [0.9]
注射部位内出血	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.5 [0.5]
注射部位発疹	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.3 [1.6]	1 (0.2) / 215.5 [0.5]
投与部位疼痛	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.5 [0.5]
浮腫	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.1 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
胸部不快感	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
注射部位知覚低下	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	1 (0.2) / 215.8 [0.5]
末梢腫脹	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	1 (0.2) / 215.9 [0.5]
末梢性浮腫	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
発熱	2 (0.7) / 122.2 [1.6]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
口渇	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
無力症	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
温度変化不耐症	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
疲労	1 (0.4) / 122.6 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
肝胆道系障害	1 (0.4) / 122.4 [0.8]	1 (1.5) / 30.1 [3.3]	1 (0.4) / 121.3 [0.8]	1 (0.7) / 63.2 [1.6]	3 (0.6) / 214.6 [1.4]
原発性胆汁性胆管炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.2 [1.6]	1 (0.2) / 215.4 [0.5]
脂肪肝	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.5 [0.5]
肝機能異常	1 (0.4) / 122.4 [0.8]	1 (1.5) / 30.1 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
胆嚢ポリープ	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
免疫系障害	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
節足動物刺傷アレルギー	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
感染症および寄生虫症	110 (41.2) / 94.4 [116.5]	28 (42.4) / 23.2 [120.9]	102 (38.5) / 95.7 [106.6]	61 (44.5) / 47.7 [128.0]	191 (40.8) / 166.5 [114.7]
上咽頭炎	78 (29.2) / 101.3 [77.0]	22 (33 3) / 24.9 [88.3]	74 (27.9) / 105.1 [70.4]	45 (32.8) / 52.1 [86.4]	141 (30.1) / 182.1 [77.4]
咽頭炎	7 (2.6) / 121.4 [5.8]	3 (4.5) / 30.1 [10.0]	10 (3.8) / 119.5 [8.4]	3 (2.2) / 62.7 [4.8]	16 (3.4) / 212.2 [7.5]
胃腸炎	8 (3.0) / 121.8 [6.6]	2 (3.0) / 30.1 [6.6]	7 (2.6) / 120.0 [5.8]	5 (3.6) / 62.3 [8.0]	14 (3.0) / 212.4 [6.6]
インフルエンザ	6 (2.2) / 121.1 [5.0]	1 (1.5) / 30.2 [3.3]	4 (1.5) / 120.6 [3.3]	1 (0.7) / 63.3 [1.6]	6 (1.3) / 214.1 [2.8]
膀胱炎	4 (1.5) / 121.7 [3.3]	1 (1.5) / 30.3 [3.3]	3 (1.1) / 121.1 [2.5]	2 (1.5) / 63.5 [3.2]	6 (1.3) / 214.9 [2.8]
気管支炎	3 (1.1) / 121.6 [2.5]	1 (1.5) / 30.1 [3.3]	1 (0.4) / 121.8 [0.8]	2 (1.5) / 62.9 [3.2]	4 (0.9) / 214.8 [1.9]
歯肉炎	0 (0.0) / 122.6 [0.0]	2 (3.0) / 30.2 [6.6]	2 (0.8) / 121.3 [1.6]	0 (0.0) / 63.7 [0.0]	4 (0.9) / 215.2 [1.9]
結膜炎	1 (0.4) / 122.3 [0.8]	1 (1.5) / 30.1 [3.3]	1 (0.4) / 121.4 [0.8]	1 (0.7) / 63.6 [1.6]	3 (0.6) / 215.0 [1.4]

表 付録-5　曝露期間で調整した発現頻度によるSOC及びPT別のすべての有害事象
（J-ISS-1：安全性解析対象集団）（続き）

System Organ Class Preferred Term	Placebo (Subj-yr = 122 6) (N = 267) n (%) / e [r]	AMG 334 28 mg QM (Subj-yr = 30.5) (N = 66) n (%) / e [r]	AMG 334 70 mg QM (Subj-yr = 121.8) (N = 265) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 63.7) (N = 137) n (%) / e [r]	AMG 334 Overall (Subj-yr = 216.0) (N = 468) n (%) / e [r]
上気道感染	3 (1.1) / 122.1 [2.5]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.2 [1.6]	1 (0.7) / 63.5 [1.6]	3 (0.6) / 215.2 [1.4]
ヘルペスウイルス感染	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.3 [1.6]	1 (0.7) / 63.5 [1.6]	3 (0.6) / 215.3 [1.4]
足部白癬	1 (0.4) / 122.1 [0.8]	2 (3.0) / 30.3 [6.6]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	3 (0.6) / 215.7 [1.4]
帯状疱疹	2 (0.7) / 122.2 [1.6]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 120.8 [1.7]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.0 [0.9]
口腔ヘルペス	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	1 (0.7) / 63.4 [1.6]	2 (0.4) / 215.3 [0.9]
副鼻腔炎	3 (1.1) / 122.3 [2.5]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.2 [1.7]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.4 [0.9]
毛包炎	1 (0.4) / 122.6 [0.8]	1 (1.5) / 30.1 [3.3]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	2 (0.4) / 215.5 [0.9]
扁桃炎	1 (0.4) / 122.3 [0.8]	1 (1.5) / 30.3 [3.3]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.5 [0.9]
扁桃周囲膿瘍	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
尿道炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
ヘリコバクター性胃炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
陰部ヘルペス	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.3 [1.6]	1 (0.2) / 215.6 [0.5]
マイコプラズマ性肺炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.3 [1.6]	1 (0.2) / 215.6 [0.5]
単純ヘルペス	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
腸結核	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.4 [1.6]	1 (0.2) / 215.7 [0.5]
レンサ球菌感染	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
Ｅ型肝炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
アデノウイルス結膜炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.5 [1.6]	1 (0.2) / 215.8 [0.5]
皮下組織膿瘍	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
ヘリコバクター感染	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
鼻炎	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.5 [1.6]	1 (0.2) / 215.8 [0.5]
ウイルス性胃腸炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
麦粒腫	2 (0.7) / 121.9 [1.6]	1 (1.5) / 30.3 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
中耳炎	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	1 (0.2) / 215.8 [0.5]
ウイルス性腸炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	1 (0.2) / 215.8 [0.5]
歯周炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	1 (0.2) / 215.9 [0.5]
感染性腸炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
細菌性結膜炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.8 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 216.0 [0.5]
外耳炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.7 [1.6]	1 (0.2) / 216.0 [0.5]
歯膿瘍	2 (0.7) / 121.9 [1.6]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
耳下腺炎	2 (0.7) / 122.1 [1.6]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
爪の皮膚糸状菌症	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
ロタウイルス感染	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
ノロウイルス性胃腸炎	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
膿疱	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
尿路感染	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
蓄膿	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
虫垂炎	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
傷害、中毒および処置合併症	12 (4.5) / 119.6 [10.0]	3 (4.5) / 30.2 [9.9]	14 (5.3) / 118.4 [11.8]	8 (5.8) / 62 3 [12.8]	25 (5.3) / 210.9 [11.9]
肋骨骨折	2 (0.7) / 122.1 [1.6]	1 (1.5) / 30.3 [3.3]	1 (0.4) / 121.3 [0.8]	1 (0.7) / 63.6 [1.6]	3 (0.6) / 215.2 [1.4]
節足動物刺傷	1 (0.4) / 122.1 [0.8]	1 (1.5) / 30.5 [3.3]	2 (0.8) / 121.1 [1.7]	0 (0.0) / 63.7 [0.0]	3 (0.6) / 215.3 [1.4]
挫傷	2 (0.7) / 122.0 [1.6]	0 (0.0) / 30.5 [0.0]	3 (1.1) / 121.5 [2.5]	0 (0.0) / 63.7 [0.0]	3 (0.6) / 215.7 [1.4]
靱帯捻挫	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	1 (0.7) / 63.3 [1.6]	2 (0.4) / 215.4 [0.9]
創傷	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	1 (0.7) / 63.7 [1.6]	2 (0.4) / 215.5 [0.9]
手骨折	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.4 [3.3]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.6 [0.9]
節足動物咬傷	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	1 (0.7) / 63.7 [1.6]	2 (0.4) / 215.9 [0.9]
脳挫傷	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.5 [0.5]
鎖骨骨折	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.5 [0.5]
頭蓋骨骨折	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.5 [0.5]
上顆炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
角膜擦過傷	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
肉離れ	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.4 [1.6]	1 (0.2) / 215.7 [0.5]
靱帯損傷	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.4 [1.6]	1 (0.2) / 215.7 [0.5]
骨折	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
腓骨骨折	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
筋挫傷	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
脳振盪	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.5 [1.6]	1 (0.2) / 215.8 [0.5]
処置による疼痛	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.5 [1.6]	1 (0.2) / 215.8 [0.5]

表 付録-5　曝露期間で調整した発現頻度によるSOC及びPT別のすべての有害事象（J-ISS-1：安全性解析対象集団）（続き）

System Organ Class Preferred Term	Placebo (Subj-yr = 122 6) (N = 267) n (%) / e [r]	AMG 334 28 mg QM (Subj-yr = 30.5) (N = 66) n (%) / e [r]	AMG 334 70 mg QM (Subj-yr = 121.8) (N = 265) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 63.7) (N = 137) n (%) / e [r]	AMG 334 Overall (Subj-yr = 216.0) (N = 468) n (%) / e [r]
熱傷	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.8 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 216.0 [0.5]
半月板損傷	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.7 [1.6]	1 (0.2) / 216.0 [0.5]
皮膚擦過傷	2 (0.7) / 122.2 [1.6]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
転倒	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
熱中症	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
関節損傷	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
動物咬傷	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
臨床検査	3 (1.1) / 121.6 [2.5]	2 (3.0) / 30.1 [6.7]	6 (2.3) / 119.6 [5.0]	3 (2.2) / 62.8 [4.8]	11 (2.4) / 212.5 [5.2]
アラニンアミノトランスフェラーゼ増加	1 (0.4) / 122.2 [0.8]	1 (1.5) / 30.3 [3.3]	2 (0.8) / 121.0 [1.7]	0 (0.0) / 63.7 [0.0]	3 (0.6) / 215.0 [1.4]
体重減少	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.3 [3.3]	1 (0.4) / 121.6 [0.8]	1 (0.7) / 63.4 [1.6]	3 (0.6) / 215.3 [1.4]
白血球数減少	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.0 [1.7]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.2 [0.9]
好中球数減少	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	1 (0.7) / 63.5 [1.6]	2 (0.4) / 215.4 [0.9]
便潜血	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
アスパラギン酸アミノトランスフェラーゼ増加	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
血中ブドウ糖増加	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.3 [1.6]	1 (0.2) / 215.6 [0.5]
血中尿酸増加	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
血中乳酸脱水素酵素増加	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
心電図Ｔ波逆転	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
代謝および栄養障害	3 (1.1) / 122.0 [2.5]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.5 [1.6]	1 (0.2) / 215.8 [0.5]
高脂血症	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.5 [1.6]	1 (0.2) / 215.8 [0.5]
高血糖	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
食欲減退	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
筋骨格系および結合組織障害	30 (11.2) /115.9 [25.9]	7 (10.6) / 28.5 [24.6]	40 (15.1) / 113.4 [35.3]	11 (8.0) / 61.1 [18.0]	58 (12.4) / 202.9 [28.6]
背部痛	8 (3.0) / 120.8 [6.6]	3 (4.5) / 29.4 [10.2]	14 (5.3) / 119.1 [11.8]	1 (0.7) / 63.3 [1.6]	18 (3.8) / 211.7 [8.5]
筋骨格硬直	3 (1.1) / 122.2 [2.5]	1 (1.5) / 30.2 [3.3]	6 (2.3) / 120.3 [5.0]	1 (0.7) / 63.3 [1.6]	8 (1.7) / 213.9 [3.7]
筋肉痛	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	4 (1.5) / 120.8 [3.3]	1 (0.7) / 63.6 [1.6]	5 (1.1) / 215.0 [2.3]
変形性脊椎症	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	3 (1.1) / 121.2 [2.5]	1 (0.7) / 63.4 [1.6]	4 (0.9) / 215.1 [1.9]
腱鞘炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	4 (1.5) / 120.9 [3.3]	0 (0.0) / 63.7 [0.0]	4 (0.9) / 215.1 [1.9]
頚部痛	3 (1.1) / 121.8 [2.5]	1 (1.5) / 30.5 [3.3]	1 (0.4) / 121.7 [0.8]	2 (1.5) / 63.4 [3.2]	4 (0.9) / 215.6 [1.9]
四肢痛	1 (0.4) / 122.6 [0.8]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.0 [1.7]	1 (0.7) / 63.6 [1.6]	3 (0.6) / 215.1 [1.4]
足底筋膜炎	1 (0.4) / 122.6 [0.8]	0 (0.0) / 30.5 [0.0]	3 (1.1) / 121.2 [2.5]	0 (0.0) / 63.7 [0.0]	3 (0.6) / 215.5 [1.4]
関節炎	1 (0.4) / 122.4 [0.8]	1 (1.5) / 30.4 [3.3]	2 (0.8) / 121.5 [1.6]	0 (0.0) / 63.7 [0.0]	3 (0.6) / 215.6 [1.4]
椎間板突出	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.4 [1.6]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.7 [0.9]
筋肉疲労	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.0 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.5 [0.5]
脛骨内側過労性症候群	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.5 [0.5]
筋痙縮	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.3 [1.6]	1 (0.2) / 215.6 [0.5]
関節周囲炎	2 (0.7) / 122.0 [1.6]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.4 [1.6]	1 (0.2) / 215.7 [0.5]
脊椎靱帯骨化症	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.2 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
全身性エリテマトーデス	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
骨粗鬆症	2 (0.7) / 122.2 [1.6]	1 (1.5) / 30.3 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
変形性関節症	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
筋膜炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	1 (0.2) / 215.8 [0.5]
筋骨格痛	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	1 (0.2) / 215.9 [0.5]
関節痛	2 (0.7) / 121.9 [1.6]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
四肢腫瘤	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 216.0 [0.5]
椎間板障害	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.7 [1.6]	1 (0.2) / 216.0 [0.5]
腱炎	2 (0.7) / 122.1 [1.6]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
筋膜疼痛症候群	1 (0.4) / 122.1 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
関節雑音	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
顎関節症候群	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
筋骨格系胸痛	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]

表 付録-5　曝露期間で調整した発現頻度によるSOC及びPT別のすべての有害事象（J-ISS-1：安全性解析対象集団）（続き）

System Organ Class Preferred Term	Placebo (Subj-yr = 122 6) (N = 267) n (%) / e [r]	AMG 334 28 mg QM (Subj-yr = 30.5) (N = 66) n (%) / e [r]	AMG 334 70 mg QM (Subj-yr = 121.8) (N = 265) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 63.7) (N = 137) n (%) / e [r]	AMG 334 Overall (Subj-yr = 216.0) (N = 468) n (%) / e [r]
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 (1.1) / 121.6 [2.5]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.8 [0.8]	2 (1.5) / 63.1 [3.2]	3 (0.6) / 215.3 [1.4]
子宮平滑筋腫	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	2 (1.5) / 63.1 [3.2]	2 (0.4) / 215.3 [0.9]
アクロコルドン	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.8 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 216.0 [0.5]
腎細胞癌	1 (0.4) / 122.1 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
卵巣腺腫	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
肝臓血管腫	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
神経系障害	19 (7.1) / 117.1 [16.2]	2 (3.0) / 29.9 [6.7]	19 (7.2) / 115.2 [16.5]	6 (4.4) / 61.9 [9.7]	27 (5.8) / 206.9 [13.0]
傾眠	1 (0.4) / 122.1 [0.8]	0 (0.0) / 30.5 [0.0]	5 (1.9) / 119.9 [4.2]	0 (0.0) / 63.7 [0.0]	5 (1.1) / 214.2 [2.3]
感覚鈍麻	2 (0.7) / 121.7 [1.6]	1 (1.5) / 30.4 [3.3]	3 (1.1) / 120.7 [2.5]	1 (0.7) / 63.5 [1.6]	5 (1.1) / 214.6 [2.3]
浮動性めまい	5 (1.9) / 121.4 [4.1]	1 (1.5) / 30.0 [3.3]	2 (0.8) / 121.2 [1.7]	1 (0.7) / 63.5 [1.6]	4 (0.9) / 214.8 [1.9]
肋間神経痛	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.1 [3.3]	1 (0.4) / 121.4 [0.8]	1 (0.7) / 63.6 [1.6]	3 (0.6) / 215.1 [1.4]
頭痛	5 (1.9) / 120.9 [4.1]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	1 (0.7) / 63.3 [1.6]	2 (0.4) / 215.1 [0.9]
頚腕症候群	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	1 (0.7) / 63.3 [1.6]	2 (0.4) / 215.2 [0.9]
神経痛	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.2 [1.6]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.4 [0.9]
後頭神経痛	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.3 [1.6]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.5 [0.9]
失神寸前の状態	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.2 [1.6]	1 (0.2) / 215.5 [0.5]
錯感覚	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.5 [0.5]
くも膜下出血	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.3 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.5 [0.5]
味覚不全	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
片頭痛	4 (1.5) / 121.7 [3.3]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
坐骨神経痛	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
頚髄神経根障害	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
製品の問題	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
医療機器破損	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
精神障害	4 (1.5) / 121.7 [3.3]	1 (1.5) / 30.3 [3.3]	5 (1.9) / 120.4 [4.2]	2 (1.5) / 63.2 [3.2]	8 (1.7) / 213.9 [3.7]
不眠症	2 (0.7) / 122.1 [1.6]	1 (1.5) / 30.3 [3.3]	3 (1.1) / 120.8 [2.5]	1 (0.7) / 63.2 [1.6]	5 (1.1) / 214.4 [2.3]
抑うつ気分	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
不安	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
急性ストレス反応	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.7 [1.6]	1 (0.2) / 216.0 [0.5]
不安障害	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
腎および尿路障害	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.4 [1.6]	1 (0.7) / 63.4 [1.6]	3 (0.6) / 215.3 [1.4]
腎結石症	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	1 (0.7) / 63.4 [1.6]	2 (0.4) / 215.6 [0.9]
尿管結石症	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
生殖系および乳房障害	4 (1.5) / 121.8 [3.3]	2 (3.0) / 30.1 [6.7]	7 (2.6) / 120.7 [5.8]	0 (0.0) / 63.7 [0.0]	9 (1.9) / 214.5 [4.2]
月経困難症	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.4 [1.6]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.6 [0.9]
不正子宮出血	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.6 [1.6]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.8 [0.9]
卵巣機能不全	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.1 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
子宮頚管ポリープ	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
多嚢胞性卵巣	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
不規則月経	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
排卵痛	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.4 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
乳房障害	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
性器出血	2 (0.7) / 122.3 [1.6]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
頻発月経	1 (0.4) / 122.1 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
卵巣嚢胞	1 (0.4) / 122.6 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
呼吸器、胸郭および縦隔障害	13 (4.9) / 118.9 [10.9]	5 (7.6) / 29.3 [17.1]	11 (4.2) / 118.7 [9.3]	6 (4.4) / 62.1 [9.7]	22 (4.7) / 210.1 [10.5]
口腔咽頭痛	1 (0.4) / 122.1 [0.8]	0 (0.0) / 30.5 [0.0]	4 (1.5) / 120.4 [3.3]	1 (0.7) / 63.6 [1.6]	5 (1.1) / 214.5 [2.3]
咳嗽	5 (1.9) / 121.4 [4.1]	1 (1.5) / 30.4 [3.3]	2 (0.8) / 121.1 [1.7]	2 (1.5) / 63.3 [3.2]	5 (1.1) / 214.8 [2.3]
鼻漏	1 (0.4) / 122.3 [0.8]	1 (1.5) / 30.1 [3.3]	3 (1.1) / 121.3 [2.5]	0 (0.0) / 63.7 [0.0]	4 (0.9) / 215.1 [1.9]
アレルギー性鼻炎	1 (0.4) / 122.3 [0.8]	1 (1.5) / 30.1 [3.3]	1 (0.4) / 121.4 [0.8]	1 (0.7) / 63.3 [1.6]	3 (0.6) / 214.9 [1.4]
上気道の炎症	1 (0.4) / 122.3 [0.8]	1 (1.5) / 30.5 [3.3]	0 (0.0) / 121.8 [0.0]	2 (1.5) / 63.3 [3.2]	3 (0.6) / 215.5 [1.4]

表 付録-5　曝露期間で調整した発現頻度によるSOC及びPT別のすべての有害事象（J-ISS-1：安全性解析対象集団）（続き）

System Organ Class Preferred Term	Placebo (Subj-yr = 122 6) (N = 267) n (%) / e [r]	AMG 334 28 mg QM (Subj-yr = 30.5) (N = 66) n (%) / e [r]	70 mg QM (Subj-yr = 121.8) (N = 265) n (%) / e [r]	140 mg QM (Subj-yr = 63.7) (N = 137) n (%) / e [r]	Overall (Subj-yr = 216.0) (N = 468) n (%) / e [r]
喘息	4 (1.5) / 121.7 [3.3]	1 (1.5) / 30.1 [3.3]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.4 [1.6]	2 (0.4) / 215.4 [0.9]
発声障害	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
アデノイド肥大	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.2 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
睡眠時無呼吸症候群	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.4 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
喉頭肉芽腫	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
逆流性喉頭炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
口腔咽頭不快感	1 (0.4) / 122.1 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
息詰まり	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
皮膚および皮下組織障害	11 (4.1) / 119.9 [9.2]	5 (7.6) / 30.0 [16.6]	22 (8.3) / 116.8 [18.8]	10 (7.3) / 62.0 [16.1]	37 (7.9) / 208.8 [17.7]
湿疹	2 (0.7) / 122.1 [1.6]	0 (0.0) / 30.5 [0.0]	5 (1.9) / 120.5 [4.1]	2 (1.5) / 63.4 [3.2]	7 (1.5) / 214.4 [3.3]
接触皮膚炎	1 (0.4) / 122.5 [0.8]	1 (1.5) / 30.3 [3.3]	2 (0.8) / 121.2 [1.6]	2 (1.5) / 62.7 [3.2]	5 (1.1) / 214.3 [2.3]
蕁麻疹	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	3 (1.1) / 121.0 [2.5]	1 (0.7) / 63.7 [1.6]	4 (0.9) / 215.2 [1.9]
皮膚炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 120.9 [1.7]	1 (0.7) / 63.7 [1.6]	3 (0.6) / 215.1 [1.4]
皮脂欠乏性湿疹	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	1 (0.7) / 63.5 [1.6]	2 (0.4) / 215.4 [0.9]
発疹	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.4 [1.6]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.6 [0.9]
ざ瘡	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	1 (0.7) / 63.6 [1.6]	2 (0.4) / 215.7 [0.9]
アレルギー性皮膚炎	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.4 [3.3]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.6 [1.6]	2 (0.4) / 215.8 [0.9]
丘疹状蕁麻疹	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	2 (0.8) / 121.6 [1.6]	0 (0.0) / 63.7 [0.0]	2 (0.4) / 215.8 [0.9]
脂漏性皮膚炎	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	1 (0.7) / 63.7 [1.6]	2 (0.4) / 215.9 [0.9]
皮脂欠乏症	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.6 [0.5]
そう痒性皮疹	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.5 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
薬疹	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
過角化	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.4 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
ざ瘡様皮膚炎	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.4 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
皮下出血	1 (0.4) / 122.5 [0.8]	1 (1.5) / 30.4 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
円形脱毛症	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
中毒性皮疹	0 (0.0) / 122.6 [0.0]	1 (1.5) / 30.5 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
特発性蕁麻疹	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.7 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.9 [0.5]
日光皮膚炎	1 (0.4) / 122.3 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.7 [1.6]	1 (0.2) / 216.0 [0.5]
異汗性湿疹	1 (0.4) / 122.1 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
水疱	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
皮膚乾燥	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
紅斑	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
血管障害	3 (1.1) / 121.7 [2.5]	1 (1.5) / 30.2 [3.3]	2 (0.8) / 121.4 [1.6]	1 (0.7) / 63.3 [1.6]	4 (0.9) / 214.9 [1.9]
静脈瘤	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	1 (0.7) / 63.3 [1.6]	1 (0.2) / 215.6 [0.5]
内出血	1 (0.4) / 122.3 [0.8]	1 (1.5) / 30.2 [3.3]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.7 [0.5]
起立性低血圧	1 (0.4) / 122.2 [0.8]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]
高血圧	1 (0.4) / 122.4 [0.8]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.6 [0.8]	0 (0.0) / 63.7 [0.0]	1 (0.2) / 215.8 [0.5]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years during the double-blind treatment period (DBTP). Total time at risk is the time from first dose of investigational product (IP) through to onset of first event or the min (end of study date (EOS), last DBTP dose date + 112, first OLTP dose date -1) if no event for study 20120309.Total time at risk is the time from first dose of IP through to onset of first event or the min (EOS, first OLTP dose date -1) if no event for study 20170609.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1



表 付録-6　SOC及びPT別の治験薬との関連ありの有害事象（J-ISS-1：安全性解析対象集団）

System Organ Class Preferred Term	Placebo (N = 267) n (%)	AMG 334 28 mg QM (N = 66) n (%)	AMG 334 70 mg QM (N = 265) n (%)	AMG 334 140 mg QM (N = 137) n (%)	AMG 334 Overall (N = 468) n (%)
Number of subjects reporting treatment-related treatment-emergent adverse events	11 (4.1)	5 (7.6)	28 (10.6)	13 (9.5)	46 (9.8)
心臓障害	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
動悸	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
眼障害	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
硝子体出血	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
胃腸障害	1 (0.4)	1 (1.5)	9 (3.4)	7 (5.1)	17 (3.6)
便秘	1 (0.4)	0 (0.0)	4 (1.5)	5 (3.6)	9 (1.9)
下腹部痛	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
口内炎	0 (0.0)	1 (1.5)	1 (0.4)	0 (0.0)	2 (0.4)
上腹部痛	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
胃炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
慢性胃炎	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
排便困難	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
悪心	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
一般・全身障害および投与部位の状態	2 (0.7)	1 (1.5)	9 (3.4)	6 (4.4)	16 (3.4)
注射部位紅斑	0 (0.0)	0 (0.0)	2 (0.8)	2 (1.5)	4 (0.9)
注射部位反応	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.7)	3 (0.6)
注射部位そう痒感	0 (0.0)	1 (1.5)	1 (0.4)	1 (0.7)	3 (0.6)
インフルエンザ様疾患	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
注射部位発疹	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
倦怠感	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
異常感	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
注射部位腫脹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
発熱	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
注射部位疼痛	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
感染症および寄生虫症	0 (0.0)	1 (1.5)	1 (0.4)	1 (0.7)	3 (0.6)
上咽頭炎	0 (0.0)	1 (1.5)	1 (0.4)	0 (0.0)	2 (0.4)
胃腸炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
臨床検査	1 (0.4)	1 (1.5)	3 (1.1)	2 (1.5)	6 (1.3)
好中球数減少	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
白血球数減少	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
アラニンアミノトランスフェラーゼ増加	1 (0.4)	1 (1.5)	1 (0.4)	0 (0.0)	2 (0.4)
体重減少	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
血中乳酸脱水素酵素増加	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
代謝および栄養障害	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
高脂血症	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
筋骨格系および結合組織障害	1 (0.4)	1 (1.5)	2 (0.8)	2 (1.5)	5 (1.1)
四肢痛	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
背部痛	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
全身性エリテマトーデス	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
筋肉疲労	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
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 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
卵巣腺腫	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
神経系障害	3 (1.1)	1 (1.5)	5 (1.9)	0 (0.0)	6 (1.3)
傾眠	1 (0.4)	0 (0.0)	4 (1.5)	0 (0.0)	4 (0.9)
後頭神経痛	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
感覚鈍麻	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
浮動性めまい	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
片頭痛	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

表 付録-6　SOC及びPT別の治験薬との関連ありの有害事象（J-ISS-1：安全性解析対象集団）（続き）

System Organ Class Preferred Term	Placebo (N = 267) n (%)	AMG 334 28 mg QM (N = 66) n (%)	AMG 334 70 mg QM (N = 265) n (%)	AMG 334 140 mg QM (N = 137) n (%)	AMG 334 Overall (N = 468) n (%)
精神障害	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
不眠症	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
呼吸器、胸郭および縦隔障害	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
喉頭肉芽腫	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
逆流性喉頭炎	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
皮膚および皮下組織障害	2 (0.7)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
円形脱毛症	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
そう痒性皮疹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
紅斑	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
蕁麻疹	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1

[redacted]

表 付録-7　SOC及びPT別のすべての有害事象（J-ISS-2：安全性解析対象集団）

System Organ Class Preferred Term	AMG 334 70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	AMG 334 Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent adverse events	328 (79.2) / 147.0 [223.1]	230 (85.5) / 96.1 [239.4]	439 (93.4) / 192.6 [227.9]
血液およびリンパ系障害	8 (1.9) / 523.5 [1.5]	8 (3.0) / 338.4 [2.4]	16 (3.4) / 853.0 [1.9]
貧血	3 (0.7) / 525.4 [0.6]	4 (1.5) / 341.6 [1.2]	7 (1.5) / 864.1 [0.8]
鉄欠乏性貧血	5 (1.2) / 526.9 [0.9]	2 (0.7) / 342.1 [0.6]	7 (1.5) / 864.7 [0.8]
リンパ節症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.7 [0.3]	1 (0.2) / 870.9 [0.1]
白血球減少症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.5 [0.3]	1 (0.2) / 871.4 [0.1]
心臓障害	4 (1.0) / 523.5 [0.8]	10 (3.7) / 333.7 [3.0]	14 (3.0) / 855.1 [1.6]
動悸	2 (0.5) / 526.5 [0.4]	4 (1.5) / 339.0 [1.2]	6 (1.3) / 863.8 [0.7]
狭心症	1 (0.2) / 527.5 [0.2]	1 (0.4) / 343.3 [0.3]	2 (0.4) / 870.8 [0.2]
心室性期外収縮	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.4 [0.3]	1 (0.2) / 870.8 [0.1]
上室性不整脈	1 (0.2) / 527.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.0 [0.1]
上室性期外収縮	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.6 [0.3]	1 (0.2) / 871.4 [0.1]
洞性頻脈	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.6 [0.3]	1 (0.2) / 871.4 [0.1]
脚ブロック	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.2 [0.3]	1 (0.2) / 872.0 [0.1]
心房細動	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.6 [0.3]	1 (0.2) / 872.4 [0.1]
耳および迷路障害	19 (4.6) / 509.4 [3.7]	16 (5.9) / 335.4 [4.8]	35 (7.4) / 832.9 [4.2]
回転性めまい	8 (1.9) / 522.5 [1.5]	5 (1.9) / 341.2 [1.5]	13 (2.8) / 859.0 [1.5]
耳鳴	4 (1.0) / 525.1 [0.8]	1 (0.4) / 342.7 [0.3]	5 (1.1) / 864.6 [0.6]
突発性難聴	1 (0.2) / 527.2 [0.2]	4 (1.5) / 342.2 [1.2]	5 (1.1) / 867.2 [0.6]
頭位性回転性めまい	2 (0.5) / 525.4 [0.4]	2 (0.7) / 343.3 [0.6]	4 (0.9) / 867.0 [0.5]
メニエール病	2 (0.5) / 526.8 [0.4]	1 (0.4) / 343.6 [0.3]	3 (0.6) / 870.4 [0.3]
難聴	1 (0.2) / 528.7 [0.2]	1 (0.4) / 342.4 [0.3]	2 (0.4) / 869.4 [0.2]
耳痛	1 (0.2) / 528.4 [0.2]	1 (0.4) / 343.8 [0.3]	2 (0.4) / 870.5 [0.2]
感音性難聴	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.8 [0.1]
鼓膜穿孔	1 (0.2) / 527.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
乗物酔い	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
耳不快感	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.0 [0.3]	1 (0.2) / 871.9 [0.1]
内分泌障害	2 (0.5) / 527.3 [0.4]	1 (0.4) / 343.8 [0.3]	3 (0.6) / 871.1 [0.3]
甲状腺腫	1 (0.2) / 527.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
甲状腺機能亢進症	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
自己免疫性甲状腺炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.8 [0.3]	1 (0.2) / 872.6 [0.1]
眼障害	23 (5.6) / 506.8 [4.5]	13 (4.8) / 331.5 [3.9]	35 (7.4) / 829.9 [4.2]
アレルギー性結膜炎	6 (1.4) / 522.2 [1.1]	5 (1.9) / 340.3 [1.5]	11 (2.3) / 859.3 [1.3]
ドライアイ	5 (1.2) / 524.7 [1.0]	2 (0.7) / 340.9 [0.6]	7 (1.5) / 863.9 [0.8]
角膜炎	3 (0.7) / 525.2 [0.6]	2 (0.7) / 342.6 [0.6]	5 (1.1) / 866.1 [0.6]
硝子体浮遊物	2 (0.5) / 526.7 [0.4]	1 (0.4) / 342.4 [0.3]	3 (0.6) / 868.7 [0.3]
眼瞼炎	2 (0.5) / 526.9 [0.4]	1 (0.4) / 342.0 [0.3]	3 (0.6) / 868.9 [0.3]
結膜出血	1 (0.2) / 527.8 [0.2]	2 (0.7) / 342.6 [0.6]	3 (0.6) / 870.4 [0.3]
眼精疲労	2 (0.5) / 527.8 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 870.3 [0.2]
眼瞼下垂	0 (0.0) / 528.8 [0.0]	2 (0.7) / 341.9 [0.6]	2 (0.4) / 870.8 [0.2]
黄斑変性	1 (0.2) / 528.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.6 [0.1]
眼痛	1 (0.2) / 527.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]
網膜血管障害	1 (0.2) / 527.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.3 [0.1]
眼充血	1 (0.2) / 527.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
眼瞼そう痒症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.8 [0.3]	1 (0.2) / 871.6 [0.1]
眼瞼浮腫	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
眼出血	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.0 [0.3]	1 (0.2) / 871.8 [0.1]
眼瞼皮膚乾燥	1 (0.2) / 528.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.0 [0.1]
霰粒腫	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.3 [0.1]
ぶどう膜炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.6 [0.3]	1 (0.2) / 872.4 [0.1]
胃腸障害	132 (31.9) / 391.6 [33.7]	73 (27.1) / 275.7 [26.5]	192 (40.9) / 628.7 [30.5]
齲歯	24 (5.8) / 506.8 [4.7]	11 (4.1) / 331.7 [3.3]	34 (7.2) / 830.4 [4.1]
便秘	21 (5.1) / 505.1 [4.2]	12 (4.5) / 334.2 [3.6]	32 (6.8) / 824.7 [3.9]
上腹部痛	24 (5.8) / 506.1 [4.7]	6 (2.2) / 339.5 [1.8]	29 (6.2) / 833.4 [3.5]
胃炎	13 (3.1) / 511.9 [2.5]	10 (3.7) / 336.5 [3.0]	22 (4.7) / 845.6 [2.6]

表 付録-7　SOC及びPT別のすべての有害事象（J-ISS-2：安全性解析対象集団）（続き）

System Organ Class Preferred Term	AMG 334 70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	AMG 334 Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
下痢	12 (2.9) / 517.8 [2.3]	5 (1.9) / 340.6 [1.5]	17 (3.6) / 854.2 [2.0]
口内炎	12 (2.9) / 517.0 [2.3]	4 (1.5) / 341.2 [1.2]	15 (3.2) / 857.0 [1.8]
胃食道逆流性疾患	9 (2.2) / 519.7 [1.7]	5 (1.9) / 338.8 [1.5]	14 (3.0) / 857.3 [1.6]
悪心	7 (1.7) / 522.0 [1.3]	5 (1.9) / 337.7 [1.5]	12 (2.6) / 858.1 [1.4]
嘔吐	4 (1.0) / 524.3 [0.8]	4 (1.5) / 340.0 [1.2]	8 (1.7) / 864.4 [0.9]
歯痛	5 (1.2) / 525.1 [1.0]	3 (1.1) / 340.7 [0.9]	8 (1.7) / 865.8 [0.9]
腹部不快感	5 (1.2) / 525.0 [1.0]	2 (0.7) / 341.8 [0.6]	7 (1.5) / 866.8 [0.8]
痔核	5 (1.2) / 523.8 [1.0]	1 (0.4) / 342.2 [0.3]	6 (1.3) / 866.0 [0.7]
腹痛	4 (1.0) / 524.4 [0.8]	2 (0.7) / 341.7 [0.6]	6 (1.3) / 866.1 [0.7]
歯周病	3 (0.7) / 526.1 [0.6]	2 (0.7) / 342.1 [0.6]	4 (0.9) / 866.7 [0.5]
腸炎	1 (0.2) / 527.8 [0.2]	3 (1.1) / 340.6 [0.9]	4 (0.9) / 868.4 [0.5]
大腸ポリープ	3 (0.7) / 526.9 [0.6]	1 (0.4) / 343.1 [0.3]	4 (0.9) / 870.0 [0.5]
腹部膨満	2 (0.5) / 525.5 [0.4]	1 (0.4) / 342.4 [0.3]	3 (0.6) / 867.5 [0.3]
下腹部痛	2 (0.5) / 527.1 [0.4]	1 (0.4) / 341.8 [0.3]	3 (0.6) / 868.9 [0.3]
過敏性腸症候群	1 (0.2) / 527.7 [0.2]	2 (0.7) / 342.0 [0.6]	3 (0.6) / 869.6 [0.3]
慢性胃炎	1 (0.2) / 527.0 [0.2]	1 (0.4) / 342.3 [0.3]	2 (0.4) / 869.3 [0.2]
アフタ性潰瘍	2 (0.5) / 527.3 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 869.9 [0.2]
小腸炎	1 (0.2) / 528.2 [0.2]	1 (0.4) / 343.6 [0.3]	2 (0.4) / 870.1 [0.2]
口内乾燥	1 (0.2) / 528.4 [0.2]	1 (0.4) / 343.6 [0.3]	2 (0.4) / 870.6 [0.2]
唾液腺結石	1 (0.2) / 527.5 [0.2]	1 (0.4) / 343.1 [0.3]	2 (0.4) / 870.6 [0.2]
消化不良	1 (0.2) / 527.9 [0.2]	1 (0.4) / 343.0 [0.3]	2 (0.4) / 870.9 [0.2]
胃潰瘍	2 (0.5) / 527.6 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.5 [0.2]
軟便	2 (0.5) / 527.8 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.7 [0.2]
排便困難	1 (0.2) / 526.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.6 [0.1]
口角口唇炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 870.7 [0.1]
大腸炎	1 (0.2) / 527.0 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.9 [0.1]
鼓腸	1 (0.2) / 527.1 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.0 [0.1]
胃ポリープ	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.3 [0.3]	1 (0.2) / 871.1 [0.1]
出血性腸憩室	1 (0.2) / 527.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
口唇症	1 (0.2) / 527.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.3 [0.1]
歯肉腫脹	1 (0.2) / 527.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
食中毒	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.8 [0.3]	1 (0.2) / 871.6 [0.1]
歯の知覚過敏	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
歯の脱落	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
口唇乾燥	1 (0.2) / 528.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.0 [0.1]
びらん性胃炎	1 (0.2) / 528.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.1 [0.1]
メレナ	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.2 [0.1]
口腔内痛	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.3 [0.1]
心窩部不快感	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.6 [0.3]	1 (0.2) / 872.4 [0.1]
口唇炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.7 [0.3]	1 (0.2) / 872.6 [0.1]
一般・全身障害および投与部位の状態	37 (8.9) / 492.2 [7.5]	27 (10.0) / 310.5 [8.7]	61 (13.0) / 785.4 [7.8]
注射部位紅斑	4 (1.0) / 523.1 [0.8]	8 (3.0) / 334.6 [2.4]	11 (2.3) / 855.9 [1.3]
注射部位反応	4 (1.0) / 525.1 [0.8]	4 (1.5) / 337.9 [1.2]	7 (1.5) / 861.3 [0.8]
注射部位腫脹	2 (0.5) / 527.7 [0.4]	5 (1.9) / 339.7 [1.5]	7 (1.5) / 862.4 [0.8]
注射部位そう痒感	2 (0.5) / 526.4 [0.4]	5 (1.9) / 339.6 [1.5]	7 (1.5) / 862.6 [0.8]
注射部位出血	3 (0.7) / 527.8 [0.6]	3 (1.1) / 339.2 [0.9]	6 (1.3) / 863.8 [0.7]
発熱	4 (1.0) / 526.1 [0.8]	1 (0.4) / 343.6 [0.3]	5 (1.1) / 869.7 [0.6]
異常感	2 (0.5) / 524.5 [0.4]	2 (0.7) / 341.6 [0.6]	4 (0.9) / 866.2 [0.5]
注射部位疼痛	2 (0.5) / 525.9 [0.4]	2 (0.7) / 341.1 [0.6]	4 (0.9) / 867.1 [0.5]
倦怠感	2 (0.5) / 528.4 [0.4]	2 (0.7) / 342.1 [0.6]	4 (0.9) / 867.5 [0.5]
末梢性浮腫	3 (0.7) / 526.9 [0.6]	0 (0.0) / 343.8 [0.0]	3 (0.6) / 870.7 [0.3]
インフルエンザ様疾患	1 (0.2) / 526.9 [0.2]	1 (0.4) / 343.4 [0.3]	2 (0.4) / 868.6 [0.2]
胸部不快感	2 (0.5) / 526.7 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 869.4 [0.2]
注射部位知覚低下	1 (0.2) / 528.7 [0.2]	1 (0.4) / 342.0 [0.3]	2 (0.4) / 869.4 [0.2]
注射部位内出血	0 (0.0) / 528.8 [0.0]	2 (0.7) / 341.1 [0.6]	2 (0.4) / 869.9 [0.2]
非心臓性胸痛	2 (0.5) / 528.1 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 870.6 [0.2]
疲労	2 (0.5) / 527.2 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.0 [0.2]
投与部位疼痛	1 (0.2) / 526.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.5 [0.1]
注射部位発疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.4 [0.3]	1 (0.2) / 870.5 [0.1]
悪寒	1 (0.2) / 527.0 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.9 [0.1]

表 付録-7　SOC及びPT別のすべての有害事象（J-ISS-2：安全性解析対象集団）（続き）

System Organ Class Preferred Term	AMG 334 70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	AMG 334 Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
末梢腫脹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.3 [0.3]	1 (0.2) / 870.9 [0.1]
潰瘍	1 (0.2) / 527.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
全身性浮腫	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.7 [0.3]	1 (0.2) / 871.5 [0.1]
浮腫	1 (0.2) / 527.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.5 [0.1]
口渇	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
注射部位血腫	1 (0.2) / 528.0 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
熱感	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.2 [0.1]
肝胆道系障害	2 (0.5) / 526.9 [0.4]	2 (0.7) / 343.0 [0.6]	4 (0.9) / 868.6 [0.5]
脂肪肝	2 (0.5) / 526.9 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 870.8 [0.2]
原発性胆汁性胆管炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.3 [0.3]	1 (0.2) / 870.8 [0.1]
非アルコール性脂肪性肝炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.4 [0.1]
免疫系障害	10 (2.4) / 520.8 [1.9]	5 (1.9) / 339.9 [1.5]	15 (3.2) / 859.5 [1.7]
季節性アレルギー	8 (1.9) / 522.2 [1.5]	3 (1.1) / 341.0 [0.9]	11 (2.3) / 861.9 [1.3]
動物アレルギー	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
節足動物刺傷アレルギー	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.3 [0.3]	1 (0.2) / 872.1 [0.1]
過敏症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.3 [0.3]	1 (0.2) / 872.2 [0.1]
ダニアレルギー	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.2 [0.1]
感染症および寄生虫症	248 (59.9) / 252.0 [98.4]	178 (66.2) / 162.6 [109.5]	370 (78.7) / 367.7 [100.6]
上咽頭炎	191 (46.1) / 317.6 [60.1]	143 (53.2) / 207.9 [68.8]	299 (63.6) / 490.6 [60.9]
インフルエンザ	49 (11.8) / 489.6 [10.0]	30 (11.2) / 317.4 [9.5]	78 (16.6) / 805.4 [9.7]
胃腸炎	29 (7.0) / 502.5 [5.8]	19 (7.1) / 328.6 [5.8]	46 (9.8) / 822.4 [5.6]
咽頭炎	26 (6.3) / 502.5 [5.2]	10 (3.7) / 333.9 [3.0]	34 (7.2) / 831.1 [4.1]
膀胱炎	19 (4.6) / 514.5 [3.7]	9 (3.3) / 337.0 [2.7]	27 (5.7) / 844.3 [3.2]
気管支炎	16 (3.9) / 515.1 [3.1]	8 (3.0) / 335.1 [2.4]	24 (5.1) / 847.1 [2.8]
結膜炎	4 (1.0) / 525.9 [0.8]	10 (3.7) / 331.8 [3.0]	14 (3.0) / 857.5 [1.6]
上気道感染	5 (1.2) / 524.7 [1.0]	8 (3.0) / 335.9 [2.4]	13 (2.8) / 860.4 [1.5]
副鼻腔炎	7 (1.7) / 521.3 [1.3]	6 (2.2) / 339.8 [1.8]	13 (2.8) / 861.2 [1.5]
口腔ヘルペス	5 (1.2) / 523.0 [1.0]	2 (0.7) / 343.1 [0.6]	7 (1.5) / 864.4 [0.8]
歯周炎	4 (1.0) / 526.0 [0.8]	3 (1.1) / 341.2 [0.9]	7 (1.5) / 865.4 [0.8]
扁桃炎	4 (1.0) / 525.9 [0.8]	3 (1.1) / 341.4 [0.9]	7 (1.5) / 867.2 [0.8]
帯状疱疹	3 (0.7) / 525.3 [0.6]	3 (1.1) / 341.7 [0.9]	6 (1.3) / 867.0 [0.7]
鼻炎	2 (0.5) / 527.4 [0.4]	3 (1.1) / 340.9 [0.9]	5 (1.1) / 868.2 [0.6]
尿路感染	5 (1.2) / 525.6 [1.0]	0 (0.0) / 343.8 [0.0]	5 (1.1) / 869.4 [0.6]
ウイルス性胃腸炎	3 (0.7) / 524.5 [0.6]	1 (0.4) / 343.1 [0.3]	4 (0.9) / 867.6 [0.5]
ヘリコバクター感染	2 (0.5) / 527.2 [0.4]	2 (0.7) / 341.5 [0.6]	4 (0.9) / 868.7 [0.5]
麦粒腫	2 (0.5) / 528.4 [0.4]	2 (0.7) / 342.6 [0.6]	4 (0.9) / 871.0 [0.5]
足部白癬	2 (0.5) / 527.0 [0.4]	1 (0.4) / 343.7 [0.3]	3 (0.6) / 869.0 [0.3]
感染性腸炎	2 (0.5) / 526.6 [0.4]	1 (0.4) / 342.7 [0.3]	3 (0.6) / 869.3 [0.3]
アデノウイルス結膜炎	1 (0.2) / 528.3 [0.2]	2 (0.7) / 342.9 [0.6]	3 (0.6) / 869.5 [0.3]
レンサ球菌性咽頭炎	0 (0.0) / 528.8 [0.0]	3 (1.1) / 340.7 [0.9]	3 (0.6) / 869.5 [0.3]
急性副鼻腔炎	2 (0.5) / 527.2 [0.4]	1 (0.4) / 342.7 [0.3]	3 (0.6) / 869.9 [0.3]
ウイルス性腸炎	1 (0.2) / 527.5 [0.2]	1 (0.4) / 343.7 [0.3]	2 (0.4) / 869.5 [0.2]
毛包炎	0 (0.0) / 528.8 [0.0]	2 (0.7) / 342.4 [0.6]	2 (0.4) / 869.6 [0.2]
外耳炎	2 (0.5) / 526.7 [0.4]	1 (0.4) / 343.8 [0.3]	2 (0.4) / 869.7 [0.2]
歯肉炎	2 (0.5) / 526.3 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 870.2 [0.2]
憩室炎	2 (0.5) / 528.0 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 870.5 [0.2]
歯冠周囲炎	1 (0.2) / 527.2 [0.2]	1 (0.4) / 343.3 [0.3]	2 (0.4) / 870.5 [0.2]
β溶血性レンサ球菌感染	1 (0.2) / 528.3 [0.2]	1 (0.4) / 342.7 [0.3]	2 (0.4) / 871.0 [0.2]
外陰部腟カンジダ症	2 (0.5) / 528.1 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.9 [0.2]
扁桃周囲膿瘍	1 (0.2) / 526.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.6 [0.1]
陰部ヘルペス	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 870.6 [0.1]
マイコプラズマ性肺炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.2 [0.3]	1 (0.2) / 870.6 [0.1]
ヘルペスウイルス感染	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.3 [0.3]	1 (0.2) / 870.7 [0.1]
Ｅ型肝炎	1 (0.2) / 526.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.8 [0.1]
皮下組織膿瘍	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.8 [0.1]
中耳炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.7 [0.3]	1 (0.2) / 870.8 [0.1]
細菌性結膜炎	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.0 [0.1]
非定型マイコバクテリア感染	1 (0.2) / 527.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.3 [0.1]

表 付録-7　SOC及びPT別のすべての有害事象（J-ISS-2：安全性解析対象集団）（続き）

System Organ Class Preferred Term	AMG 334 70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	AMG 334 Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
慢性副鼻腔炎	1 (0.2) / 527.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.3 [0.1]
肺結核	1 (0.2) / 527.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.3 [0.1]
ウイルス性髄膜炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.5 [0.3]	1 (0.2) / 871.4 [0.1]
アデノイド咽頭炎	1 (0.2) / 527.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
術後創感染	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.6 [0.3]	1 (0.2) / 871.4 [0.1]
歯髄炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.6 [0.3]	1 (0.2) / 871.4 [0.1]
蓄膿	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.6 [0.3]	1 (0.2) / 871.5 [0.1]
マイコバクテリア感染	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.7 [0.3]	1 (0.2) / 871.5 [0.1]
耳下腺炎	1 (0.2) / 527.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.5 [0.1]
感染性瘻孔	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
腟感染	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.9 [0.3]	1 (0.2) / 871.7 [0.1]
椎間板炎	1 (0.2) / 528.0 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
皮膚播種性帯状疱疹	1 (0.2) / 528.0 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.9 [0.1]
卵巣炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.2 [0.3]	1 (0.2) / 872.0 [0.1]
喉頭炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.3 [0.3]	1 (0.2) / 872.1 [0.1]
細菌性胃腸炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.3 [0.3]	1 (0.2) / 872.1 [0.1]
咽頭扁桃炎	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.2 [0.1]
腸結核	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.4 [0.1]
爪囲炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.4 [0.1]
単純ヘルペス	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.6 [0.3]	1 (0.2) / 872.4 [0.1]
レンサ球菌感染	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
唾液腺炎	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.5 [0.1]
口腔カンジダ症	1 (0.2) / 528.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.5 [0.1]
傷害、中毒および処置合併症	50 (12.1) / 485.6 [10.3]	36 (13.4) / 315.1 [11.4]	84 (17.9) / 792.9 [10.6]
挫傷	10 (2.4) / 518.7 [1.9]	9 (3.3) / 337.1 [2.7]	19 (4.0) / 855.8 [2.2]
靱帯捻挫	9 (2.2) / 522.2 [1.7]	3 (1.1) / 341.0 [0.9]	12 (2.6) / 860.1 [1.4]
歯牙破折	6 (1.4) / 523.7 [1.1]	1 (0.4) / 342.6 [0.3]	7 (1.5) / 866.4 [0.8]
処置による疼痛	3 (0.7) / 528.2 [0.6]	3 (1.1) / 342.3 [0.9]	6 (1.3) / 869.2 [0.7]
上顆炎	3 (0.7) / 524.3 [0.6]	2 (0.7) / 343.2 [0.6]	5 (1.1) / 867.5 [0.6]
創傷	3 (0.7) / 527.2 [0.6]	2 (0.7) / 343.6 [0.6]	5 (1.1) / 869.1 [0.6]
靱帯損傷	0 (0.0) / 528.8 [0.0]	4 (1.5) / 341.0 [1.2]	4 (0.9) / 869.3 [0.5]
節足動物咬傷	2 (0.5) / 527.8 [0.4]	1 (0.4) / 343.8 [0.3]	3 (0.6) / 868.5 [0.3]
筋断裂	2 (0.5) / 527.1 [0.4]	1 (0.4) / 342.8 [0.3]	3 (0.6) / 869.9 [0.3]
肋骨骨折	1 (0.2) / 528.5 [0.2]	2 (0.7) / 341.5 [0.6]	3 (0.6) / 869.9 [0.3]
熱射病	2 (0.5) / 527.2 [0.4]	1 (0.4) / 343.5 [0.3]	3 (0.6) / 870.7 [0.3]
皮膚裂傷	1 (0.2) / 527.6 [0.2]	1 (0.4) / 342.9 [0.3]	2 (0.4) / 870.4 [0.2]
半月板損傷	1 (0.2) / 528.3 [0.2]	1 (0.4) / 342.2 [0.3]	2 (0.4) / 870.5 [0.2]
四肢損傷	2 (0.5) / 526.7 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 870.6 [0.2]
熱傷	2 (0.5) / 527.2 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.0 [0.2]
手骨折	1 (0.2) / 528.5 [0.2]	1 (0.4) / 342.5 [0.3]	2 (0.4) / 871.0 [0.2]
皮膚擦過傷	1 (0.2) / 527.7 [0.2]	1 (0.4) / 343.6 [0.3]	2 (0.4) / 871.2 [0.2]
膝蓋骨骨折	1 (0.2) / 528.5 [0.2]	1 (0.4) / 342.8 [0.3]	2 (0.4) / 871.3 [0.2]
肉離れ	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.1 [0.3]	1 (0.2) / 870.7 [0.1]
腓骨骨折	1 (0.2) / 526.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.7 [0.1]
節足動物刺傷	1 (0.2) / 526.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.8 [0.1]
脳振盪	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.0 [0.3]	1 (0.2) / 870.8 [0.1]
サンバーン	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.3 [0.3]	1 (0.2) / 871.1 [0.1]
低圧症	1 (0.2) / 527.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
鎖骨骨折	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
腱断裂	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
橈骨骨折	1 (0.2) / 528.0 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.9 [0.1]
熱中症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.1 [0.3]	1 (0.2) / 871.9 [0.1]
頚部損傷	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.1 [0.3]	1 (0.2) / 872.0 [0.1]
熱疲労	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.2 [0.3]	1 (0.2) / 872.0 [0.1]
軟骨損傷	1 (0.2) / 528.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.1 [0.1]
処置後合併症	1 (0.2) / 528.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.1 [0.1]
外傷性骨折	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.2 [0.1]
耳介血腫	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.3 [0.1]
足骨折	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.4 [0.1]
術後イレウス	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]

表 付録-7　SOC及びPT別のすべての有害事象（J-ISS-2：安全性解析対象集団）（続き）

System Organ Class Preferred Term	AMG 334 70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	AMG 334 Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
骨挫傷	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.6 [0.3]	1 (0.2) / 872.4 [0.1]
臨床検査	21 (5.1) / 503.5 [4.2]	12 (4.5) / 337.0 [3.6]	31 (6.6) / 835.9 [3.7]
体重減少	7 (1.7) / 519.7 [1.3]	3 (1.1) / 342.4 [0.9]	9 (1.9) / 861.1 [1.0]
白血球数減少	6 (1.4) / 520.0 [1.2]	0 (0.0) / 343.8 [0.0]	6 (1.3) / 862.7 [0.7]
体重増加	3 (0.7) / 527.0 [0.6]	1 (0.4) / 343.8 [0.3]	4 (0.9) / 870.9 [0.5]
好中球数減少	2 (0.5) / 525.1 [0.4]	1 (0.4) / 343.6 [0.3]	3 (0.6) / 867.0 [0.3]
アスパラギン酸アミノトランスフェラーゼ増加	2 (0.5) / 526.1 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 869.9 [0.2]
便潜血	1 (0.2) / 528.4 [0.2]	1 (0.4) / 343.0 [0.3]	2 (0.4) / 870.8 [0.2]
血中ブドウ糖増加	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 870.6 [0.1]
アラニンアミノトランスフェラーゼ増加	1 (0.2) / 526.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.6 [0.1]
血中クレアチンホスホキナーゼ増加	1 (0.2) / 527.1 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.0 [0.1]
肝機能検査異常	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.7 [0.3]	1 (0.2) / 871.5 [0.1]
血中コレステロール増加	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.7 [0.3]	1 (0.2) / 871.5 [0.1]
尿量減少	1 (0.2) / 528.1 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.9 [0.1]
血中尿酸増加	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.1 [0.3]	1 (0.2) / 872.0 [0.1]
骨密度減少	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.2 [0.3]	1 (0.2) / 872.1 [0.1]
心電図異常	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.3 [0.1]
代謝および栄養障害	4 (1.0) / 526.7 [0.8]	7 (2.6) / 339.5 [2.1]	11 (2.3) / 864.5 [1.3]
脱水	2 (0.5) / 527.1 [0.4]	1 (0.4) / 343.6 [0.3]	3 (0.6) / 870.7 [0.3]
石灰沈着性関節周囲炎	1 (0.2) / 528.6 [0.2]	1 (0.4) / 343.8 [0.3]	2 (0.4) / 872.4 [0.2]
高脂血症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.6 [0.3]	1 (0.2) / 870.8 [0.1]
糖尿病	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.6 [0.3]	1 (0.2) / 871.4 [0.1]
低カリウム血症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.7 [0.3]	1 (0.2) / 871.5 [0.1]
脂質異常症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.8 [0.3]	1 (0.2) / 871.6 [0.1]
２型糖尿病	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.8 [0.3]	1 (0.2) / 871.6 [0.1]
高コレステロール血症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.3 [0.1]
高尿酸血症	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
筋骨格系および結合組織障害	84 (20.3) / 453.4 [18.5]	49 (18.2) / 291.0 [16.8]	127 (27.0) / 720.6 [17.6]
背部痛	34 (8.2) / 498.4 [6.8]	8 (3.0) / 335.2 [2.4]	41 (8.7) / 827.7 [5.0]
頚部痛	8 (1.9) / 523.6 [1.5]	6 (2.2) / 338.9 [1.8]	14 (3.0) / 858.9 [1.6]
関節痛	9 (2.2) / 520.5 [1.7]	5 (1.9) / 338.6 [1.5]	14 (3.0) / 859.1 [1.6]
腱鞘炎	6 (1.4) / 521.6 [1.2]	4 (1.5) / 340.0 [1.2]	10 (2.1) / 861.7 [1.2]
四肢痛	7 (1.7) / 524.7 [1.3]	2 (0.7) / 343.1 [0.6]	9 (1.9) / 862.3 [1.0]
筋骨格硬直	5 (1.2) / 523.1 [1.0]	3 (1.1) / 340.4 [0.9]	8 (1.7) / 861.8 [0.9]
筋肉痛	5 (1.2) / 525.2 [1.0]	3 (1.1) / 340.6 [0.9]	8 (1.7) / 864.5 [0.9]
椎間板突出	5 (1.2) / 524.2 [1.0]	2 (0.7) / 341.2 [0.6]	7 (1.5) / 864.6 [0.8]
関節周囲炎	3 (0.7) / 527.1 [0.6]	4 (1.5) / 340.9 [1.2]	7 (1.5) / 864.8 [0.8]
変形性脊椎症	2 (0.5) / 526.6 [0.4]	4 (1.5) / 338.2 [1.2]	6 (1.3) / 863.5 [0.7]
筋骨格痛	4 (1.0) / 526.7 [0.8]	3 (1.1) / 340.3 [0.9]	6 (1.3) / 865.7 [0.7]
変形性関節症	3 (0.7) / 524.7 [0.6]	2 (0.7) / 341.3 [0.6]	5 (1.1) / 866.0 [0.6]
関節炎	3 (0.7) / 527.1 [0.6]	1 (0.4) / 342.7 [0.3]	4 (0.9) / 868.2 [0.5]
関節腫脹	3 (0.7) / 527.4 [0.6]	0 (0.0) / 343.8 [0.0]	3 (0.6) / 871.2 [0.3]
顎関節症候群	2 (0.5) / 525.6 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 869.5 [0.2]
筋痙縮	1 (0.2) / 527.5 [0.2]	1 (0.4) / 343.4 [0.3]	2 (0.4) / 870.0 [0.2]
滑液嚢腫	1 (0.2) / 527.7 [0.2]	1 (0.4) / 343.3 [0.3]	2 (0.4) / 871.0 [0.2]
筋膜炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.0 [0.3]	1 (0.2) / 870.9 [0.1]
椎間板障害	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.1 [0.3]	1 (0.2) / 871.0 [0.1]
肩回旋筋腱板症候群	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.2 [0.3]	1 (0.2) / 871.1 [0.1]
軟骨疾患	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.2 [0.3]	1 (0.2) / 871.1 [0.1]
筋骨格系胸痛	1 (0.2) / 528.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
弾発指	1 (0.2) / 528.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
側弯症	1 (0.2) / 527.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.3 [0.1]
筋力低下	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.5 [0.3]	1 (0.2) / 871.3 [0.1]
関節リウマチ	1 (0.2) / 527.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
関節石灰化	1 (0.2) / 527.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
筋骨格不快感	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.9 [0.3]	1 (0.2) / 871.7 [0.1]
骨壊死	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.9 [0.3]	1 (0.2) / 871.8 [0.1]
足底筋膜炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.9 [0.3]	1 (0.2) / 871.8 [0.1]

表 付録-7　SOC及びPT別のすべての有害事象（J-ISS-2：安全性解析対象集団）（続き）

System Organ Class Preferred Term	AMG 334 70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	AMG 334 Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
脊柱管狭窄症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.1 [0.3]	1 (0.2) / 871.9 [0.1]
四肢拘縮	1 (0.2) / 528.1 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.9 [0.1]
筋膜疼痛症候群	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.2 [0.3]	1 (0.2) / 872.0 [0.1]
腰部脊柱管狭窄症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.4 [0.3]	1 (0.2) / 872.2 [0.1]
全身性エリテマトーデス	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
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）	10 (2.4) / 521.4 [1.9]	4 (1.5) / 342.1 [1.2]	14 (3.0) / 860.0 [1.6]
子宮平滑筋腫	1 (0.2) / 527.4 [0.2]	2 (0.7) / 343.2 [0.6]	3 (0.6) / 868.9 [0.3]
皮膚乳頭腫	2 (0.5) / 527.6 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.4 [0.2]
アクロコルドン	1 (0.2) / 528.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.0 [0.1]
大腸腺腫	1 (0.2) / 527.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
眼瞼の良性新生物	1 (0.2) / 527.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.5 [0.1]
肺の良性新生物	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.7 [0.3]	1 (0.2) / 871.6 [0.1]
脂肪腫	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
乳房の良性新生物	1 (0.2) / 528.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.0 [0.1]
乳癌	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
乳管内増殖性病変	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
乳管内乳頭腫	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.8 [0.3]	1 (0.2) / 872.6 [0.1]
神経系障害	46 (11.1) / 482.2 [9.5]	32 (11.9) / 309.6 [10.3]	77 (16.4) / 784.7 [9.8]
浮動性めまい	12 (2.9) / 523.1 [2.3]	6 (2.2) / 337.1 [1.8]	18 (3.8) / 857.0 [2.1]
片頭痛	9 (2.2) / 523.9 [1.7]	9 (3.3) / 335.9 [2.7]	18 (3.8) / 859.8 [2.1]
感覚鈍麻	4 (1.0) / 524.2 [0.8]	3 (1.1) / 339.8 [0.9]	7 (1.5) / 863.5 [0.8]
頚腕症候群	3 (0.7) / 524.1 [0.6]	3 (1.1) / 339.1 [0.9]	6 (1.3) / 862.9 [0.7]
傾眠	4 (1.0) / 521.4 [0.8]	2 (0.7) / 341.7 [0.6]	6 (1.3) / 863.0 [0.7]
神経痛	3 (0.7) / 525.8 [0.6]	2 (0.7) / 341.6 [0.6]	5 (1.1) / 867.4 [0.6]
頭痛	1 (0.2) / 526.7 [0.2]	3 (1.1) / 342.4 [0.9]	4 (0.9) / 867.4 [0.5]
後頭神経痛	3 (0.7) / 526.0 [0.6]	1 (0.4) / 342.7 [0.3]	4 (0.9) / 868.7 [0.5]
緊張性頭痛	1 (0.2) / 528.4 [0.2]	3 (1.1) / 340.9 [0.9]	4 (0.9) / 869.3 [0.5]
肋間神経痛	2 (0.5) / 526.6 [0.4]	1 (0.4) / 342.4 [0.3]	3 (0.6) / 868.6 [0.3]
坐骨神経痛	1 (0.2) / 527.2 [0.2]	1 (0.4) / 342.9 [0.3]	2 (0.4) / 870.1 [0.2]
振戦	2 (0.5) / 526.4 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 870.2 [0.2]
失神寸前の状態	1 (0.2) / 527.8 [0.2]	1 (0.4) / 343.4 [0.3]	2 (0.4) / 870.9 [0.2]
錯感覚	1 (0.2) / 527.9 [0.2]	1 (0.4) / 343.4 [0.3]	1 (0.2) / 870.5 [0.1]
頚原性回転性めまい	1 (0.2) / 527.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.0 [0.1]
頚髄神経根障害	1 (0.2) / 527.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]
前兆を伴う片頭痛	1 (0.2) / 527.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.5 [0.1]
脊髄症	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
頭蓋内動脈瘤	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.0 [0.3]	1 (0.2) / 871.8 [0.1]
第３脳神経麻痺	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.2 [0.3]	1 (0.2) / 872.0 [0.1]
痙攣発作	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
手根管症候群	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
妊娠、産褥および周産期の状態	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.8 [0.3]	1 (0.2) / 872.6 [0.1]
切迫流産	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.8 [0.3]	1 (0.2) / 872.6 [0.1]
精神障害	26 (6.3) / 506.2 [5.1]	12 (4.5) / 336.4 [3.6]	37 (7.9) / 838.4 [4.4]
不眠症	11 (2.7) / 519.0 [2.1]	4 (1.5) / 340.1 [1.2]	15 (3.2) / 857.7 [1.7]
不安	4 (1.0) / 524.7 [0.8]	0 (0.0) / 343.8 [0.0]	4 (0.9) / 868.5 [0.5]
抑うつ気分	2 (0.5) / 525.9 [0.4]	1 (0.4) / 343.0 [0.3]	3 (0.6) / 868.9 [0.3]
不安障害	1 (0.2) / 528.2 [0.2]	1 (0.4) / 343.5 [0.3]	2 (0.4) / 871.7 [0.2]
うつ病	0 (0.0) / 528.8 [0.0]	2 (0.7) / 342.9 [0.6]	2 (0.4) / 871.8 [0.2]
睡眠障害	0 (0.0) / 528.8 [0.0]	2 (0.7) / 343.0 [0.6]	2 (0.4) / 871.8 [0.2]
急性ストレス反応	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.8 [0.3]	1 (0.2) / 871.0 [0.1]
中期不眠症	1 (0.2) / 527.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
パニック発作	1 (0.2) / 528.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.3 [0.1]
社交不安障害	1 (0.2) / 527.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
身体症状症	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
ストレス	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
閉経期うつ病	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.0 [0.3]	1 (0.2) / 871.9 [0.1]
予期不安	1 (0.2) / 528.1 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.9 [0.1]

表 付録-7　SOC及びPT別のすべての有害事象（J-ISS-2：安全性解析対象集団）（続き）

System Organ Class Preferred Term	AMG 334 70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	AMG 334 Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
パニック障害	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.2 [0.1]
不快気分	1 (0.2) / 528.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.6 [0.1]
身体疾患による不安障害	1 (0.2) / 528.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.7 [0.1]
腎および尿路障害	7 (1.7) / 520.9 [1.3]	2 (0.7) / 342.4 [0.6]	9 (1.9) / 860.3 [1.0]
腎結石症	1 (0.2) / 528.3 [0.2]	1 (0.4) / 343.5 [0.3]	2 (0.4) / 868.9 [0.2]
腎嚢胞	1 (0.2) / 527.4 [0.2]	1 (0.4) / 342.7 [0.3]	2 (0.4) / 870.1 [0.2]
尿管結石症	1 (0.2) / 526.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.7 [0.1]
排尿困難	1 (0.2) / 527.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]
頻尿	1 (0.2) / 527.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
夜間頻尿	1 (0.2) / 528.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.0 [0.1]
ループス腎炎	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.3 [0.1]
蛋白尿	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.3 [0.1]
生殖系および乳房障害	26 (6.3) / 509.9 [5.1]	10 (3.7) / 336.6 [3.0]	36 (7.7) / 840.8 [4.3]
月経困難症	6 (1.4) / 524.2 [1.1]	3 (1.1) / 342.1 [0.9]	9 (1.9) / 864.7 [1.0]
不規則月経	2 (0.5) / 526.1 [0.4]	2 (0.7) / 341.8 [0.6]	4 (0.9) / 867.9 [0.5]
不正子宮出血	4 (1.0) / 526.4 [0.8]	0 (0.0) / 343.8 [0.0]	4 (0.9) / 868.9 [0.5]
閉経期症状	2 (0.5) / 528.3 [0.4]	2 (0.7) / 343.3 [0.6]	4 (0.9) / 870.2 [0.5]
子宮頚部上皮異形成	2 (0.5) / 525.7 [0.4]	1 (0.4) / 342.3 [0.3]	3 (0.6) / 868.0 [0.3]
性器出血	2 (0.5) / 528.4 [0.4]	1 (0.4) / 343.5 [0.3]	3 (0.6) / 871.9 [0.3]
月経過多	1 (0.2) / 527.6 [0.2]	1 (0.4) / 342.8 [0.3]	2 (0.4) / 870.4 [0.2]
月経前症候群	2 (0.5) / 526.7 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 870.5 [0.2]
卵巣嚢胞	2 (0.5) / 527.8 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.6 [0.2]
萎縮性外陰腟炎	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]
卵巣機能不全	1 (0.2) / 528.1 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.9 [0.1]
乳房痛	1 (0.2) / 528.1 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.0 [0.1]
閉経期障害	1 (0.2) / 528.1 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.0 [0.1]
機能不全性子宮出血	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.4 [0.3]	1 (0.2) / 872.2 [0.1]
子宮頚管ポリープ	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
無排卵性出血	1 (0.2) / 528.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.5 [0.1]
呼吸器、胸郭および縦隔障害	58 (14.0) / 480.2 [12.1]	27 (10.0) / 319.1 [8.5]	83 (17.7) / 789.5 [10.5]
上気道の炎症	12 (2.9) / 518.5 [2.3]	11 (4.1) / 334.8 [3.3]	23 (4.9) / 849.3 [2.7]
口腔咽頭痛	15 (3.6) / 517.1 [2.9]	2 (0.7) / 341.5 [0.6]	17 (3.6) / 857.2 [2.0]
アレルギー性鼻炎	13 (3.1) / 515.9 [2.5]	3 (1.1) / 340.1 [0.9]	16 (3.4) / 856.0 [1.9]
咳嗽	9 (2.2) / 522.9 [1.7]	4 (1.5) / 341.7 [1.2]	13 (2.8) / 859.6 [1.5]
喘息	7 (1.7) / 522.3 [1.3]	3 (1.1) / 341.9 [0.9]	10 (2.1) / 862.6 [1.2]
アレルギー性咳嗽	2 (0.5) / 528.6 [0.4]	3 (1.1) / 340.4 [0.9]	5 (1.1) / 869.0 [0.6]
鼻出血	0 (0.0) / 528.8 [0.0]	2 (0.7) / 341.5 [0.6]	2 (0.4) / 870.3 [0.2]
口腔咽頭不快感	2 (0.5) / 527.2 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.1 [0.2]
過換気	2 (0.5) / 528.0 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.9 [0.2]
喉頭肉芽腫	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.9 [0.1]
逆流性喉頭炎	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.9 [0.1]
鼻漏	1 (0.2) / 527.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
呼吸困難	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
鼻乾燥	1 (0.2) / 527.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
湿性咳嗽	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.9 [0.3]	1 (0.2) / 871.8 [0.1]
咽喉乾燥	1 (0.2) / 528.0 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
副鼻腔痛	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.3 [0.1]
皮膚および皮下組織障害	60 (14.5) / 473.5 [12.7]	43 (16.0) / 308.9 [13.9]	99 (21.1) / 768.4 [12.9]
湿疹	14 (3.4) / 516.0 [2.7]	11 (4.1) / 333.5 [3.3]	25 (5.3) / 846.8 [3.0]
蕁麻疹	9 (2.2) / 521.0 [1.7]	6 (2.2) / 338.8 [1.8]	15 (3.2) / 856.7 [1.8]
ざ瘡	7 (1.7) / 525.2 [1.3]	4 (1.5) / 340.6 [1.2]	11 (2.3) / 864.1 [1.3]
そう痒症	4 (1.0) / 525.9 [0.8]	3 (1.1) / 341.2 [0.9]	7 (1.5) / 865.8 [0.8]
皮膚炎	3 (0.7) / 526.0 [0.6]	3 (1.1) / 339.9 [0.9]	6 (1.3) / 865.9 [0.7]
発疹	3 (0.7) / 524.0 [0.6]	2 (0.7) / 341.5 [0.6]	5 (1.1) / 865.5 [0.6]
接触皮膚炎	2 (0.5) / 526.4 [0.4]	3 (1.1) / 341.8 [0.9]	5 (1.1) / 866.5 [0.6]
汗疹	4 (1.0) / 526.4 [0.8]	0 (0.0) / 343.8 [0.0]	4 (0.9) / 869.1 [0.5]
脂漏性皮膚炎	2 (0.5) / 525.9 [0.4]	1 (0.4) / 342.1 [0.3]	3 (0.6) / 868.0 [0.3]
アレルギー性皮膚炎	2 (0.5) / 526.0 [0.4]	1 (0.4) / 342.0 [0.3]	3 (0.6) / 868.0 [0.3]

表 付録-7　SOC及びPT別のすべての有害事象（J-ISS-2：安全性解析対象集団）（続き）

	AMG 334		
	70 mg QM (Subj-yr = 528.8)	140 mg QM (Subj-yr = 343.8)	Combined (Subj-yr = 872.7)
System Organ Class Preferred Term	(N = 414) n (%) / e [r]	(N = 269) n (%) / e [r]	(N = 470) n (%) / e [r]
過角化	0 (0.0) / 528.8 [0.0]	3 (1.1) / 341.9 [0.9]	3 (0.6) / 870.7 [0.3]
皮脂欠乏性湿疹	1 (0.2) / 528.2 [0.2]	1 (0.4) / 343.6 [0.3]	2 (0.4) / 868.7 [0.2]
皮脂欠乏症	1 (0.2) / 528.2 [0.2]	1 (0.4) / 342.7 [0.3]	2 (0.4) / 869.5 [0.2]
嵌入爪	1 (0.2) / 528.5 [0.2]	1 (0.4) / 343.4 [0.3]	2 (0.4) / 870.7 [0.2]
丘疹状蕁麻疹	2 (0.5) / 527.1 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.0 [0.2]
皮膚嚢腫	2 (0.5) / 527.2 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.0 [0.2]
皮膚乾燥	2 (0.5) / 527.8 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.7 [0.2]
脱毛症	1 (0.2) / 528.8 [0.2]	1 (0.4) / 343.4 [0.3]	2 (0.4) / 872.2 [0.2]
日光皮膚炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.8 [0.3]	1 (0.2) / 871.0 [0.1]
多汗症	1 (0.2) / 527.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.0 [0.1]
爪の障害	1 (0.2) / 527.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]
肝斑	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.5 [0.3]	1 (0.2) / 871.3 [0.1]
丘疹	1 (0.2) / 527.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
皮下出血	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.5 [0.3]	1 (0.2) / 871.4 [0.1]
多形紅斑	1 (0.2) / 527.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
中毒性皮疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.7 [0.3]	1 (0.2) / 871.5 [0.1]
皮膚腫脹	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
アンドロゲン性脱毛症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.1 [0.3]	1 (0.2) / 871.9 [0.1]
アレルギー性そう痒症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.1 [0.3]	1 (0.2) / 871.9 [0.1]
乏汗症	1 (0.2) / 528.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.0 [0.1]
特発性蕁麻疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.2 [0.3]	1 (0.2) / 872.0 [0.1]
紅斑	1 (0.2) / 528.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.1 [0.1]
皮膚刺激	1 (0.2) / 528.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.1 [0.1]
円形脱毛症	1 (0.2) / 528.3 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.1 [0.1]
手皮膚炎	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.3 [0.1]
紅斑性皮疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.4 [0.1]
そう痒性皮疹	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
慢性蕁麻疹	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
薬疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.8 [0.3]	1 (0.2) / 872.6 [0.1]
血管障害	12 (2.9) / 520.2 [2.3]	5 (1.9) / 341.6 [1.5]	17 (3.6) / 857.1 [2.0]
高血圧	8 (1.9) / 523.4 [1.5]	3 (1.1) / 342.3 [0.9]	11 (2.3) / 863.9 [1.3]
静脈瘤	1 (0.2) / 528.7 [0.2]	1 (0.4) / 343.4 [0.3]	2 (0.4) / 869.1 [0.2]
起立性低血圧	1 (0.2) / 527.0 [0.2]	1 (0.4) / 343.6 [0.3]	2 (0.4) / 870.5 [0.2]
レイノー現象	1 (0.2) / 528.0 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
末梢血管障害	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1



表 付録-8　SOC及びPT別の治験薬との関連ありの有害事象（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (Subj-yr = 528 8)	140 mg QM (Subj-yr = 343.8)	Combined (Subj-yr = 872.7)
System Organ Class Preferred Term	(N = 414) n (%) / e [r]	(N = 269) n (%) / e [r]	(N = 470) n (%) / e [r]
All treatment-related treatment-emergent adverse events	42 (10.1) / 480.0 [8.8]	26 (9.7) / 315.1 [8.3]	64 (13.6) / 775.5 [8.3]
心臓障害	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 870.7 [0.1]
動悸	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 870.7 [0.1]
内分泌障害	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
甲状腺機能亢進症	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
胃腸障害	14 (3.4) / 512.4 [2.7]	7 (2.6) / 338.5 [2.1]	20 (4.3) / 837.6 [2.4]
便秘	7 (1.7) / 523.2 [1.3]	5 (1.9) / 341.0 [1.5]	11 (2.3) / 852.5 [1.3]
上腹部痛	1 (0.2) / 527.4 [0.2]	1 (0.4) / 343.4 [0.3]	2 (0.4) / 869.1 [0.2]
胃炎	1 (0.2) / 527.2 [0.2]	1 (0.4) / 343.6 [0.3]	2 (0.4) / 869.1 [0.2]
下腹部痛	1 (0.2) / 528.5 [0.2]	1 (0.4) / 341.8 [0.3]	2 (0.4) / 870.3 [0.2]
排便困難	1 (0.2) / 526.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.6 [0.1]
口内炎	1 (0.2) / 526.9 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.7 [0.1]
慢性胃炎	1 (0.2) / 527.0 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.8 [0.1]
出血性腸憩室	1 (0.2) / 527.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
一般・全身障害および投与部位の状態	12 (2.9) / 512.7 [2.3]	16 (5.9) / 325.3 [4.9]	26 (5.5) / 831.2 [3.1]
注射部位紅斑	4 (1.0) / 523.1 [0.8]	6 (2.2) / 336.1 [1.8]	9 (1.9) / 859.1 [1.0]
注射部位反応	4 (1.0) / 525.1 [0.8]	4 (1.5) / 337.9 [1.2]	7 (1.5) / 861.3 [0.8]
注射部位そう痒感	1 (0.2) / 527.2 [0.2]	4 (1.5) / 340.1 [1.2]	5 (1.1) / 865.7 [0.6]
注射部位腫脹	1 (0.2) / 528.0 [0.2]	3 (1.1) / 340.3 [0.9]	4 (0.9) / 868.3 [0.5]
インフルエンザ様疾患	1 (0.2) / 526.9 [0.2]	1 (0.4) / 343.4 [0.3]	2 (0.4) / 868.6 [0.2]
異常感	1 (0.2) / 526.7 [0.2]	1 (0.4) / 342.8 [0.3]	2 (0.4) / 869.5 [0.2]
注射部位発疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.4 [0.3]	1 (0.2) / 870.5 [0.1]
倦怠感	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 870.6 [0.1]
注射部位疼痛	1 (0.2) / 527.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.0 [0.1]
感染症および寄生虫症	3 (0.7) / 524.1 [0.6]	2 (0.7) / 342.3 [0.6]	5 (1.1) / 864.8 [0.6]
帯状疱疹	2 (0.5) / 526.2 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 870.1 [0.2]
上咽頭炎	1 (0.2) / 526.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.6 [0.1]
胃腸炎	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 870.6 [0.1]
マイコバクテリア感染	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.7 [0.3]	1 (0.2) / 871.5 [0.1]
臨床検査	6 (1.4) / 520.8 [1.2]	2 (0.7) / 343.3 [0.6]	7 (1.5) / 861.2 [0.8]
白血球数減少	5 (1.2) / 521.5 [1.0]	0 (0.0) / 343.8 [0.0]	5 (1.1) / 864.1 [0.6]
好中球数減少	2 (0.5) / 525.1 [0.4]	1 (0.4) / 343.6 [0.3]	3 (0.6) / 867.0 [0.3]
体重減少	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.6 [0.3]	1 (0.2) / 870.7 [0.1]
アスパラギン酸アミノトランスフェラーゼ増加	1 (0.2) / 528.1 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.0 [0.1]
筋骨格系および結合組織障害	3 (0.7) / 526.8 [0.6]	2 (0.7) / 341.6 [0.6]	5 (1.1) / 865.4 [0.6]
四肢痛	1 (0.2) / 528.3 [0.2]	1 (0.4) / 343.7 [0.3]	2 (0.4) / 869.0 [0.2]
背部痛	0 (0.0) / 528.8 [0.0]	1 (0.4) / 341.7 [0.3]	1 (0.2) / 870.5 [0.1]
関節リウマチ	1 (0.2) / 527.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
全身性エリテマトーデス	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
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 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
乳癌	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
神経系障害	4 (1.0) / 521.4 [0.8]	0 (0.0) / 343.8 [0.0]	4 (0.9) / 865.2 [0.5]
傾眠	3 (0.7) / 522.6 [0.6]	0 (0.0) / 343.8 [0.0]	3 (0.6) / 866.4 [0.3]
振戦	1 (0.2) / 527.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.5 [0.1]
精神障害	1 (0.2) / 528.6 [0.2]	1 (0.4) / 341.7 [0.3]	2 (0.4) / 870.2 [0.2]
不眠症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 341.7 [0.3]	1 (0.2) / 870.5 [0.1]
不安	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
腎および尿路障害	2 (0.5) / 527.0 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 870.8 [0.2]
頻尿	1 (0.2) / 527.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.2 [0.1]
ループス腎炎	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.3 [0.1]

表 付録-8　SOC及びPT別の治験薬との関連ありの有害事象（J-ISS-2：安全性解析対象集団）（続き）

System Organ Class Preferred Term	AMG 334 70 mg QM (Subj-yr = 528 8) (N = 414) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	AMG 334 Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
生殖系および乳房障害	1 (0.2) / 527.2 [0.2]	1 (0.4) / 342.3 [0.3]	2 (0.4) / 869.5 [0.2]
子宮頚部上皮異形成	1 (0.2) / 527.2 [0.2]	1 (0.4) / 342.3 [0.3]	2 (0.4) / 869.5 [0.2]
呼吸器、胸郭および縦隔障害	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.9 [0.1]
喉頭肉芽腫	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.9 [0.1]
逆流性喉頭炎	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.9 [0.1]
皮膚および皮下組織障害	4 (1.0) / 524.6 [0.8]	2 (0.7) / 342.4 [0.6]	6 (1.3) / 867.0 [0.7]
発疹	1 (0.2) / 527.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.1 [0.1]
丘疹状蕁麻疹	1 (0.2) / 527.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.5 [0.1]
蕁麻疹	1 (0.2) / 527.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.5 [0.1]
中毒性皮疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.7 [0.3]	1 (0.2) / 871.5 [0.1]
紅斑性皮疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.4 [0.1]
そう痒性皮疹	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
血管障害	3 (0.7) / 526.3 [0.6]	0 (0.0) / 343.8 [0.0]	3 (0.6) / 870.1 [0.3]
高血圧	3 (0.7) / 526.3 [0.6]	0 (0.0) / 343.8 [0.0]	3 (0.6) / 870.1 [0.3]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1

[redacted]

表 付録-9　死亡一覧（20120178試験：安全性解析対象集団）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	UNITED STATES	5[redacted] M WHITE	AMG334QM 70MG	OLTP	動脈硬化症	20[redacted]-	650	1	Y	Grade 5	NOT RELATED	FATAL	DOSE NOT CHANGED	NO ACTION TAKEN	Y
[redacted]	UNITED STATES	4[redacted] M BLACK OR AFRICAN AMERICAN	AMG334QM 140MG	OLTP	死亡	20[redacted]-	1943	1	Y	Grade 5	NOT RELATED	FATAL	DOSE NOT CHANGED	UNKNOWN	Y

Coded using CTCAE version 4.03; MedDRA version 22.1
DBTP = Double-blind treatment period; OLTP = Open-label treatment period
Study Day = Study day of onset of adverse event; Outcome = Outcome of serious adverse event; Action Taken = Action taken with study treatment

[redacted]

表 付録-10　死亡一覧（20120296試験：安全性解析対象集団）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	CZECH REPUBLIC	4[redacted] M WHITE	AMG334QM140MG	ATP	不整脈原性右室異形成症	20[redacted]-	275	1	Y	Grade 5	NOT RELATED	FATAL	DRUG WITHDRAWN	NO ACTION TAKEN	Y

Coded using CTCAE version 4.03; MedDRA version 20.0
DBTP = Double-blind treatment period; OLTP = Open-label treatment period
Study Day = Study day of onset of adverse event; Outcome = Outcome of serious adverse event; Action Taken = Action taken with study treatment

[redacted]

表 付録-11　重篤な有害事象を発現した被験者一覧（20120309試験：安全性解析対象集団）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 70MG	OLTP	乳管内増殖性病変	20[redacted]-	197	28	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	OTHER	
[redacted]	JAPAN	4[redacted] M ASIAN	AMG334QM 140MG	OLTP	手骨折	20[redacted]-	287	65	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/ PROLONGED HOSPITALIZATION, MEDICATION TAKEN, OTHER	
[redacted]	JAPAN	3[redacted] F ASIAN	AMG334QM 70MG	OLTP	憩室炎	20[redacted]-	546	46	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/ PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	JAPAN	5[redacted] F ASIAN	PLACEBO	DBTP	片頭痛	20[redacted]-	89	46	Y	Grade 3	RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	EMERGENCY ROOM VISIT, MEDICATION TAKEN	
[redacted]	JAPAN	6[redacted] F ASIAN	AMG334QM 70MG	OLTP	鎖骨骨折	20[redacted]-	403	107	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
[redacted]	JAPAN	5[redacted] F ASIAN	AMG334QM 70MG	OLTP	脊髄症	20[redacted]-	439	340	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED/ PROLONGED HOSPITALIZATION, OTHER	
[redacted]	JAPAN	5[redacted] F ASIAN	AMG334QM 70MG	OLTP	乳癌	20[redacted]-	640		Y	Grade 3	RELATED	NOT RECOVERED/ NOT RESOLVED	DRUG WITHDRAWN	OTHER, MEDICATION TAKEN	
[redacted]	JAPAN	3[redacted] F ASIAN	AMG334QM 70MG	OLTP	腸炎	20[redacted]-	392	4	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DRUG INTERRUPTED	HOSPITALIZED/ PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	JAPAN	5[redacted] F ASIAN	AMG334QM 140MG	OLTP	マイコバクテリア感染	20[redacted]-	364		Y	Grade 2	RELATED	NOT RECOVERED/ NOT RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/ PROLONGED HOSPITALIZATION	
[redacted]	JAPAN	5[redacted] F ASIAN	PLACEBO	DBTP	腎細胞癌	20[redacted]-	79	90	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	

表 付録-11　重篤な有害事象を発現した被験者一覧（20120309試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 70MG	OLTP	痔核	20[redacted]-	706		Y	Grade 3	NOT RELATED	NOT RECOVERED /NOT RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/ PROLONGED HOSPITALIZATION	
[redacted]	JAPAN	4[redacted] M ASIAN	AMG334QM 70MG	OLTP	筋断裂	20[redacted]-	436	36	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DRUG INTERRUPTED	OTHER	
[redacted]	JAPAN	4[redacted] M ASIAN	AMG334QM 70MG	OLTP	腱断裂	20[redacted]-	436	36	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DRUG INTERRUPTED	OTHER	
			AMG334QM 70MG	OLTP	四肢拘縮	20[redacted]-	510	18	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/ PROLONGED HOSPITALIZATION, OTHER	
[redacted]	JAPAN	4[redacted] M ASIAN	AMG334QM 70MG	OLTP	腱断裂	20[redacted]-	526	30	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/ PROLONGED HOSPITALIZATION, OTHER	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 140MG	OLTP	頭蓋内動脈瘤	20[redacted]-	468	96	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	JAPAN	3[redacted] M ASIAN	AMG334QM 70MG	OLTP	半月板損傷	20[redacted]-	602	134	Y	Grade 2	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	JAPAN	5[redacted] F ASIAN	AMG334QM 140MG	OLTP	頭位性回転性めまい	20[redacted]-	606	79	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 70MG	DBTP	全身性エリテマトーデス	20[redacted]-	146		Y	Grade 4	RELATED	NOT RECOVERED /NOT RESOLVED	DRUG WITHDRAWN	MEDICATION TAKEN	
[redacted]	JAPAN	3[redacted] F ASIAN	PLACEBO	DBTP	プリンツメタル狭心症	20[redacted]-	155		Y	Grade 2	NOT RELATED	NOT RECOVERED /NOT RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
[redacted]	JAPAN	5[redacted] F ASIAN	AMG334QM 140MG	OLTP	軟骨疾患	20[redacted]-	205	27	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	OTHER, OTHER	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 140MG	OLTP	眼瞼下垂	20[redacted]-	404	150	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/PROLONGED HOSPITALIZATION, MEDICATION TAKEN, OTHER	

表 付録-11　重篤な有害事象を発現した被験者一覧（20120309試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 140MG	OLTP	眼瞼下垂	20[redacted]- [redacted]-	404	270	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/ PROLONGED HOSPITALIZATION, MEDICATION TAKEN, OTHER	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 28MG	DBTP	手骨折	20[redacted]- [redacted]-	120	77	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
[redacted]	JAPAN	5[redacted] F ASIAN	AMG334QM 70MG	OLTP	大腸ポリープ	20[redacted]- [redacted]-	452	2	Y	Grade 2	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 140MG	DBTP	胃腸炎	20[redacted]- [redacted]-	111	16	Y	Grade 2	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	OTHER, MEDICATION TAKEN	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 140MG	DBTP	腸結核	20[redacted]- [redacted]-	140		Y	Grade 2	NOT RELATED	NOT RECOVERED /NOT RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 70MG	OLTP	咽頭炎	20[redacted]- [redacted]-	334	22	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 70MG	OLTP	扁桃炎	20[redacted]- [redacted]-	334	22	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
[redacted]	JAPAN	2[redacted] F ASIAN	AMG334QM 70MG	OLTP	脱水	20[redacted]- [redacted]-	461	2	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED/ PROLONGED HOSPITALIZATION	
[redacted]	JAPAN	4[redacted] M ASIAN	AMG334QM 70MG	OLTP	出血性腸憩室	20[redacted]- [redacted]-	257	6	Y	Grade 3	RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	UNKNOWN, EMERGENCY ROOM VISIT	
			AMG334QM 70MG	OLTP	大腸腺腫	20[redacted]- [redacted]-	258	45	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 70MG	OLTP	子宮平滑筋腫	20[redacted]- [redacted]-	280	392	Y	Grade 2	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/PRO LONGED HOSPITALIZATION, OTHER	
[redacted]	JAPAN	3[redacted] M ASIAN	AMG334QM 140MG	OLTP	うつ病	20[redacted]- [redacted]-	515	30	Y	Grade 2	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/PRO LONGED HOSPITALIZATION	

表 付録-11　重篤な有害事象を発現した被験者一覧（20120309試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	JAPAN	3[redacted] M ASIAN	AMG334QM 140MG	OLTP	うつ病	20[redacted]-	682	58	Y	Grade 2	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED/ PROLONGED HOSPITALIZATION	
[redacted]	JAPAN	6[redacted] F ASIAN	AMG334QM 140MG	OLTP	骨壊死	20[redacted]-	449		Y	Grade 3	NOT RELATED	NOT RECOVERED /NOT RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/ PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 140MG	OLTP	ウイルス性髄膜炎	20[redacted]-	305	61	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED/ PROLONGED HOSPITALIZATION	
			AMG334QM 140MG	OLTP	頭痛	20[redacted]-	728	58	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/ PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 70MG	OLTP	歯牙破折	20[redacted]-	200	68	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	JAPAN	5[redacted] F ASIAN	AMG334QM 70MG	OLTP	軟骨損傷	20[redacted]-	576	22	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/ PROLONGED HOSPITALIZATION, MEDICATION TAKEN, OTHER	
[redacted]	JAPAN	5[redacted] F ASIAN	PLACEBO	DBTP	痔核	20[redacted]-	23	70	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	OTHER, OTHER	
[redacted]	JAPAN	5[redacted] F ASIAN	AMG334QM 70MG	OLTP	術後イレウス	20[redacted]-	504	100	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, OTHER, OTHER, MEDICATION TAKEN	
[redacted]	JAPAN	2[redacted] F ASIAN	AMG334QM 70MG	OLTP	子宮頚部上皮異形成	20[redacted]-	224	121	Y	Grade 3	NOT RELATED	RECOVERED /RESOLVED	DOSE NOT CHANGED	OTHER	

Coded using CTCAE version 4.03; MedDRA version 22.0
DBTP = Double-blind treatment period; OLTP = Open-label treatment period
Study Day = Study day of onset of adverse event; Outcome = Outcome of serious adverse event; Action Taken = Action taken with study treatment

[redacted]

表 付録-12　重篤な有害事象を発現した被験者一覧（20170609試験：安全性解析対象集団）

Subject Identifier for the Study	Country	Age Sex Race Migraine	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	JAPAN	3[redacted] F ASIAN EM	AMG334QM 70MG	DBTP	椎間板突出	20[redacted]	137	26	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED/PROLONGED HOSPITALIZATION	
[redacted]	JAPAN	5[redacted] F ASIAN EM	AMG334QM 70MG	DBTP	くも膜下出血	20[redacted]	26	164	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DRUG INTERRUPTED	HOSPITALIZED/PROLONGED HOSPITALIZATION, EMERGENCY ROOM VISIT	
				DBTP	創傷	20[redacted]	26	164	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DRUG INTERRUPTED	HOSPITALIZED/PROLONGED HOSPITALIZATION, EMERGENCY ROOM VISIT	
				DBTP	脳挫傷	20[redacted]	26	164	Y	Grade 1	NOT RELATED	RECOVERED/ RESOLVED	DRUG INTERRUPTED	HOSPITALIZED/PROLONGED HOSPITALIZATION, EMERGENCY ROOM VISIT	
				DBTP	鎖骨骨折	20[redacted]	26	164	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DRUG INTERRUPTED	HOSPITALIZED/PROLONGED HOSPITALIZATION, EMERGENCY ROOM VISIT	
				DBTP	頭蓋骨骨折	20[redacted]	26	164	Y	Grade 1	NOT RELATED	RECOVERED/ RESOLVED	DRUG INTERRUPTED	HOSPITALIZED/PROLONGED HOSPITALIZATION, EMERGENCY ROOM VISIT	
[redacted]	JAPAN	4[redacted] F ASIAN CM	PLACEBO	DBTP	卵巣腺腫	20[redacted]	58	196	Y	Grade 3	RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/PROLONGED HOSPITALIZATION	
[redacted]	JAPAN	6[redacted] F ASIAN EM	PLACEBO	DBTP	虫垂炎	20[redacted]	135	7	Y	Grade 4	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED/PROLONGED HOSPITALIZATION	

Coded using CTCAE version 4.03; MedDRA version 22.1
DBTP = Double-blind treatment period; EM = Episodic migraine; CM = Chronic migraine
Study Day = Study day of onset of adverse event; Outcome = Outcome of serious adverse event; Action Taken = Action taken with study treatment

[redacted]

表 付録-13　重篤な有害事象を発現した被験者一覧（20120178試験：安全性解析対象集団）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	DENMARK	3[redacted] F WHITE	AMG334QM 7MG	DBTP	卵巣嚢胞破裂	20[redacted]-	57	8	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 70MG	OLTP	胃腸炎	20[redacted]-	87	2	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 140MG	OLTP	回転性めまい	20[redacted]-	1214	2	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	DENMARK	4[redacted] F WHITE	AMG334QM 140MG	OLTP	原発性アルドステロン症	20[redacted]-	1064	8	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	DENMARK	4[redacted] F WHITE	AMG334QM 140MG	OLTP	発育性股関節形成不全	20[redacted]-	1417	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	DENMARK	4[redacted] F WHITE	AMG334QM 140MG	OLTP	低血糖	20[redacted]-	1010	2	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 140MG	OLTP	クレブシエラ菌性肺炎	20[redacted]-	1636	4	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	DENMARK	4[redacted] F WHITE	PLACEBO	DBTP	尿路感染	20[redacted]-	42	885	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 70MG	OLTP	肝嚢胞	20[redacted]-	672	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	FINLAND	5[redacted] F WHITE	AMG334QM 70MG	OLTP	変形性関節症	20[redacted]-	115	4	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION, OTHER	
[redacted]	FINLAND	4[redacted] M WHITE	AMG334QM 140MG	OLTP	靱帯断裂	20[redacted]-	1824	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	

表 付録-13　重篤な有害事象を発現した被験者一覧（20120178試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	FINLAND	3[redacted] F WHITE	AMG334QM 70MG	OLTP	視力障害	20[redacted]-	378	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DRUG INTERRUPTED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	FINLAND	3[redacted] F WHITE	AMG334QM 70MG	OLTP	卵巣嚢胞	20[redacted]-	116	26	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
			AMG334QM 140MG	OLTP	虫垂炎	20[redacted]-	1035	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	FINLAND	4[redacted] F WHITE	AMG334QM 70MG	OLTP	乳癌	20[redacted]-	169		Y	Grade 2	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DRUG WITHDRAWN	OTHER, HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	GERMANY	5[redacted] F WHITE	AMG334QM 70MG	OLTP	適応障害	20[redacted]-	463	67	Y	Grade 1	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	
			AMG334QM 140MG	OLTP	頚腕症候群	20[redacted]-	1285	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	GERMANY	3[redacted] F WHITE	AMG334QM 140MG	OLTP	適応障害	20[redacted]	1033	297	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 140MG	OLTP	自殺企図	20[redacted]-	1257	1	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	OTHER	
[redacted]	GERMANY	5[redacted] F WHITE	AMG334QM 70MG	OLTP	中足骨痛	20[redacted]-	403		Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	GERMANY	5[redacted] F WHITE	AMG334QM 70MG	OLTP	心筋虚血	20[redacted]-	149	42	Y	Grade 2	RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	GERMANY	4[redacted] F WHITE	AMG334QM 70MG	OLTP	腰髄神経根障害	20[redacted]-	677	9	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	

表 付録-13　重篤な有害事象を発現した被験者一覧（20120178試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	GERMANY	5[redacted] F WHITE	AMG334QM 70MG	OLTP	子宮付属器嚢胞	20[redacted]-	677	4	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, OTHER	
			AMG334QM 140MG	OLTP	冠動脈狭窄	20[redacted]-	1859	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	GERMANY	5[redacted] F WHITE	AMG334QM 140MG	OLTP	膀胱脱	20[redacted]-	1279	23	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 140MG	OLTP	靭帯断裂	20[redacted]-	1409	100	Y	Grade 1	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	GERMANY	4[redacted] F WHITE	AMG334QM 70MG	OLTP	子宮平滑筋腫	20[redacted]-	795	5	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	GERMANY	3[redacted] F WHITE	AMG334QM 70MG	OLTP	失神	20[redacted]-	383	9	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	GERMANY	4[redacted] F WHITE	AMG334QM 70MG	OLTP	糞塊	20[redacted]-	298	12	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 140MG	OLTP	卵管卵巣膿瘍	20[redacted]-	1046	11	Y	Grade 4	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, OTHER, MEDICATION TAKEN, OTHER	
[redacted]	SWEDEN	4[redacted] F WHITE	AMG334QM 70MG	OLTP	靭帯断裂	20[redacted]-	815	2	Y	Grade 1	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	SWEDEN	2[redacted] F WHITE	AMG334QM 140MG	OLTP	憩室炎	20[redacted]-	1087	3	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	SWEDEN	3[redacted] F WHITE	AMG334QM 70MG	DBTP	片頭痛	20[redacted]-	9	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 70MG	DBTP	回転性めまい	20[redacted]-	29	21	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, OTHER	

表 付録-13　重篤な有害事象を発現した被験者一覧（20120178試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	UNITED STATES	3[redacted] F WHITE	AMG334QM 140MG	OLTP	子宮頚部腺癌	20[redacted]-	1192	23	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	UNITED STATES	3[redacted] F WHITE	AMG334QM 70MG	OLTP	失神	20[redacted]-	609		Y	Grade 3	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DRUG WITHDRAWN	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	UNITED STATES	5[redacted] M WHITE	AMG334QM 70MG	OLTP	憩室	20[redacted]-	688	272	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 70MG	OLTP	虚血性大腸炎	20[redacted]-	688	6	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	OLTP	胆嚢炎	20[redacted]-	513	120	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
			AMG334QM 70MG	OLTP	腹部ヘルニア	20[redacted]-	625	8	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 70MG	OLTP	腹部癒着	20[redacted]-	625	8	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	5[redacted] M WHITE	AMG334QM 70MG	OLTP	動脈硬化症	20[redacted]-	650	1	Y	Grade 5	NOT RELATED	FATAL	DOSE NOT CHANGED	NO ACTION TAKEN	Y
			AMG334QM 70MG	OLTP	高血圧性心疾患	20[redacted]-	650	1	Y	Grade 4	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	NO ACTION TAKEN	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	OLTP	膵嚢胞	20[redacted]-	487	76	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	MEDICATION TAKEN	
[redacted]	UNITED STATES	3[redacted] M WHITE	AMG334QM 140MG	OLTP	非感染性虫垂炎	20[redacted]-	1404	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER, HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 140MG	OLTP	椎間板突出	20[redacted]-	1617	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	

表 付録-13　重篤な有害事象を発現した被験者一覧（20120178試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	UNITED STATES	4[redacted] F WHITE	AMG334QM 140MG	OLTP	骨盤部尿管閉塞	20[redacted]-	1002	3	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	OLTP	蜂巣炎	20[redacted]-	534	8	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 140MG	OLTP	脊椎圧迫骨折	20[redacted]-	1122	10	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER, HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 140MG	OLTP	腰部脊柱管狭窄症	20[redacted]-	1122	4	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER, HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 140MG	OLTP	馬尾症候群	20[redacted]-	1122	4	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER, HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	4[redacted] F WHITE	AMG334QM 70MG	OLTP	乳癌	20[redacted]-	181		Y	Grade 3	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	4[redacted] F WHITE	AMG334QM 70MG	OLTP	乳腺浸潤性小葉癌	20[redacted]-	743		Y	Grade 3	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DRUG WITHDRAWN	OTHER	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 140MG	OLTP	変形性関節症	20[redacted]-	1547	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION	

表 付録-13　重篤な有害事象を発現した被験者一覧（20120178試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	OLTP	深部静脈血栓症	20[redacted]- [redacted]-	232	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 70MG	OLTP	筋骨格系胸痛	20[redacted]- [redacted]-	232	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, EMERGENCY ROOM VISIT	
			AMG334QM 70MG	OLTP	肺塞栓症	20[redacted]- [redacted]-	232	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 70MG	OLTP	血栓症	20[redacted]- [redacted]-	232	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION, EMERGENCY ROOM VISIT	
[redacted]	UNITED STATES	3[redacted] F WHITE	AMG334QM 70MG	OLTP	月経過多	20[redacted]- [redacted]-	373	2	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	UNITED STATES	2[redacted] F WHITE	AMG334QM 70MG	OLTP	視神経炎	20[redacted]- [redacted]-	926	40	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	3[redacted] F WHITE	AMG334QM 140MG	OLTP	脂肪腫	20[redacted]- [redacted]-	1662	6	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, EMERGENCY ROOM VISIT, OTHER, MEDICATION TAKEN	

表 付録-13　重篤な有害事象を発現した被験者一覧（20120178試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	UNITED STATES	4[redacted] F OTHER	AMG334QM 70MG	OLTP	クローン病	20[redacted]- [redacted]-	752		Y	Grade 2	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, EMERGENCY ROOM VISIT, HOSPITALIZED / PROLONGED HOSPITALIZATION, OTHER	
			AMG334QM 140MG	OLTP	腹部膿瘍	20[redacted]- [redacted]-	1835	36	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
			AMG334QM 140MG	OLTP	胸水	20[redacted]- [redacted]-	1838	38	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN, OTHER	
			AMG334QM 140MG	OLTP	深部静脈血栓症	20[redacted]- [redacted]-	1841	37	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
			AMG334QM 140MG	OLTP	腹腔内血腫	20[redacted]- [redacted]-	1842	29	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, OTHER	
[redacted]	UNITED STATES	1[redacted] M WHITE	AMG334QM 140MG	OLTP	虫垂炎	20[redacted]- [redacted]-	1659	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	OLTP	胃腸出血	20[redacted]- [redacted]-	285	16	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 70MG	OLTP	腹膜出血	20[redacted]- [redacted]-	285	4	Y	Grade 1	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 140MG	OLTP	アスパラギン酸アミノトランスフェラーゼ増加	20[redacted]- [redacted]-	1960	8	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	UNITED STATES	5[redacted] M WHITE	AMG334QM 140MG	OLTP	前立腺癌	20[redacted]- [redacted]-	1527		Y	Grade 4	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	UNITED STATES	2[redacted] F WHITE	AMG334QM 140MG	OLTP	直腸脱	20[redacted]- [redacted]-	873	92	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	

表 付録-13　重篤な有害事象を発現した被験者一覧（20120178試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	OLTP	非心臓性胸痛	20[redacted]- [redacted]-	364	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	4[redacted] F WHITE	AMG334QM 140MG	OLTP	子宮平滑筋腫	20[redacted]- [redacted]-	1069	5	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION, EMERGENCY ROOM VISIT, OTHER	
			AMG334QM 140MG	OLTP	貧血	20[redacted]- [redacted]-	1069	5	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, EMERGENCY ROOM VISIT, OTHER	
[redacted]	UNITED STATES	5[redacted] F BLACK OR AFRICAN AMERICAN	AMG334QM 70MG	OLTP	肺腺癌第３期	20[redacted]- [redacted]-	669		Y	Grade 3	NOT RELATED	UNKNOWN	DRUG WITHDRAWN	HOSPITALIZED / PROLONGED HOSPITALIZATION, OTHER	
[redacted]	UNITED STATES	4[redacted] M BLACK OR AFRICAN AMERICAN	AMG334QM 140MG	OLTP	死亡	20[redacted]- [redacted]-	1943	1	Y	Grade 5	NOT RELATED	FATAL	DOSE NOT CHANGED	UNKNOWN	Y
			AMG334QM 140MG	OLTP	頭痛	20[redacted]- [redacted]-	1943		Y	Grade 3	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DOSE NOT CHANGED	UNKNOWN	

Coded using CTCAE version 4.03; MedDRA version 22.1
DBTP = Double-blind treatment period; OLTP = Open-label treatment period
Study Day = Study day of onset of adverse event; Outcome = Outcome of serious adverse event; Action Taken = Action taken with study treatment

[redacted]

表 付録-14　重篤な有害事象を発現した被験者一覧（20120295試験：安全性解析対象集団）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	FINLAND	2[redacted] F WHITE	PLACEBO	DBTP	片頭痛	20[redacted]-	60	2	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	GERMANY	1[redacted] F WHITE	PLACEBO	DBTP	耳下腺炎	20[redacted]-	24	48	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, OTHER, MEDICATION TAKEN	
[redacted]	GERMANY	4[redacted] F WHITE	AMG334QM 140MG	DBTP	腹痛	20[redacted]-	43	15	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
					腹部癒着	20[redacted]-	43	15	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	GERMANY	4[redacted] F WHITE	AMG334QM 70MG	DBTP	橈骨骨折	20[redacted]-	94		Y	Grade 3	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	GERMANY	4[redacted] F WHITE	AMG334QM 70MG	DBTP	椎間板突出	20[redacted]-	79	6	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
					椎間板突出	20[redacted]-	85		Y	Grade 3	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	NORWAY	4[redacted] F WHITE	PLACEBO	DBTP	尿路感染	20[redacted]-	25	11	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	NORWAY	3[redacted] F WHITE	AMG334QM 140MG	DBTP	軟骨損傷	20[redacted]-	48	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	POLAND	4[redacted] M WHITE	AMG334QM 70MG	DBTP	虫垂炎	20[redacted]-	4	4	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	

表 付録-14　重篤な有害事象を発現した被験者一覧（20120295試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	DBTP	非心臓性胸痛	20[redacted]- [redacted]-	70	4	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	UNITED STATES	4[redacted] F WHITE	PLACEBO	DBTP	胆嚢炎	20[redacted]- [redacted]-	65	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	UNITED STATES	3[redacted] F WHITE	PLACEBO	DBTP	椎間板突出	20[redacted]- [redacted]-	86	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	UNITED STATES	4[redacted] F WHITE	PLACEBO	DBTP	嘔吐	20[redacted]- [redacted]-	2	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, OTHER	
[redacted]	UNITED STATES	5[redacted] F WHITE	PLACEBO	DBTP	膵炎	20[redacted]- [redacted]-	21	34	Y	Grade 1	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	4[redacted] F WHITE	AMG334QM 70MG	DBTP	肋軟骨炎	20[redacted]- [redacted]-	77	2	Y	Grade 4	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN, EMERGENCY ROOM VISIT	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	DBTP	線維腫	20[redacted]- [redacted]-	3	4	Y	Grade 1	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	

Coded using CTCAE version 4.03; MedDRA version 19.0
DBTP = Double-blind treatment period; OLTP = Open-label treatment period
Study Day = Study day of onset of adverse event; Outcome = Outcome of serious adverse event; Action Taken = Action taken with study treatment

[redacted]

表 付録-15　重篤な有害事象を発現した被験者一覧（20130255試験：安全性解析対象集団）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	CZECH REPUBLIC	4[redacted] F WHITE	AMG334QM 70MG	OLTP	アルコール症	20[redacted]-	306	70	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION	
			AMG334QM 70MG	OLTP	アルコール性肝疾患	20[redacted]-	336	89	Y	Grade 2	NOT RELATED		DRUG WITHDRAWN	MEDICATION TAKEN	
[redacted]	CZECH REPUBLIC	6[redacted] F WHITE	AMG334QM 140MG	OLTP	根症候群	20[redacted]-	231	217	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	DENMARK	4[redacted] F WHITE	AMG334QM 70MG	OLTP	片頭痛	20[redacted]-	272	3	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	DENMARK	3[redacted] M WHITE	AMG334QM 140MG	OLTP	片頭痛	20[redacted]-	431	2	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	DENMARK	4[redacted] F WHITE	AMG334QM 140MG	OLTP	肋軟骨炎	20[redacted]-	135	89	Y	Grade 2	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	DENMARK	6[redacted] M WHITE	AMG334QM 140MG	OLTP	一過性脳虚血発作	20[redacted]-	209	2	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	FINLAND	4[redacted] F WHITE	AMG334QM 140MG	OLTP	片頭痛	20[redacted]-	426	10	Y	Grade 2	NOT RELATED		DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	GERMANY	3[redacted] F WHITE	AMG334QM 70MG	OLTP	椎間板突出	20[redacted]-	219	73	Y	Grade 3	NOT RELATED		DRUG WITHDRAWN	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	GERMANY	4[redacted] F WHITE	AMG334QM 140MG	OLTP	肩回旋筋腱板症候群	20[redacted]-	120		Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	GERMANY	5[redacted] M WHITE	AMG334QM 70MG	OLTP	薬物乱用頭痛	20[redacted]-	264	8	Y	Grade 2	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
			AMG334QM 70MG	OLTP	椎間板突出	20[redacted]-	284	8	Y	Grade 2	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	GERMANY	4[redacted] F WHITE	AMG334QM 70MG	OLTP	うつ病	20[redacted]-	200	34	Y	Grade 3	RELATED		DRUG WITHDRAWN	MEDICATION TAKEN	

表 付録-15　重篤な有害事象を発現した被験者一覧（20130255試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	GERMANY	4[redacted] F WHITE	AMG334QM 70MG	OLTP	椎間板突出	20[redacted]-	2	7	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
			AMG334QM 70MG	OLTP	椎間板突出	20[redacted]-	55	11	Y	Grade 3	NOT RELATED		DRUG INTERRUPTED	HOSPITALIZED / PROLONGED HOSPITALIZATION, OTHER	
[redacted]	GERMANY	4[redacted] F WHITE	AMG334QM 70MG	OLTP	前庭性片頭痛	20[redacted]-	396	5	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, MEDICATION TAKEN	
[redacted]	POLAND	3[redacted] F WHITE	AMG334QM 140MG	OLTP	失神寸前の状態	20[redacted]-	233	8	Y	Grade 2	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED KINGDOM	2[redacted] F WHITE	AMG334QM 140MG	OLTP	食道炎	20[redacted]-	302	3	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	OLTP	腹痛	20[redacted]-	81	5	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	3[redacted] F WHITE	AMG334QM 70MG	OLTP	ウイルス性胃腸炎	20[redacted]-	148	2	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, EMERGENCY ROOM VISIT	
[redacted]	UNITED STATES	4[redacted] F WHITE	AMG334QM 70MG	OLTP	虫垂炎	20[redacted]-	109	11	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	MEDICATION TAKEN, HOSPITALIZED / PROLONGED HOSPITALIZATION, OTHER	
[redacted]	UNITED STATES	2[redacted] F WHITE	AMG334QM 140MG	OLTP	処置後浮腫	20[redacted]-	23	2	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	2[redacted] F WHITE	AMG334QM 70MG	OLTP	片頭痛	20[redacted]-	77	6	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	4[redacted] F BLACK OR AFRICAN AMERICAN	AMG334QM 70MG	OLTP	心筋ブリッジ	20[redacted]-	357		Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	MEDICATION TAKEN	

表 付録-15　重篤な有害事象を発現した被験者一覧（20130255試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	UNITED STATES	4[redacted] F WHITE	AMG334QM 70MG	OLTP	うつ病	20[redacted]- [redacted]-	58	4	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	4[redacted] F WHITE	AMG334QM 70MG	OLTP	腸の軸捻転	20[redacted]- [redacted]-	233	6	Y	Grade 3	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION	
[redacted]	UNITED STATES	6[redacted] F WHITE	AMG334QM 140MG	OLTP	肺炎	20[redacted]- [redacted]-	249	6	Y	Grade 2	NOT RELATED		DOSE NOT CHANGED	HOSPITALIZED / PROLONGED HOSPITALIZATION, OTHER, OTHER	

Coded using CTCAE version 4.03; MedDRA version 20.0
DBTP = Double-blind treatment period; OLTP = Open-label treatment period
Study Day = Study day of onset of adverse event; Outcome = Outcome of serious adverse event; Action Taken = Action taken with study treatment

[redacted]

表 付録-16　重篤な有害事象を発現した被験者一覧（20120296試験：安全性解析対象集団）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	AUSTRIA	2[redacted] F WHITE	AMG334QM 70MG	DBTP	急性腎盂腎炎	20[redacted]-	87	20	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER, OTHER	
[redacted]	AUSTRIA	2[redacted] F WHITE	AMG334QM 70MG	ATP	術後膿瘍	20[redacted]-	322	17	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
[redacted]	CZECH REPUBLIC	4[redacted] M WHITE	AMG334QM 140MG	ATP	不整脈原性右室異形成症	20[redacted]-	275	1	Y	Grade 5	NOT RELATED	FATAL	DRUG WITHDRAWN	NO ACTION TAKEN	Y
[redacted]	CZECH REPUBLIC	5[redacted] F WHITE	PLACEBO	DBTP	関節痛	20[redacted]-	90	5	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	CZECH REPUBLIC	4[redacted] F WHITE	AMG334QM 70MG	DBTP	胆石症	20[redacted]-	21	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER, MEDICATION TAKEN, OTHER	
			AMG334QM 70MG	ATP	消化不良	20[redacted]-	172	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER, MEDICATION TAKEN	
[redacted]	CZECH REPUBLIC	4[redacted] F WHITE	AMG334QM 140MG	DBTP	脊椎痛	20[redacted]-	143	10	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
			AMG334QM 140MG	ATP	乳房嚢胞	20[redacted]-	355	32	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	FINLAND	3[redacted] F WHITE	AMG334QM 140MG	ATP	憩室炎	20[redacted]-	310	33	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	FINLAND	5[redacted] F WHITE	AMG334QM 70MG	ATP	特発性眼窩炎症	20[redacted]-	210		Y	Grade 1	RELATED	NOT RECOVERED/ NOT RESOLVED	DRUG WITHDRAWN	MEDICATION TAKEN, OTHER	
[redacted]	FINLAND	2[redacted] F WHITE	AMG334QM 140MG	DBTP	失神	20[redacted]-	8	5	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT	
			AMG334QM 70MG	ATP	失神	20[redacted]-	247	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT	
[redacted]	GERMANY	5[redacted] F WHITE	AMG334QM 140MG	DBTP	前庭神経炎	20[redacted]-	32	33	Y	Grade 3	RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	EMERGENCY ROOM VISIT, MEDICATION TAKEN	
[redacted]	GERMANY	4[redacted] M WHITE	PLACEBO	DBTP	転倒	20[redacted]-	45	1	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	

表 付録-16　重篤な有害事象を発現した被験者一覧（20120296試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	GERMANY	5[redacted] F WHITE	AMG334QM 70MG	DBTP	背部痛	20[redacted]-	74	2	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	GERMANY	5[redacted] F WHITE	AMG334QM 140MG	ATP	乳癌	20[redacted]-	396		Y	Grade 3	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DOSE NOT CHANGED	OTHER, OTHER, MEDICATION TAKEN	
[redacted]	GERMANY	3[redacted] F WHITE	AMG334QM 70MG	DBTP	卵巣嚢胞	20[redacted]-	23	9	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DRUG INTERRUPTED	OTHER, MEDICATION TAKEN	
[redacted]	GERMANY	4[redacted] F WHITE	AMG334QM 140MG	ATP	子宮平滑筋腫	20[redacted]-	396	36	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER, OTHER	
[redacted]	GERMANY	4[redacted] F WHITE	AMG334QM 140MG	DBTP	ウイルス性胃腸炎	20[redacted]-	113	5	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	GERMANY	2[redacted] F WHITE	AMG334QM 140MG	ATP	虫垂炎	20[redacted]-	241	5	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER, OTHER	
[redacted]	GERMANY	5[redacted] F WHITE	AMG334QM 70MG	ATP	大腿骨骨折	20[redacted]-	181	99	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	GERMANY	5[redacted] F WHITE	AMG334QM 70MG	ATP	胃炎	20[redacted]-	175	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	GERMANY	5[redacted] F WHITE	AMG334QM 70MG	DBTP	片頭痛	20[redacted]-	95	30	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	GERMANY	6[redacted] F WHITE	PLACEBO	DBTP	変形性関節症	20[redacted]-	115	25	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
[redacted]	GERMANY	2[redacted] F WHITE	AMG334QM 70MG	ATP	うつ病	20[redacted]-	186	61	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DRUG INTERRUPTED	OTHER, MEDICATION TAKEN	
[redacted]	POLAND	4[redacted] F WHITE	AMG334QM 140MG	ATP	乳腺線維腫	20[redacted]-	326	34	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	OTHER	
[redacted]	POLAND	4[redacted] F WHITE	AMG334QM 140MG	ATP	プロラクチン産生性下垂体腫瘍	20[redacted]-	348		Y	Grade 2	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	

表 付録-16　重篤な有害事象を発現した被験者一覧（20120296試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	POLAND	3[redacted] F WHITE	AMG334QM 140MG	ATP	橈骨骨折	20[redacted]-	235	75	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, MEDICATION TAKEN	
[redacted]	SLOVAKIA	5[redacted] F WHITE	AMG334QM 140MG	DBTP	子宮平滑筋腫	20[redacted]-	1	448	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	SWEDEN	2[redacted] F WHITE	PLACEBO	DBTP	過敏症	20[redacted]-	28	3	Y	Grade 3	RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	EMERGENCY ROOM VISIT, MEDICATION TAKEN	
[redacted]	SWEDEN	4[redacted] M WHITE	AMG334QM 140MG	ATP	丹毒	20[redacted]-	346	13	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	TURKEY	4[redacted] F WHITE	PLACEBO	DBTP	子宮内膜症	20[redacted]-	7	4	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER, MEDICATION TAKEN	
[redacted]	TURKEY	3[redacted] F WHITE	AMG334QM 70MG	ATP	創傷	20[redacted]-	199	11	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT	
[redacted]	TURKEY	4[redacted] F WHITE	AMG334QM 140MG	DBTP	足関節部骨折	20[redacted]-	83	28	Y	Grade 1	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	TURKEY	5[redacted] F WHITE	AMG334QM 70MG	ATP	鼻中隔弯曲	20[redacted]-	355	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	UNITED STATES	2[redacted] F BLACK OR AFRICAN AMERICAN	AMG334QM 70MG	ATP	特発性頭蓋内圧亢進症	20[redacted]-	418	6	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER, OTHER, MEDICATION TAKEN	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	ATP	前兆を伴う片頭痛	20[redacted]-	172	2	Y	Grade 3	RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	UNITED STATES	3[redacted] F WHITE	PLACEBO	DBTP	企図的過量投与	20[redacted]-	156	3	Y	Grade 4	NOT RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	EMERGENCY ROOM VISIT	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 140MG	ATP	心膜炎	20[redacted]-	432		Y	Grade 3	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	

表 付録-16　重篤な有害事象を発現した被験者一覧（20120296試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	UNITED STATES	3[redacted] F WHITE	AMG334QM 140MG	DBTP	非心臓性胸痛	20[redacted]-	165	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	ATP	深部静脈血栓症	20[redacted]-	241	13	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER, MEDICATION TAKEN	
[redacted]	UNITED STATES	4[redacted] F WHITE	AMG334QM 70MG	DBTP	外傷後頚部症候群	20[redacted]-	83	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	ATP	胃食道逆流性疾患	20[redacted]-	322	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, OTHER, MEDICATION TAKEN	
[redacted]	UNITED STATES	3[redacted] M WHITE	PLACEBO	DBTP	非心臓性胸痛	20[redacted]-	93	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, MEDICATION TAKEN	
[redacted]	UNITED STATES	2[redacted] F WHITE	AMG334QM 140MG	ATP	脱水	20[redacted]-	195	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	UNITED STATES	2[redacted] F MULTIPLE	AMG334QM 70MG	ATP	中毒性脳症	20[redacted]-	242	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, OTHER	
[redacted]	UNITED STATES	4[redacted] F WHITE	AMG334QM 140MG	DBTP	腎感染	20[redacted]-	50	20	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, EMERGENCY ROOM VISIT, OTHER	
			AMG334QM 140MG	DBTP	クロストリジウム・ディフィシレ大腸炎	20[redacted]-	53	17	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
			AMG334QM 140MG	DBTP	敗血症	20[redacted]-	53	17	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
			AMG334QM 140MG	DBTP	腎盂腎炎	20[redacted]-	53	17	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
			AMG334QM 140MG	DBTP	大脳静脈血栓症	20[redacted]-	108		Y	Grade 3	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, EMERGENCY ROOM VISIT, OTHER	

表 付録-16　重篤な有害事象を発現した被験者一覧（20120296試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 140MG	ATP	憩室炎	20[redacted]- [redacted]	255	18	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER, MEDICATION TAKEN	
[redacted]	UNITED STATES	3[redacted] M WHITE	AMG334QM 140MG	ATP	硬膜下血腫	20[redacted]- [redacted]	250	41	Y	Grade 4	NOT RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	OTHER, OTHER, OTHER	
[redacted]	UNITED STATES	3[redacted] F WHITE	AMG334QM 70MG	DBTP	胆石症	20[redacted]- [redacted]	61	3	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER, MEDICATION TAKEN	
[redacted]	UNITED STATES	6[redacted] F WHITE	AMG334QM 70MG	DBTP	非心臓性胸痛	20[redacted]- [redacted]	108	5	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, MEDICATION TAKEN	

Coded using CTCAE version 4.03; MedDRA version 20.0
DBTP = Double-blind treatment period; OLTP = Open-label treatment period
Study Day = Study day of onset of adverse event; Outcome = Outcome of serious adverse event; Action Taken = Action taken with study treatment

[redacted]

表 付録-17　重篤な有害事象を発現した被験者一覧（20120297試験：安全性解析対象集団）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	DENMARK	2[redacted] F WHITE	PLACEBO	DBTP	側腹部痛	20[redacted]-	52	4	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT	
[redacted]	DENMARK	5[redacted] F WHITE	AMG334QM 70MG	DBTP	椎間板突出	20[redacted]-	71	4	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	DENMARK	6[redacted] F WHITE	AMG334QM 70MG	OLTP	蕁麻疹	20[redacted]-	184	12	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	DENMARK	3[redacted] F WHITE	AMG334QM 70MG	OLTP	子宮内膜症	20[redacted]-	194	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
			AMG334QM 70MG	OLTP	処置後感染	20[redacted]	200	15	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DRUG INTERRUPTED	MEDICATION TAKEN	
[redacted]	DENMARK	5[redacted] M WHITE	PLACEBO	DBTP	片頭痛	20[redacted]-	50		Y	Grade 3	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	DENMARK	4[redacted] F WHITE	PLACEBO	DBTP	過敏症	20[redacted]-	59	26	Y	Grade 3	RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	DENMARK	6[redacted] M WHITE	AMG334QM 70MG	OLTP	うつ病	20[redacted]-	167	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
[redacted]	DENMARK	3[redacted] F WHITE	AMG334QM 70MG	OLTP	歯膿瘍	20[redacted]-	264	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
[redacted]	DENMARK	4[redacted] M WHITE	AMG334QM 70MG	OLTP	靭帯断裂	20[redacted]-	257	14	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, EMERGENCY ROOM VISIT, OTHER	
			AMG334QM 70MG	OLTP	処置後肺塞栓症	20[redacted]-	267	4	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
			AMG334QM 70MG	OLTP	肺炎	20[redacted]-	282	11	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	

表 付録-17　重篤な有害事象を発現した被験者一覧（20120297試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	PORTUGAL	4[redacted] F WHITE	AMG334QM 70MG	DBTP	片頭痛	20[redacted]-	29	2	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, MEDICATION TAKEN	
			AMG334QM 70MG	DBTP	片頭痛	20[redacted]-	41	1	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, MEDICATION TAKEN	
			AMG334QM 70MG	DBTP	片頭痛	20[redacted]-	50	1	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, MEDICATION TAKEN	
[redacted]	PORTUGAL	4[redacted] F WHITE	AMG334QM 70MG	OLTP	下腹部痛	20[redacted]-	255	4	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, MEDICATION TAKEN, OTHER	
[redacted]	SPAIN	4[redacted] F WHITE	AMG334QM 70MG	OLTP	視力低下	20[redacted]-	214	71	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	EMERGENCY ROOM VISIT, MEDICATION TAKEN, OTHER	
[redacted]	SPAIN	4[redacted] F WHITE	AMG334QM 70MG	OLTP	乳頭様甲状腺癌	20[redacted]-	85		Y	Grade 4	NOT RELATED	NOT RECOVERED/ NOT RESOLVED	DRUG WITHDRAWN	OTHER, OTHER	
[redacted]	SWITZERLAND	5[redacted] F WHITE	PLACEBO	DBTP	子宮平滑筋腫	20[redacted]-	23	4	Y	Grade 2	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
			PLACEBO	DBTP	低ナトリウム血症	20[redacted]-	24	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	SWITZERLAND	2[redacted] F WHITE	AMG334QM 70MG	OLTP	虹彩毛様体炎	20[redacted]-	259	62	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, MEDICATION TAKEN	
[redacted]	SWITZERLAND	2[redacted] F WHITE	AMG334QM 70MG	OLTP	鼻中隔手術	20[redacted]-	196	2	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, OTHER	
[redacted]	UNITED STATES	5[redacted] M WHITE	AMG334QM 70MG	OLTP	喉頭血腫	20[redacted]-	114	28	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, MEDICATION TAKEN, OTHER	

表 付録-17　重篤な有害事象を発現した被験者一覧（20120297試験：安全性解析対象集団）（続き）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	OLTP	肺炎球菌性菌血症	20[redacted]-	132	15	Y	Grade 4	NOT RELATED	RECOVERED/ RESOLVED	DRUG INTERRUPTED	OTHER, MEDICATION TAKEN	
			AMG334QM 70MG	OLTP	急性呼吸窮迫症候群	20[redacted]-	136	11	Y	Grade 4	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	
			AMG334QM 70MG	OLTP	心房細動	20[redacted]-	139	8	Y	Grade 4	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN	
			AMG334QM 70MG	OLTP	心筋虚血	20[redacted]-	139	8	Y	Grade 4	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER	
[redacted]	UNITED STATES	2[redacted] F WHITE	AMG334QM 70MG	DBTP	尿路感染	20[redacted]-	55	3	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DRUG INTERRUPTED	EMERGENCY ROOM VISIT, OTHER, MEDICATION TAKEN	
[redacted]	UNITED STATES	4[redacted] F WHITE	AMG334QM 70MG	OLTP	子宮平滑筋腫	20[redacted]-	169	24	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	OTHER, MEDICATION TAKEN	
[redacted]	UNITED STATES	5[redacted] F WHITE	AMG334QM 70MG	OLTP	失神	20[redacted]-	123	9	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	MEDICATION TAKEN, EMERGENCY ROOM VISIT	
[redacted]	UNITED STATES	3[redacted] F WHITE	AMG334QM 70MG	OLTP	乳頭様甲状腺癌	20[redacted]-	182	100	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	OTHER, OTHER	
[redacted]	UNITED STATES	4[redacted] F WHITE	PLACEBO	DBTP	急性胆嚢炎	20[redacted]-	85	7	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DOSE NOT CHANGED	EMERGENCY ROOM VISIT, MEDICATION TAKEN, OTHER	

Coded using CTCAE version 4.03; MedDRA version 20.0
DBTP = Double-blind treatment period; OLTP = Open-label treatment period
Study Day = Study day of onset of adverse event; Outcome = Outcome of serious adverse event; Action Taken = Action taken with study treatment

[redacted]

表 付録-18　治験薬の投与中止に至った有害事象を発現した被験者一覧（20120309試験：安全性解析対象集団）

Subject Identifier for the Study	Country	Age Sex Race	Actual Treatment	Treatment Phase	Adverse Event in Preferred Term	AE Onset Date	Study Day	Duration in Days	Serious Event	Toxicity Grade	Causality	Outcome	Action Taken	Other Action Taken	Results in Death
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 70MG	OLTP	乳管内増殖性病変	20[redacted]- [redacted]-	197	28	Y	Grade 3	NOT RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	OTHER	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 140MG	OLTP	紅斑性皮疹	20[redacted]- [redacted]-	279		N	Grade 2	RELATED		DRUG WITHDRAWN	MEDICATION TAKEN	
			AMG334QM 140MG	OLTP	紅斑性皮疹	20[redacted]- [redacted]-	279		N	Grade 2	RELATED		DRUG WITHDRAWN	MEDICATION TAKEN	
[redacted]	JAPAN	5[redacted] F ASIAN	PLACEBO	DBTP	片頭痛	20[redacted]- [redacted]-	89	46	Y	Grade 3	RELATED	RECOVERED/ RESOLVED	DRUG WITHDRAWN	EMERGENCY ROOM VISIT, MEDICATION TAKEN	
[redacted]	JAPAN	5[redacted] F ASIAN	AMG334QM 70MG	OLTP	乳癌	20[redacted]- [redacted]-	640		Y	Grade 3	RELATED	NOT RECOVERED/ NOT RESOLVED	DRUG WITHDRAWN	OTHER, MEDICATION TAKEN	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 70MG	OLTP	甲状腺機能亢進症	20[redacted]- [redacted]-	251		N	Grade 2	RELATED		DRUG WITHDRAWN	NO ACTION TAKEN	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 70MG	DBTP	そう痒性皮疹	20[redacted]- [redacted]-	5	109	N	Grade 2	RELATED		DRUG WITHDRAWN	MEDICATION TAKEN	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 70MG	DBTP	全身性エリテマトーデス	20[redacted]- [redacted]	146		Y	Grade 4	RELATED	NOT RECOVERED/ NOT RESOLVED	DRUG WITHDRAWN	MEDICATION TAKEN	
[redacted]	JAPAN	3[redacted] F ASIAN	AMG334QM 140MG	OLTP	緊張性頭痛	20[redacted]- [redacted]-	535		N	Grade 2	NOT RELATED		DRUG WITHDRAWN	MEDICATION TAKEN	
[redacted]	JAPAN	4[redacted] F ASIAN	AMG334QM 70MG	OLTP	片頭痛	20[redacted]- [redacted]-	396		N	Grade 3	NOT RELATED		DRUG WITHDRAWN	MEDICATION TAKEN	

Coded using CTCAE version 4.03; MedDRA version 22.0
DBTP = Double-blind treatment period; OLTP = Open-label treatment period
Study Day = Study day of onset of adverse event; Outcome = Outcome of serious adverse event; Action Taken = Action taken with study treatment

[redacted]

表 付録-19　過敏症SMQに該当するPT別の有害事象（J-ISS-1：安全性解析対象集団）

Preferred Term	Placebo (N = 267) n (%)	AMG 334 28 mg QM (N = 66) n (%)	AMG 334 70 mg QM (N = 265) n (%)	AMG 334 140 mg QM (N = 137) n (%)	AMG 334 Overall (N = 468) n (%)
Number of subjects reporting treatment-emergent hypersensitivity event of interest	6 (2.2)	5 (7.6)	22 (8.3)	10 (7.3)	37 (7.9)
湿疹	2 (0.7)	0 (0.0)	5 (1.9)	2 (1.5)	7 (1.5)
接触皮膚炎	1 (0.4)	1 (1.5)	2 (0.8)	2 (1.5)	5 (1.1)
蕁麻疹	1 (0.4)	0 (0.0)	3 (1.1)	1 (0.7)	4 (0.9)
皮膚炎	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.7)	3 (0.6)
アレルギー性鼻炎	1 (0.4)	1 (1.5)	1 (0.4)	1 (0.7)	3 (0.6)
アレルギー性結膜炎	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)
アレルギー性皮膚炎	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.7)	2 (0.4)
発疹	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
丘疹状蕁麻疹	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
注射部位発疹	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
薬疹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
歯肉腫脹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
特発性蕁麻疹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
そう痒性皮疹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
ざ瘡様皮膚炎	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
中毒性皮疹	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
アレルギー性角膜炎	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1
Based on hypersensitivity standard MedDRA query (SMQ; narrow)

[redacted]

表 付録-20　過敏症SMQに該当するPT別の有害事象（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (Subj-yr = 528 8) (N = 414)	140 mg QM (Subj-yr = 343.8) (N = 269)	Combined (Subj-yr = 872.7) (N = 470)
Preferred Term	n (%) / e [r]	n (%) / e [r]	n (%) / e [r]
All treatment-emergent hypersensitivity event of interest	53 (12.8) / 475.8 [11.1]	41 (15.2) / 307.6 [13.3]	92 (19.6) / 772.5 [11.9]
湿疹	14 (3.4) / 516.0 [2.7]	11 (4.1) / 333.5 [3.3]	25 (5.3) / 846.8 [3.0]
アレルギー性鼻炎	13 (3.1) / 515.9 [2.5]	3 (1.1) / 340.1 [0.9]	16 (3.4) / 856.0 [1.9]
蕁麻疹	9 (2.2) / 521.0 [1.7]	6 (2.2) / 338.8 [1.8]	15 (3.2) / 856.7 [1.8]
アレルギー性結膜炎	6 (1.4) / 522.2 [1.1]	5 (1.9) / 340.3 [1.5]	11 (2.3) / 859.3 [1.3]
皮膚炎	3 (0.7) / 526.0 [0.6]	3 (1.1) / 339.9 [0.9]	6 (1.3) / 865.9 [0.7]
発疹	3 (0.7) / 524.0 [0.6]	2 (0.7) / 341.5 [0.6]	5 (1.1) / 865.5 [0.6]
接触皮膚炎	2 (0.5) / 526.4 [0.4]	3 (1.1) / 341.8 [0.9]	5 (1.1) / 866.5 [0.6]
アレルギー性咳嗽	2 (0.5) / 528.6 [0.4]	3 (1.1) / 340.4 [0.9]	5 (1.1) / 869.0 [0.6]
アレルギー性皮膚炎	2 (0.5) / 526.0 [0.4]	1 (0.4) / 342.0 [0.3]	3 (0.6) / 868.0 [0.3]
丘疹状蕁麻疹	2 (0.5) / 527.1 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.0 [0.2]
注射部位発疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.4 [0.3]	1 (0.2) / 870.5 [0.1]
多形紅斑	1 (0.2) / 527.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
中毒性皮疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 342.7 [0.3]	1 (0.2) / 871.5 [0.1]
歯肉腫脹	1 (0.2) / 527.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
眼瞼浮腫	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
アレルギー性そう痒症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.1 [0.3]	1 (0.2) / 871.9 [0.1]
特発性蕁麻疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.2 [0.3]	1 (0.2) / 872.0 [0.1]
過敏症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.3 [0.3]	1 (0.2) / 872.2 [0.1]
手皮膚炎	1 (0.2) / 528.4 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.3 [0.1]
紅斑性皮疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.4 [0.1]
そう痒性皮疹	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
慢性蕁麻疹	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]
薬疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.8 [0.3]	1 (0.2) / 872.6 [0.1]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1
Based on hypersensitivity standard MedDRA query (SMQ; narrow)



表 付録-21　アナフィラキシー反応SMQに該当するPT別の有害事象
（J-ISS-1：安全性解析対象集団）

		AMG 334			
Preferred Term	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
Number of subjects reporting treatment-emergent anaphylactic reaction event of interest	12 (4.5)	3 (4.5)	11 (4.2)	3 (2.2)	17 (3.6)
咳嗽	5 (1.9)	1 (1.5)	2 (0.8)	2 (1.5)	5 (1.1)
蕁麻疹	1 (0.4)	0 (0.0)	3 (1.1)	1 (0.7)	4 (0.9)
喘息	4 (1.5)	1 (1.5)	0 (0.0)	1 (0.7)	2 (0.4)
発疹	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
丘疹状蕁麻疹	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
胸部不快感	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
そう痒性皮疹	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
浮腫	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.2)
息詰まり	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
紅斑	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1
Based on anaphylactic reaction standard MedDRA query (SMQ; narrow and broad)

[redacted]

表 付録-22　アナフィラキシー反応SMQに該当するPT別の有害事象（J-ISS-2：安全性解析対象集団）

Preferred Term	AMG 334 70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	AMG 334 Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent anaphylactic reaction event of interest	41 (9.9) / 493.2 [8.3]	19 (7.1) / 328.6 [5.8]	57 (12.1) / 814.4 [7.0]
蕁麻疹	9 (2.2) / 521.0 [1.7]	6 (2.2) / 338.8 [1.8]	15 (3.2) / 856.7 [1.8]
咳嗽	9 (2.2) / 522.9 [1.7]	4 (1.5) / 341.7 [1.2]	13 (2.8) / 859.6 [1.5]
喘息	7 (1.7) / 522.3 [1.3]	3 (1.1) / 341.9 [0.9]	10 (2.1) / 862.6 [1.2]
そう痒症	4 (1.0) / 525.9 [0.8]	3 (1.1) / 341.2 [0.9]	7 (1.5) / 865.8 [0.8]
発疹	3 (0.7) / 524.0 [0.6]	2 (0.7) / 341.5 [0.6]	5 (1.1) / 865.5 [0.6]
胸部不快感	2 (0.5) / 526.7 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 869.4 [0.2]
丘疹状蕁麻疹	2 (0.5) / 527.1 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.0 [0.2]
過換気	2 (0.5) / 528.0 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.9 [0.2]
眼充血	1 (0.2) / 527.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.4 [0.1]
浮腫	1 (0.2) / 527.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.5 [0.1]
呼吸困難	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
眼瞼浮腫	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.6 [0.1]
皮膚腫脹	1 (0.2) / 527.8 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.7 [0.1]
アレルギー性そう痒症	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.1 [0.3]	1 (0.2) / 871.9 [0.1]
紅斑	1 (0.2) / 528.2 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.1 [0.1]
紅斑性皮疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.5 [0.3]	1 (0.2) / 872.4 [0.1]
そう痒性皮疹	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1
Based on anaphylactic reaction standard MedDRA query (SMQ; narrow and broad)

[redacted]

表 付録-23　注射部位反応AMQに該当するPT別の有害事象（J-ISS-1：安全性解析対象集団）

Preferred Term	Placebo (N = 267) n (%)	AMG 334 28 mg QM (N = 66) n (%)	AMG 334 70 mg QM (N = 265) n (%)	AMG 334 140 mg QM (N = 137) n (%)	AMG 334 Overall (N = 468) n (%)
Number of subjects reporting treatment-emergent injection site reaction event of interest	4 (1.5)	3 (4.5)	11 (4.2)	6 (4.4)	20 (4 3)
注射部位紅斑	0 (0.0)	0 (0.0)	2 (0.8)	3 (2.2)	5 (1.1)
注射部位腫脹	1 (0.4)	0 (0.0)	2 (0.8)	2 (1.5)	4 (0.9)
注射部位そう痒感	0 (0.0)	1 (1.5)	1 (0.4)	2 (1.5)	4 (0.9)
注射部位出血	1 (0.4)	0 (0.0)	2 (0.8)	1 (0.7)	3 (0.6)
注射部位反応	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.7)	3 (0.6)
注射部位疼痛	2 (0.7)	2 (3.0)	0 (0.0)	0 (0.0)	2 (0.4)
注射部位知覚低下	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
注射部位発疹	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.2)
投与部位疼痛	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
注射部位内出血	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1
Based on injection site reaction Amgen MedDRA query (AMQ; narrow)

[redacted]

表 付録-24　注射部位反応AMQに該当するPT別の有害事象（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (Subj-yr = 528.8) (N = 414)	140 mg QM (Subj-yr = 343.8) (N = 269)	Combined (Subj-yr = 872.7) (N = 470)
Preferred Term	n (%) / e [r]	n (%) / e [r]	n (%) / e [r]
All treatment-emergent injection site reaction event of interest	18 (4.3) / 511.2 [3.5]	20 (7.4) / 317.6 [6.3]	36 (7.7) / 817.5 [4.4]
注射部位紅斑	4 (1.0) / 523.1 [0.8]	8 (3.0) / 334.6 [2.4]	11 (2 3) / 855.9 [1.3]
注射部位反応	4 (1.0) / 525.1 [0.8]	4 (1.5) / 337.9 [1.2]	7 (1.5) / 861.3 [0.8]
注射部位腫脹	2 (0.5) / 527.7 [0.4]	5 (1.9) / 339.7 [1.5]	7 (1.5) / 862.4 [0.8]
注射部位そう痒感	2 (0.5) / 526.4 [0.4]	5 (1.9) / 339.6 [1.5]	7 (1.5) / 862.6 [0.8]
注射部位出血	3 (0.7) / 527.8 [0.6]	3 (1.1) / 339.2 [0.9]	6 (1.3) / 863.8 [0.7]
注射部位疼痛	2 (0.5) / 525.9 [0.4]	2 (0.7) / 341.1 [0.6]	4 (0.9) / 867.1 [0.5]
注射部位知覚低下	1 (0.2) / 528.7 [0.2]	1 (0.4) / 342.0 [0.3]	2 (0.4) / 869.4 [0.2]
注射部位内出血	0 (0.0) / 528.8 [0.0]	2 (0.7) / 341.1 [0.6]	2 (0.4) / 869.9 [0.2]
投与部位疼痛	1 (0.2) / 526.7 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 870.5 [0.1]
注射部位発疹	0 (0.0) / 528.8 [0.0]	1 (0.4) / 343.4 [0.3]	1 (0.2) / 870.5 [0.1]
注射部位血腫	1 (0.2) / 528.0 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1
Based on injection site reaction Amgen MedDRA query (AMQ; narrow)

[redacted]

表 付録-25　便秘AMQに該当するPT別の有害事象（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (N = 267)	28 mg QM (N = 66)	70 mg QM (N = 265)	140 mg QM (N = 137)	Overall (N = 468)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects reporting treatment-emergent constipation event of interest	4 (1.5)	0 (0.0)	14 (5 3)	8 (5.8)	22 (4.7)
便秘	4 (1.5)	0 (0.0)	13 (4.9)	7 (5.1)	20 (4.3)
腹部膨満	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.7)	2 (0.4)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1
Based on constipation Amgen MedDRA query (AMQ; narrow and broad)

[redacted]

表 付録-26　曝露期間で調整した発現頻度による便秘AMQに該当する有害事象の概要（J-ISS-1：安全性解析対象集団）

	Placebo (Subj-yr = 122.6) (N = 267) n (%) / e [r]	AMG 334 28 mg QM (Subj-yr = 30.5) (N = 66) n (%) / e [r]	AMG 334 70 mg QM (Subj-yr = 121.8) (N = 265) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 63.7) (N = 137) n (%) / e [r]	AMG 334 Overall (Subj-yr = 216.0) (N = 468) n (%) / e [r]
All treatment-emergent constipation event of interest	4 (1.5) / 122.1 [3.3]	0 (0.0) / 30.5 [0.0]	14 (5 3) / 117.0 [12.0]	8 (5.8) / 61.0 [13.1]	22 (4.7) / 208.5 [10.6]
Grade ≥ 2	2 (0.7) / 122.5 [1.6]	0 (0.0) / 30.5 [0.0]	3 (1.1) / 120.7 [2.5]	2 (1.5) / 63.5 [3.2]	5 (1.1) / 214.7 [2.3]
Grade ≥ 3	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
Grade ≥ 4	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
Serious adverse events	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
Leading to discontinuation of investigational product	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
Fatal adverse events	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	0 (0.0) / 121.8 [0.0]	0 (0.0) / 63.7 [0.0]	0 (0.0) / 216.0 [0.0]
Treatment-related treatment-emergent adverse events	1 (0.4) / 122.5 [0.8]	0 (0.0) / 30.5 [0.0]	4 (1.5) / 120.0 [3.3]	5 (3.6) / 62.1 [8.1]	9 (1.9) / 212.6 [4.2]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years during the double-blind treatment period (DBTP). Total time at risk is the time from first dose of investigational product (IP) through to onset of first event or the min (end of study date (EOS), last DBTP dose date + 112, first OLTP dose date -1) if no event for study 20120309.Total time at risk is the time from first dose of IP through to onset of first event or the min (EOS, first OLTP dose date -1) if no event for study 20170609.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Grading categories determined using CTCAE version 4.03
Based on constipation Amgen MedDRA query (AMQ; narrow and broad)

[redacted]

表 付録-27　曝露期間で調整した発現頻度による便秘AMQに該当するPT別の有害事象（J-ISS-1：安全性解析対象集団）

Preferred Term	Placebo (Subj-yr = 122.6) (N = 267) n (%) / e [r]	AMG 334 28 mg QM (Subj-yr = 30.5) (N = 66) n (%) / e [r]	AMG 334 70 mg QM (Subj-yr = 121.8) (N = 265) n (%) / e [r]	AMG 334 140 mg QM (Subj-yr = 63.7) (N = 137) n (%) / e [r]	AMG 334 Overall (Subj-yr = 216.0) (N = 468) n (%) / e [r]
All treatment-emergent constipation event of interest	4 (1.5) / 122.1 [3.3]	0 (0.0) / 30.5 [0.0]	14 (5.3) / 117 0 [12.0]	8 (5.8) / 61.0 [13.1]	22 (4.7) / 208.5 [10.6]
便秘	4 (1.5) / 122.1 [3.3]	0 (0.0) / 30.5 [0.0]	13 (4.9) / 117.4 [11.1]	7 (5.1) / 61.2 [11.4]	20 (4.3) / 209.1 [9.6]
腹部膨満	0 (0.0) / 122.6 [0.0]	0 (0.0) / 30.5 [0.0]	1 (0.4) / 121.4 [0.8]	1 (0.7) / 63.5 [1.6]	2 (0.4) / 215.4 [0.9]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years during the double-blind treatment period (DBTP). Total time at risk is the time from first dose of investigational product (IP) through to onset of first event or the min (end of study date (EOS), last DBTP dose date + 112, first OLTP dose date -1) if no event for study 20120309.Total time at risk is the time from first dose of IP through to onset of first event or the min (EOS, first OLTP dose date -1) if no event for study 20170609.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1
Based on constipation Amgen MedDRA query (AMQ; narrow and broad)

[redacted]

表 付録-28　便秘AMQに該当するPT別の有害事象（J-ISS-2：安全性解析対象集団）

	AMG 334		
Preferred Term	70 mg QM (Subj-yr = 528 8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent constipation event of interest	25 (6 0) / 499.8 [5.0]	13 (4.8) / 332.7 [3.9]	37 (7.9) / 817.6 [4.5]
便秘	21 (5.1) / 505.1 [4.2]	12 (4.5) / 334.2 [3.6]	32 (6.8) / 824.7 [3.9]
腹部膨満	2 (0.5) / 525.5 [0.4]	1 (0.4) / 342.4 [0.3]	3 (0.6) / 867.5 [0.3]
鼓腸	1 (0.2) / 527.1 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.0 [0.1]
術後イレウス	1 (0.2) / 528.6 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1
Based on constipation Amgen MedDRA query (AMQ; narrow and broad)

[redacted]

表 付録-29　虚血性中枢神経系血管障害SMQに該当する有害事象の概要（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
All treatment-emergent ischaemic central nervous system vascular conditions event of interest	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)
Grade ≥ 3	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)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Based on ischaemic central nervous system vascular conditions standardized MedDRA query (SMQ; narrow)

[redacted]

表 付録-30　虚血性中枢神経系血管障害SMQに該当する有害事象の概要（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent ischaemic central nervous system vascular conditions event of interest	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Grade ≥ 2	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Grade ≥ 3	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Grade ≥ 4	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Serious adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Leading to discontinuation of investigational product	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Fatal adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Treatment-related treatment-emergent adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Grading categories determined using CTCAE version 4.03
Based on ischaemic central nervous system vascular conditions standardized MedDRA query (SMQ; narrow)

[redacted]

表 付録-31　虚血性心疾患SMQに該当する有害事象の概要（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
All treatment-emergent ischaemic heart disease event of interest	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade ≥ 2	1 (0.4)	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	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Based on ischaemic heart disease standardized MedDRA query (SMQ; narrow and broad)

[redacted]

表 付録-32　虚血性心疾患SMQに該当するPT別の有害事象（J-ISS-1：安全性解析対象集団）

		AMG 334			
Preferred Term	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
Number of subjects reporting treatment-emergent ischaemic heart disease event of interest	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
心電図T波逆転	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
プリンツメタル狭心症	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1
Based on ischaemic heart disease standardized MedDRA query (SMQ; narrow and broad)

[redacted]

表 付録-33　虚血性心疾患SMQに該当する有害事象の概要（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent ischaemic heart disease event of interest	2 (0.5) / 525.8 [0.4]	1 (0.4) / 343.3 [0.3]	3 (0.6) / 869.1 [0.3]
Grade ≥ 2	1 (0.2) / 527.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.3 [0.1]
Grade ≥ 3	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Grade ≥ 4	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Serious adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Leading to discontinuation of investigational product	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Fatal adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Treatment-related treatment-emergent adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Grading categories determined using CTCAE version 4.03
Based on ischaemic heart disease standardized MedDRA query (SMQ; narrow and broad)

[redacted]

表 付録-34　虚血性心疾患SMQに該当するPT別の有害事象（J-ISS-2：安全性解析対象集団）

	AMG 334		
Preferred Term	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent ischaemic heart disease event of interest	2 (0.5) / 525.8 [0.4]	1 (0.4) / 343.3 [0.3]	3 (0.6) / 869.1 [0.3]
狭心症	1 (0.2) / 527.5 [0.2]	1 (0.4) / 343.3 [0.3]	2 (0.4) / 870.8 [0.2]
血中クレアチンホスホキナーゼ増加	1 (0.2) / 527.1 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.0 [0.1]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1
Based on ischaemic heart disease standardized MedDRA query (SMQ; narrow and broad)

[redacted]

表 付録-35　末梢動脈疾患AMQに該当する有害事象の概要（J-ISS-1：安全性解析対象集団）

		AMG 334			
	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
All treatment-emergent peripheral arterial disease event of interest	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)
Grade ≥ 3	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)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Grading categories determined using CTCAE version 4.03
Based on peripheral arterial disease standardized MedDRA query (SMQ; narrow)

[redacted]

表 付録-36　末梢動脈疾患AMQに該当する有害事象の概要（J-ISS-2：安全性解析対象集団）

	AMG 334		
	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent peripheral arterial disease event of interest	2 (0.5) / 527.7 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.5 [0.2]
Grade ≥ 2	1 (0.2) / 528.0 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
Grade ≥ 3	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Grade ≥ 4	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Serious adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Leading to discontinuation of investigational product	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Fatal adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]
Treatment-related treatment-emergent adverse events	0 (0.0) / 528.8 [0.0]	0 (0.0) / 343.8 [0.0]	0 (0.0) / 872.7 [0.0]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Grading categories determined using CTCAE version 4.03
Based on peripheral arterial disease standardized MedDRA query (SMQ; narrow)

[redacted]

表 付録-37　末梢動脈疾患AMQに該当するPT別の有害事象（J-ISS-2：安全性解析対象集団）

	AMG 334		
Preferred Term	70 mg QM (Subj-yr = 528.8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent peripheral arterial disease event of interest	2 (0.5) / 527.7 [0.4]	0 (0.0) / 343.8 [0.0]	2 (0.4) / 871.5 [0.2]
レイノー現象	1 (0.2) / 528.0 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 871.8 [0.1]
末梢血管障害	1 (0.2) / 528.5 [0.2]	0 (0.0) / 343.8 [0.0]	1 (0.2) / 872.4 [0.1]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1
Based on peripheral arterial disease standardized MedDRA query (SMQ; narrow)

[redacted]

表 付録-38　高血圧SMQに該当するPT別の有害事象（J-ISS-1：安全性解析対象集団）

		AMG 334			
Preferred Term	Placebo (N = 267) n (%)	28 mg QM (N = 66) n (%)	70 mg QM (N = 265) n (%)	140 mg QM (N = 137) n (%)	Overall (N = 468) n (%)
Number of subjects reporting treatment-emergent hypertension event of interest	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
高血圧	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
Coded using MedDRA version 22.1
Based on hypertension standardized MedDRA query (SMQ; narrow and broad)

[redacted]

表 付録-39　高血圧SMQに該当するPT別の有害事象（J-ISS-2：安全性解析対象集団）

	AMG 334		
Preferred Term	70 mg QM (Subj-yr = 528 8) (N = 414) n (%) / e [r]	140 mg QM (Subj-yr = 343.8) (N = 269) n (%) / e [r]	Combined (Subj-yr = 872.7) (N = 470) n (%) / e [r]
All treatment-emergent hypertension event of interest	8 (1.9) / 523.4 [1.5]	3 (1.1) / 342.3 [0.9]	11 (2.3) / 863.9 [1.3]
高血圧	8 (1.9) / 523.4 [1.5]	3 (1.1) / 342.3 [0.9]	11 (2.3) / 863.9 [1.3]

N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event
% = n / N * 100
e = Sum across all subjects, the total time at risk in years. Time at risk is the time at the specific dose level before the first event onset of a specific treatment-emergent adverse event or the time at the specific dose level during the entire study period if no event. Total time at risk for reporting a specific treatment-emergent adverse event at a dose level = sum of all subjects' time at risk for the treatment-emergent adverse event at the dose level / 365.25.
r = Exposure adjusted subject rate per 100 subject years (n / e * 100)
Coded using MedDRA version 22.1
Based on hypertension standardized MedDRA query (SMQ; narrow and broad)

[redacted]

表 付録-40　Hy's law基準に該当した被験者（J-ISS-1：安全性解析対象集団）

	Placebo (N = 267) n / N1 (%)	AMG 334 28 mg QM (N = 66) n / N1 (%)	AMG 334 70 mg QM (N = 265) n / N1 (%)	AMG 334 140 mg QM (N = 137) n / N1 (%)	AMG 334 Overall (N = 468) n / N1 (%)
ALT or AST > 3 x ULN					
Baseline	1 / 267 (0.4)	0 / 66 (0.0)	1 / 265 (0.4)	0 / 137 (0.0)	1 / 468 (0.2)
On study	1 / 267 (0.4)	0 / 66 (0.0)	4 / 264 (1.5)	1 / 137 (0.7)	5 / 467 (1.1)
Total bilirubin > 2 x ULN					
Baseline	0 / 267 (0.0)	0 / 66 (0.0)	0 / 265 (0.0)	0 / 137 (0.0)	0 / 468 (0.0)
On study	0 / 267 (0.0)	0 / 66 (0.0)	0 / 264 (0.0)	0 / 137 (0.0)	0 / 467 (0.0)
ALT or AST > 3 x ULN and Total bilirubin > 2 x ULN and ALP < 2 x ULN					
Baseline	0 / 267 (0.0)	0 / 66 (0.0)	0 / 265 (0.0)	0 / 137 (0.0)	0 / 468 (0.0)
On study within ± 7 days	0 / 267 (0.0)	0 / 66 (0.0)	0 / 264 (0.0)	0 / 137 (0.0)	0 / 467 (0.0)

N = Number of subjects in the analysis set
N1 = Number of subjects with observed data for specified Hy's law parameter(s) at each time point
n = Number of subjects meeting criterion
% = n / N1 * 100
ALT = Alanine aminotransferase
AST = Aspartate aminotransferase
ALP = Alkaline phosphatase; ULN = Upper limit of normal
Hy's law predicts potential for drug-related hepatotoxicity.

[redacted]

表 付録-41　Hy's law基準に該当した被験者（J-ISS-2：安全性解析対象集団）

	AMG 334 70 mg QM only (N = 201) n / N1 (%)	AMG 334 140 mg QM only (N = 56) n / N1 (%)	AMG 334 70/140 mg QM (N = 213) n / N1 (%)	AMG 334 Combined (N = 470) n / N1 (%)
ALT or AST > 3 x ULN				
Pre-AMG 334 baseline	1 / 201 (0.5)	0 / 56 (0.0)	0 / 213 (0.0)	1 / 470 (0.2)
On study	5 / 201 (2.5)	2 / 56 (3.6)	2 / 213 (0.9)	9 / 470 (1.9)
Total bilirubin > 2 x ULN				
Pre-AMG 334 baseline	0 / 201 (0.0)	0 / 56 (0.0)	0 / 213 (0.0)	0 / 470 (0.0)
On study	0 / 201 (0.0)	0 / 56 (0.0)	0 / 213 (0.0)	0 / 470 (0.0)
ALT or AST > 3 x ULN and Total bilirubin > 2 x ULN and ALP < 2 x ULN				
Pre-AMG 334 baseline	0 / 201 (0.0)	0 / 56 (0.0)	0 / 213 (0.0)	0 / 470 (0.0)
On study within ± 7 days	0 / 201 (0.0)	0 / 56 (0.0)	0 / 213 (0.0)	0 / 470 (0.0)

N = Number of subjects in the analysis set
N1 = Number of subjects with observed data for specified Hy's law parameter(s) at each time point
n = Number of subjects meeting criterion
% = n / N1 * 100
ALT = Alanine aminotransferase
AST = Aspartate aminotransferase
ALP = Alkaline phosphatase
ULN = Upper limit of normal
Hy's law predicts potential for drug-related hepatotoxicity.
Pre-AMG 334 baseline is defined as the last observed measurement for the endpoint of interest taken before the first dose of AMG 334 70/140 mg.

[redacted]

参考文献

臨床概要で引用した参考文献リストは以下の各文書の参考文献の項に記載し、各文献はモジュール5.4項に添付した。

2.7.1　生物薬剤学試験及び関連する分析法の概要
2.7.2　臨床薬理の概要
2.7.3　臨床的有効性の概要
2.7.4　臨床的安全性の概要