エイフスチラ静注用

2.7　臨床概要

2.7.4　臨床的安全性の概要

CSL ベーリング株式会社

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略語・略号一覧

略語・略号	略していない表現（英語）	略していない表現（日本語）
ADA	Anti-drug antibody	抗薬物抗体
ADR	Adverse drug reaction	副作用
AE	Adverse event	有害事象
AESI	Adverse event of special interest	注目すべき有害事象
BU	Bethesda Units	ベセスダ単位
CHO	Chinese hamster ovary	チャイニーズハムスター卵巣
CSL627	Sponsor-assigned drug code for rVIII-SingleChain	遺伝子組換え単鎖血液凝固第 VIII 因子の治験薬コード
CSR	Clinical Study Report	治験総括報告書
ED	Exposure day	投与日数
EMA	European Medicines Agency	欧州医薬品庁
FDA	Food and Drug Administration	アメリカ食品医薬品局
FVIII	Factor VIII	血液凝固第 VIII 因子
HIV	Human immunodeficiency virus	ヒト免疫不全ウイルス
IgG	Immunoglobulin G	免疫グロブリン G
IgM	Immunoglobulin M	免疫グロブリン M
IR	Incremental recovery	回収率
IU	International Units	国際単位
JAN	Japanese Accepted Name	医薬品名称調査会承認名
MedDRA	Medical Dictionary for Regulatory Activities	ICH 国際医薬用語集
PK	Pharmacokinetic(s)	薬物動態
PMDA	Pharmaceuticals and Medical Devices Agency	医薬品医療機器総合機構
PT	Preferred term	基本語
PTP	Previously treated patient	治療歴のある患者
PUP	Previously untreated patient	治療歴のない患者
rVIII-SingleChain	Recombinant single-chain factor VIII	遺伝子組換え単鎖血液凝固第 VIII 因子
SAE	Serious adverse event	重篤な有害事象
SMQ	Standardized MedDRA query	MedDRA 標準検索式
SOC	System organ class	器官別大分類
TEAE	Treatment-emergent adverse event	治験治療下で発現した有害事象
TEE	Thromboembolic event	血栓塞栓事象
TESAE	Treatment-emergent serious adverse event	治験治療下で発現した重篤な有害事象
WFH	World Federation of Hemophilia	世界血友病連盟

本項の記載に関する説明

本項では以下の用語及び基準を用いた。

- 遺伝子組換え単鎖血液凝固第 VIII 因子（recombinant single-chain factor VIII：単鎖 rVIII）の開発コードは「CSL627」であった。本項では、「単鎖 rVIII」の略語又は「本剤」と記載する。
- 本項で要約した全臨床試験の正式な試験番号は治験依頼者の治験薬コード（CSL627）に続いて下線及び 4 桁の数字を付した番号である。本項で記載する試験番号は 4 桁の数字で示す（例えば、CSL627_1001 試験は 1001 試験）。
- 「以前の FVIII 製剤」の用語は、被験者が本剤の試験参加前に用いていた血液凝固第 VIII 因子（factor VIII：FVIII）補充製剤を指す。「以前の FVIII 製剤」は、rFVIII 製剤又は血漿由来 FVIII 製剤である。
- FVIII 活性は原資料では「FVIII 濃度（FVIII concentration：FVIII:C）」の用語を用いているが、本項では「FVIII 活性」の用語を用いる。
- 非中和抗薬物抗体（anti-drug antibody：ADA）は原資料中では「rFVIII に対する抗体」の用語を用いているが、本項では「抗薬物抗体（ADA）」の用語を用いる。
- 「グローバル患者集団」は日本人被験者を含むすべての被験者を指す。「日本人患者集団」はすべての日本人被験者を指す。「日本人以外の患者集団」は日本人被験者を除くグローバル患者集団を指す。
- 1001 試験に関する英語の原資料中では、Part 1 の PK 評価に用いた対照薬の名称は「octocog alfa」である。本項においては日本での当該対照薬の医薬品名称調査会承認名（Japanese Accepted Name：JAN）コードである「ルリオクトコグアルファ」で表記した。

2.7.4　臨床的安全性

2.7.4.1　医薬品への曝露

2.7.4.1.1　総括的安全性評価計画及び安全性試験の記述

血友病 A［血液凝固第 VIII 因子（coagulation factor VIII：FVIII）欠乏症］はまれに起こる重篤な X 染色体連鎖劣性出血性疾患であり、FVIII タンパク質の欠失・欠乏に起因する。血友病 A の症状は臨床上の重大な懸念である。患者には自然出血エピソードや傷害時の止血の大幅な遅延が見られ、まれにではあるが生命を脅かす出血例もある。血友病 A の最もよく見られる症状は、再発性の自然出血で、好発部位は足首、肘、膝などの関節である（Mulder and Llinás, 2004）。重度の FVIII 欠損（FVIII 活性 1%未満）患者では、自然出血を繰り返すことによって慢性的で、日常生活に支障をきたす程度の関節障害をきたすことが多い（Berntorp et al., 2014）。したがって、FVIII 補充製剤を用いた定期的な投与の主な目標の 1 つは、血友病 A 及びその後の臨床的後遺症の重症度を低下させるために FVIII 活性の「トラフ値」を 1%～5%に維持することである（Srivastava et al., 2013 及び WFH, 2012）。

血友病 A 患者の出血エピソードに対する治療又は出血傾向の抑制の推奨療法は凝固因子補充療法、すなわち精製した FVIII の投与である。

遺伝子組換え FVIII（recombinant rFVIII：rFVIII）製剤として分類される薬剤に共通する作用には、インヒビター産生及び過敏症反応がある。FVIII に対するインヒビターを産生した患者は補充療法に抵抗性を認めるようになることがある。FVIII に対するインヒビターを産生する患者の実際の割合は報告された文献によって異なるが、血友病 A 患者全体の最大 33%が FVIII に対するインヒビターを産生すると報告されている。インヒビター産生は、民族を問わず、血漿由来及び rFVIII 製剤のいずれにおいても認められることが分かっている（DiMichele, 2007）。

上記の血友病 A 患者の治療用に、CSL ベーリング社は新規の遺伝子組換え単鎖血液凝固第 VIII 因子（recombinant, single-chain coagulation FVIII：単鎖 rVIII、以下本剤と記載する）補充療法を開発した。単鎖 rVIII は、チャイニーズハムスター卵巣（Chinese hamster ovary：CHO）細胞内で生産されるタンパク質を修飾した分子である。野生型 FVIII に存在する B ドメインと a3 ドメイン間のフューリン切断部位が取り除かれたため、単鎖 rVIII は単鎖 FVIII 分子として発現する。この単鎖構造は分子の統合性を大幅に強化することが分かっており、その結果、他の FVIII 製剤よりも安定性が高い均質な製剤が得られる。さらに、in vitro 試験では本剤は天然の担体タンパク質であるフォン・ヴィレブランド因子に対して極めて高い親和性を示し（Schulte, 2013）、FVIII の生理活性やクリアランスに重要な影響を果たすことが示されている。

血友病 A 患者における本剤の安全性及び忍容性を示すデータは、12 歳以上 65 歳以下の患者を対象としたピボタル第 I／III 相試験（1001 試験）及び 0 歳以上 12 歳未満の患者を対象とした第 III 相ピボタル試験（3002 試験）より得られている。これらの試験から得られたデータは、第 VIII 因子欠乏患者に対する出血傾向の抑制における本剤の安全性を裏付けている。安全性は、以下の治療状況下で検討した。

- 出血エピソードの管理及び抑制

- 出血エピソードの抑制又は低減のための定期的な投与
- 周術期の補充療法（外科手術時の補充療法）

本剤臨床開発プログラムは、欧州医薬品庁（European Medicines Agency：EMA）のガイドライン「Guideline on the Clinical Investigation of Recombinant and Human Plasma-derived Factor VIII Products（EMA, 2011）」及びアメリカ食品医薬品局（Food and Drug Administration：FDA）及び日本の医薬品医療機器総合機構（Pharmaceuticals and Medical Devices Agency：PMDA）のガイダンスに従って進められている。これらの試験は、医薬品の臨床試験の実施に関する基準のガイドライン及びその他の規制要件に従って実施した。

EMA ガイドライン並びに FDA 及び PMDA のガイダンスに従い、FVIII に対するインヒビターの産生率が臨床試験における安全性の主要目的であった。さらに、非中和抗薬物抗体（ADA）及び CHO 細胞由来タンパク質に対する抗体の有無について検証することにより、本剤の免疫原性の変化についても検討した。

その他の安全性評価は、アナフィラキシー反応、過敏症、及び血栓塞栓事象（thromboembolic event：TEE）に焦点を合わせた有害事象（adverse event：AE）報告、並びに局所忍容性、安全性に関する臨床検査（生化学検査及び血液学的検査）、バイタルサイン、及び身体的診察の評価に基づいて実施した。

以上を総合すると、この「臨床的安全性の概要」で提示したデータにより、本剤は、他の FVIII 製剤と同様に、この種の治療及び適応症で予想されるような好ましい安全性及び忍容性プロファイルを有していることが示されている。

2.7.4.1.1.1　安全性評価を実施した試験

本申請の裏付けとなる安全性データは以下の 2 つの完了した臨床評価試験から得られている。

- 1001 試験：治療歴のある患者（previously treated patient：PTP）を対象としたピボタル成人／青年試験：12 歳以上 65 歳以下の重度血友病 A PTP を対象とした本剤の安全性、有効性、及び薬物動態（pharmacokinetic：PK）を検討する第 I／III 相非盲検多施設共同試験。本試験は以下の 3 つのパートから構成される（2.7.3 項、図 2.7.3-1 参照）。Part 1 は、ルリオクトコグアルファ［50 国際単位（IU）/kg］と本剤（50 IU/kg）の単回投与クロスオーバーPK 比較試験であった。Part 2 及び Part 3 では、本剤によるオンデマンド療法及び定期的な投与の有効性及び安全性を評価した。Part 3 では本剤の初回及び反復投与後の PK 評価も実施した。本試験には、Part 2 及び Part 3 に登録された被験者を対象に外科的 substudy を含めた。グローバル患者集団及びそれに対応する日本人患者集団（表番号末尾の「J」で示す）から得られたデータについては、1001 試験の最終 CSR の 5.3.5.1 項を参照。

- 3002 試験（PTP を対象としたピボタル小児試験）：0 歳以上 12 歳未満の重度血友病 A PTP を対象とした本剤の PK、有効性、及び安全性を検討する第 III 相非盲検試験。5.3.5.2 項に記載した 3002 試験の最終 CSR を参照。

現在、以下の継続投与試験を実施している。

- 3001 試験：重度血友病 A 患者を対象とした本剤の安全性及び有効性を評価する第 III 相非盲検多施設共同継続投与試験。本試験参加中に手術を要するすべての患者が外科的 substudy に参加することができる。

本剤の各試験は、EMA ガイドラインに明記された以下の要件を達成するようデザインした。つまり、（1）1001 試験では、12 歳以上の被験者 50 名以上が、投与日数（曝露日数、以下 ED と示す）50 ED 以上の本剤投与を受けること、（2）3002 試験では、12 歳未満の被験者 50 名以上［2 つの年齢群（0 歳以上 6 歳未満及び 6 歳以上 12 歳未満）でそれぞれ被験者が 25 名以上、PK 評価では 2 つの年齢群でそれぞれ被験者が 12 名以上］が、50 ED 以上の本剤投与を受けることであった。さらに、FDA の要請に従い、1001 試験の Part 2 及び Part 3 の被験者は各治療レジメンによる 50 ED 以上の投与を受けるものとし、計 104 名以上がこの最低曝露量に達するまで（インヒビター産生の評価のために）投与を継続した。

最初に 18 歳以上 65 歳以下の治療歴のある血友病 A 患者を対象にデータを収集し（1001 試験の Part 1 及び Part 2）、次に 12 歳以上 65 歳以下の患者を対象にデータを収集した（1001 試験の Part 3）。この集団で 50 ED 以上に達した 20 名以上の被験者で PK 及び安全性が確立された後に、0 歳以上 12 歳未満の被験者を対象にデータを収集した（3002 試験）。

1001 試験及び 3002 試験は、治療歴があり FVIII に対するインヒビター産生の既往が確認されていない血友病 A（FVIII 活性 1%以下）男性被験者を対象としたプロスペクティブ非盲検多施設共同試験であった。以前使用していた FVIII 製剤の ED の要件は、1001 試験で 150 ED 超、3002 試験で 50 ED 超とした。

1001 試験及び 3002 試験における安全性の主要評価項目は、初回投与時点から試験終了来院までの期間で評価した本剤に対するインヒビター産生率であった。インヒビター産生は、反復検査により同定・確認されたインヒビター［0.6 ベセスダ単位（Bethesda Units : BU）/mL 以上］として定義した。いずれの検査も中央測定機関で実施することとした。

本剤を 1 回以上投与したすべての被験者を安全性解析集団に含めた。

1001 試験及び 3002 試験を完了した被験者は、実施中の継続投与試験である 3001 試験で本剤治療を継続することができる。3001 試験は、100 ED 以上（1001 試験及び 3002 試験における本剤の初回投与日から起算）の治療歴を有する PTP 200 名以上を対象に、本剤の使用に関する追加的な安全性データを得ることで、EMA による市販後の要件を満たすようデザインした（EMA,

2011)。さらに、3001 試験では、治療歴のない患者（previously untreated patient：PUP）を含めるように治験実施計画書を改訂している（治験実施計画書の 2 回目の重要な変更)。

本剤のピボタル試験に参加した 258 名の被験者のうち、10 名が日本人（成人 8 名、青年 2 名）で、1001 試験の Part 3 に参加した。3002 試験に参加した日本人被験者はいなかった。

これらの試験のデザイン及び目的に関する詳細を表 2.7.4-1 に示す。各試験のさらに具体的な記述は、2.7.3.2.1 項（1001 試験）及び 2.7.3.2.2 項（3002 試験）に示しており、5.3.5.1 項（1001 試験）及び 5.3.5.2 項（3002 試験）の CSR でも提示している。

表 2.7.4-1　本剤の臨床評価試験の概要

試験番号 報告書記載箇所 進行状況	試験の相 試験デザイン	治験実施施設の所在地（N）	主要目的	被験者集団 年齢：平均値（最小値、最大値）	製剤、投与経路、用量	評価した安全性評価項目
1001 試験 5.3.5.1 項 完了	12 歳以上 65 歳以下の被験者を対象とする第 I／III 相、非盲検、多施設共同、単回投与クロスオーバー（Part 1）及び反復投与（Part 2 及び 3）試験	オーストラリア（2） オーストリア（2） カナダ（1） チェコ（1） ドイツ（6） ハンガリー（1） イタリア（4） 日本（8） レバノン（1） マレーシア（1） オランダ（1） フィリピン（2） ポーランド（3） ルーマニア（1） ロシア（2） 南アフリカ（2） スペイン（3） ウクライナ（2） 英国（1） 米国（9）	本剤の PK プロファイルの特徴を明らかにする。 出血エピソードの抑制及び治療における有効性を立証する。 定期的な投与がオンデマンド療法よりも有効であることを立証する。 外科手術時の補充療法における本剤の有効性を立証する。 インヒビター産生率を明らかにする。	グローバル患者集団： 重度血友病 A（FVIII 活性 1%未満）男性 PTP 174 名 Part 1 及び 2[a]： 18 歳以上 65 歳以下 Part 3： 12 歳以上 65 歳以下 全体の平均値： 31.3（12、64）歳 日本人患者集団： 重度血友病 A（FVIII 活性 1%未満）男性 PTP 10 名 全体の平均値： 28.3（12、46）歳	Part 1 PK 評価（クロスオーバー）： ルリオクトコグアルファ（IV）50 IU/kg 単回投与 本剤（IV）50 IU/kg 単回投与 Part 2 及び 3（50 ED 以上に達するまで投与）： 本剤（IV） オンデマンド療法： 試験前に同じタイプの出血エピソードに使用していた第 VIII 因子製剤と同程度の用量で治験責任医師の裁量で行う。 定期的な投与： 20～40 IU/kg を 2 日ごと、又は 20～50 IU/kg を週 2～3 回投与、若しくは治験責任医師が判断した用量、頻度で投与 外科的 substudy： FVIII 活性が WFH ガイドライン（WFH, 2012）の推奨レベルに到達し、維持できるように手術の種類及び被験者の臨床状況に基づき個別に用量を決定する。 Part 3 PK 評価： 初回及び反復投与後の PK 評価のため本剤（IV）50 IU/kg 単回投与	FVIII に対するインヒビター、非中和抗薬物抗体、CHO 細胞由来タンパク質に対する抗体、有害事象、局所忍容性、安全性に関する臨床検査（血液学的検査、生化学検査）、バイタルサイン、及び身体的診察

表 2.7.4-1　本剤の臨床試験の概要（続き）

試験番号 報告書記載箇所 進行状況	試験の相 試験デザイン	治験実施施設の所在地（N）	主要目的	被験者集団 年齢：平均値（最小値、最大値）	製剤、投与経路、用量	評価した安全性評価項目
3002 試験 5.3.5.2 項 完了	0 歳以上 12 歳未満の被験者を対象とした第 III 相、プロスペクティブ、非盲検、多施設共同試験	オーストラリア（1） オーストリア（2） フランス（5） ジョージア（1） ドイツ（4） イタリア（1） レバノン（1） マレーシア（1） オランダ（3） フィリピン（2） ポーランド（1） ポルトガル（1） ルーマニア（1） スペイン（1） スイス（1） タイ（5） トルコ（3） ウクライナ（1） 米国（2）	治験責任医師による 4 点評価スケールに基づき、大出血及び小出血の治療における本剤の有効性を評価する。	重度血友病 A（FVIII 活性 1%未満）男性 PTP 84 名 6.6（1、11）歳 本試験に日本人 PTP は含まれていなかった。	単回投与 PK 評価： 本剤（IV）50 IU/kg を単回投与 反復投与（50 ED 以上に達するまで投与）： オンデマンド療法： WFH 推奨用量（WFH、2012）に基づき治験責任医師が指示した用量 定期的な投与： 15～50 IU/kg を 2 日ごと、又は 1 週間に 2～3 回、若しくは治験責任医師が判断した用量及び頻度	FVIII に対するインヒビター、非中和抗薬物抗体、CHO 細胞由来タンパク質に対する抗体、有害事象（過敏症及び血栓塞栓事象を含む）、局所忍容性、安全性に関する臨床検査（血液学的検査及び生化学検査）、バイタルサイン、及び身体的診察

略語：CHO、チャイニーズハムスター卵巣；ED、投与日数；FVIII、血液凝固第 VIII 因子；IU、国際単位；IV、静脈内（注射）；N、治験実施施設数；PK、薬物動態；PTP、治療歴のある患者；本剤、遺伝子組換え単鎖血液凝固第 VIII 因子；WFH、世界血友病連盟

[a]　Part 2 の被験者はすべて Part 1 にも参加した。

引用：5.3.5.1 項、1001 試験 CSR；5.3.5.1 項、表 14.1.5.1J；5.3.5.2 項、3002 試験 CSR

表 2.7.4-2　実施中の本剤の継続投与試験の概要

試験番号 報告書記載箇所 進行状況	試験の相 試験デザイン	主要目的	予定被験者集団	製剤、投与経路、用量	評価した安全性評価項目
3001 試験 該当せず 実施中	0 歳以上 65 歳以下の被験者を対象とした第 III 相プロスペクティブ非盲検多施設共同継続投与試験	**PTP**： 1001 試験又は 3002 試験に参加していた被験者並びに本剤の投与を受けたことのない PTP におけるインヒビター産生について本剤の長期安全性プロファイルの特性を明らかにする。 **PUP**： －インヒビター産生について本剤の安全性の特性を明らかにする。 －本剤を用いたオンデマンド療法及び定期的な投与の有効性を評価する。	**PTP**：100 ED[a]以上に達した PTP 200 名以上 **PUP**：50 ED 以上に達した PUP 50 名以上	*オンデマンド療法*： 推奨される FVIII 活性レベル（WFH、2012）の達成を目標に、出血エピソードの種類及び重症度に基づいて治験責任医師が事前に決定した用量。 *定期的な投与*： 治験責任医師が WFH ガイドライン（WFH, 2012）を考慮して決定した用量及び投与頻度。PTP では、治験責任医師は、さらに被験者の PK プロファイル及び出血の表現型（可能な場合）、本剤の PK プロファイル、本試験参加前に使用していた FVIII 製剤の用法・用量及びピボタル試験ではほとんどの被験者が開始用量 15～50 IU/kg を週 2～3 回投与する定期的な投与を受けたという事実に基づき用量及び投与頻度を決定する。 *外科的 substudy*： WFH ガイドライン（WFH, 2012）で推奨されている FVIII 活性レベルを達成し維持するために、手術の種類及び被験者の臨床状況に基づき個別に決定された用量	FVIII に対するインヒビター、非中和抗薬物抗体、CHO 細胞由来タンパク質、有害事象（過敏症及び血栓塞栓事象を含む）、局所忍容性、安全性に関する臨床検査（血液学的検査）、バイタルサイン、身体的診察[d]、及び回収率

略語：CHO、チャイニーズハムスター卵巣；ED、投与日数；FVIII、血液凝固第 VIII 因子；IU、国際単位；IV、静脈内（注射）；N、治験実施施設数；PK、薬物動態；PUP、治療歴のない患者；PTP、治療歴のある患者；本剤、遺伝子組換え単鎖血液凝固第 VIII 因子；WFH、世界血友病連盟

[a]　ピボタル試験である 1001 試験又は 3002 試験から移行した被験者の ED は、これらの試験での本剤の初回投与日から起算した。

2.7.4.1.1.2　安全性データが得られた本剤試験の記述

1001 試験及び 3002 試験の記述は、2.7.3.2.1 項（1001 試験）及び 2.7.3.2.2 項（3002 試験）に示す。

2.7.4.1.1.3　安全性データの提示

1001 試験及び 3002 試験から得られたデータを試験ごとに提示する。副作用（ADR）の解析（2.7.4.2.1.7 項）を除き、これらの試験では被験者年齢に差があるため、2 つの試験を統合した安全性データの統合解析は実施していない。

1001 試験では、すべての試験パート及び治療レジメンの被験者を統合して、グローバル安全性解析集団（N = 174）に加え、日本人安全性解析集団（N = 10）について被験者背景データ、曝露量、及び完全な安全性データを提示している（ただし、安全性データを個別に提示している外科的 substudy は除く）。FVIII に対するインヒビター産生が認められた被験者の数及び割合を表に要約し、インヒビター産生に対する 95%の正確な二項信頼区間を提示した。解析の母数は、本試験で 50 ED 以上の本剤投与を受けた被験者とした。信頼区間上限値が許容上限値 6.8%を下回ったことから、安全性の主要評価項目が達成された。

3002 試験では、安全性解析集団全体（N = 84）について被験者背景データ、曝露量、及び完全な安全性データを提示している。特に明記しない限り、安全性解析集団全体に加え、年齢群（0 歳以上 6 歳未満、6 歳以上 12 歳未満）別にデータを要約している。

ADR は、治験責任医師及び／又は治験依頼者により本剤と関連ありと判定された AE であり、2.7.4.2.1.7 項に詳細を示す。

2.7.4.1.2　全般的な曝露状況

1001 試験及び 3002 試験では、12 歳以上 65 歳以下の被験者 120 名、6 歳以上 12 歳未満の被験者 38 名、0 歳以上 6 歳未満の被験者 27 名が 50 ED 以上に達し（表 2.7.4-4）、EMA ガイドラインの最低限の被験者数及び ED に関する要件（EMA, 2011）を満たすとともに、それを上回った。

小児を対象としたピボタル試験である 3002 試験の開始が遅く、0 歳以上 12 歳未満の被験者数が少ないことから、0 歳以上 12 歳未満の被験者の全体的な曝露量は少なくなることが予想された。

1001 試験

1001 試験では、グローバル患者集団の被験者 174 名が平均（SD）82.2（61.35）ED の投与を受け、試験期間の平均値（SD）は 258.8（163.52）日（8.5 箇月）であった（表 2.7.4-3）。50 ED 以上の被験者が 104 名以上という FDA 要件を達成した。50 ED 以上に達した被験者は 120 名（69.0%）で、100 ED 以上に達した被験者は 52 名（29.9%）であった。

日本人患者集団の 10 名の被験者における曝露量はグローバル患者集団と同程度であり、被験者は平均（SD）83.2（31.89）ED の投与を受け、試験期間の平均値（SD）が 314.2（97.91）日（10.3 箇月）であった。

3002 試験

3002 試験では、治療を受けた 84 名の被験者が平均（SD）62.4（24.73）ED の投与を受け、試験期間の平均値（SD）は 183.5（61.16）日（6.0 箇月）であった（表 2.7.4-3）。50 ED 以上に達した被験者は 65 名（77.4%）で、100 ED 以上に達した被験者は 8 名（9.5%）であった。

表 2.7.4-3　臨床試験における本剤投与日数（安全性解析集団、1001 試験及び 3002 試験）

	1001 試験		**3002 試験**
	グローバル患者集団	**日本人患者集団**	
	（N = 174）	**（N = 10）**	**（N = 84）**
投与日数（ED）[a]			
平均値（SD）	82.2 (61.35)	83.2 (31.89)	62.4 (24.73)
中央値（最大値、最小値）	63.5 (1, 395)	91.5 (23, 130)	58.5 (4, 142)
50 ED 未満、n（%）	54 (31.0)	2 (20.0)	19 (22.6)
50 ED 以上、n（%）	120 (69.0)	8 (80.0)	65 (77.4)
100 ED 以上、n（%）	52 (29.9)	3 (30.0)	8 (9.5)
ED の総計	14306	832	5239
試験期間、日数			
平均値（SD）	258.8 (163.52)	314.2 (97.91)	183.5 (61.16)
中央値（最大値、最小値）	219.0 (5, 758)	317.5 (119, 462)	171.0 (30, 346)
試験期間、月数			
平均値（SD）	8.5 (5.37)	10.3 (3.22)	6.0 (2.01)
中央値（最大値、最小値）	7.2 (0, 25)	10.4 (4, 15)	5.6 (1, 11)
被験者・年の総計[b]	122.7	8.6	42.2
被験者ごとの本剤の投与回数			
平均値（SD）	83.9 (61.96)	83.8 (31.21)	63.3 (25.77)
中央値（最大値、最小値）	67.0 (1, 395)	91.5 (23, 130)	59.0 (4, 145)
本剤の合計投与回数	14592	838	5313

略語：ED、投与日数；N、各試験の安全性解析集団における被験者数；n、基準に該当する被験者数；本剤、遺伝子組換え単鎖血液凝固第 VIII 因子

[a]　ED は、同日の投与回数にかかわらず本剤の投与を受けた日である。

[b]　被験者・年 =［(最終来院日) － (本剤の初回投与日、治療期間の Day 1 の日付のいずれか早い日付) + 1］/ 365.25

引用：

5.3.5.1 項、1001 試験 CSR、表 14.1.4.1 及び表 14.1.12.1；5.3.5.1 項、表 14.1.4.1J 及び表 14.1.12.1J

5.3.5.2 項、3002 試験 CSR、表 14.1.8.1 及び表 14.1.8.5.1

表 2.7.4-4　年齢別の本剤投与日数（グローバル安全性解析集団、1001 試験及び 3002 試験）

	1001 試験		**3002 試験**	
	12 歳以上 18 歳未満 (N = 14)	**18 歳以上 65 歳以下 (N = 160)**	**0 歳以上 6 歳未満 (N = 35)**	**6 歳以上 12 歳未満 (N = 49)**
投与日数 [a]				
平均値（SD）	64.1 (36.43)	83.8 (62.89)	56.7 (18.90)	66.4 (27.64)
中央値（最小値、最大値）	58.0 (15, 130)	64.0 (1, 395)	52.0 (4, 98)	59.0 (9, 142)
50 ED 未満、n（%）	6 (42.9)	48 (30.0)	8 (22.9)	11 (22.4)
50 ED 以上、n（%）	8 (57.1)	112 (70.0)	27 (77.1)	38 (77.6)
100 ED 以上、n（%）	2 (14.3)	50 (31.3)	0	8 (16.3)
ED の総計	897	13409	1984	3255
試験期間、日数				
平均値（SD）	209.1 (131.40)	263.2 (165.66)	178.5 (58.00)	187.0 (63.67)
中央値（最小値、最大値）	168.0 (53, 462)	222.5 (5, 758)	162.0 (64, 346)	172.0 (30, 343)
試験期間、月数				
平均値（SD）	6.9 (4.32)	8.6 (5.44)	5.9 (1.91)	6.1 (2.09)
中央値（最小値、最大値）	5.5 (2, 15)	7.3 (0, 25)	5.3 (2, 11)	5.7 (1, 11)
被験者・年の総計 [b]	8.0	114.7	17.1	25.1
被験者ごとの本剤の投与回数				
平均値（SD）	64.6 (36.32)	85.6 (63.51)	56.9 (19.20)	67.8 (28.93)
中央値（最小値、最大値）	58.0 (15, 130)	67.5 (1, 395)	52.0 (4, 100)	60.0 (9, 145)
本剤の合計投与回数	904	13688	1991	3322

略語：ED、投与日数；N、各年齢群の被験者総数；n、基準に該当する被験者数；本剤、遺伝子組換え単鎖血液凝固第 VIII 因子

[a]　ED は、同じ日に投与した回数に関係なく本剤を投与した日数である。

[b]　被験者・年 =［(最終来院日) − (本剤の初回投与日、治療期間の Day 1 の日付のうち早い日付) + 1)］/ 365.25

引用：5.3.5.1 項、1001 試験 CSR、表 14.1.4.3 及び表 14.1.12.3；5.3.5.2 項、3002 試験 CSR、表 14.1.8.1 及び表 14.1.8.5.1

オンデマンド療法又は定期的な投与に加えて、本剤の予防及び追加投与も許容した。予防投与は、出血の抑制又は低減を目的とした運動前又は軽微な手術前の投与と定義した。追加投与は、止血管理の必要量を超える用量での投与と定義した。

1001 試験のグローバル患者集団で本剤の予防投与を受けた被験者の割合は、予想されたように、オンデマンド療法群（77.8%）の方が定期的投与群（16.4%）と比較して高かった。同様に、本剤の追加投与を受けた被験者の割合は、オンデマンド療法群（55.6%）の方が定期的投与群（12.3%）と比較して高かった。本試験で被験者に対して使用した本剤の予防投与及び追加投与の要約は、1001 試験、表 14.1.13 に示している。

日本人患者集団でも、予防投与においてグローバル患者集団と同様な違いが認められた（すなわち、オンデマンド療法群の 1 名の被験者が 16 回の予防投与を受けたのに対し、定期的投与群の 3 名の被験者は計 7 回の予防投与を受けた）。ただし、被験者数が少ないため、決定的な比較はできない。追加投与を受けた日本人被験者はいなかった（1001 試験、表 14.1.13J）。

3002 試験では、オンデマンド療法を受けた被験者の数（N = 3）が定期的な投与を受けた被験者の数（N = 80）と比較して少なかったため、この 2 つの療法間で予防投与及び追加投与について意味のある比較はできなかった。本試験で被験者に指示した本剤の予防投与及び追加投与の要約は、3002 試験、表 14.1.8.7.1 に示している。

2.7.4.1.3　治験対象集団の人口統計学的背景及びその他の特性

2.7.4.1.3.1　被験者背景及びベースライン時の被験者背景

1001 試験及び 3002 試験の被験者背景は、各試験で年齢群が異なることを考慮すると、試験に登録された集団に特有なものであった。いずれの試験でも被験者はすべて男性であった。

1001 試験におけるグローバル安全性解析集団の被験者は 174 名であった。被験者年齢は、12～64 歳（平均年齢 31.3 歳）で、18 歳以上 65 歳以下の被験者が 92.0%（160 名）を占めていた。全体として、白人が 72.4%（126 名）であった（表 2.7.4-5 及び 1001 試験 CSR、11.2 項）。

日本人安全性解析集団の被験者は 10 名であった。被験者年齢は、12～46 歳（平均年齢 28.3 歳）で、12 歳以上 18 歳未満の被験者が 2 名、18 歳以上 65 歳以下の被験者が 8 名であった。全体として、本試験では、被験者背景及びベースライン時の特性において、日本人患者集団とグローバル患者集団との間に意味のある違いは認められなかった。

3002 試験における安全性解析集団は、登録された全被験者の 84 名であった。被験者年齢は、1～11 歳（平均年齢 6.6 歳）で、6 歳以上 12 歳未満の被験者が 58.3%（49 名）を占めていた。全体として、白人が 72.6%（61 名）であった（表 2.7.4-5 及び 3002 試験 CSR、11.2.1 項）。

表 2.7.4-5　本剤臨床試験における被験者背景（安全性解析集団、1001 試験及び 3002 試験）

被験者背景	1001 試験 グローバル患者集団 (N = 174)	1001 試験 日本人患者集団 (N = 10)	3002 試験 (N = 84)
年齢、歳			
平均値（SD）	31.3 (11.77)	28.3 (11.62)	6.6 (3.11)
中央値（最小値、最大値）	29.5 (12, 64)	31.5 (12, 46)	7.0 (1, 11)
年齢群、n（%）			
0 歳以上 12 歳未満	**0**	**0**	**84 (100)**
0 歳以上 6 歳未満	0	0	35 (41.7)
6 歳以上 12 歳未満	0	0	49 (58.3)
12 歳以上 65 歳以下	**174 (100)**	**10 (100)**	**0**
12 歳以上 18 歳未満	14 (8.0)	2 (20.0)	0
18 歳以上 65 歳以下	160 (92.0)	8 (80.0)	0
体重、kg			
平均値（SD）	74.6 (16.99)	57.7 (10.83)	27.60 (13.45)
中央値（最小値、最大値）	75.0 (27, 120)	59.3 (38, 74)	25.00 (10.0, 87.5)
人種、n（%）			
白人	126 (72.4)	0	61 (72.6)
アジア人	31 (17.8)	10 (100)	22 (26.2)
黒人又はアフリカ系アメリカ人	14 (8.0)	0	0
その他	3 (1.7)	0	1 (1.2)
民族、n（%）			
ヒスパニック／ラテンアメリカ系	12 (6.9)	0	2 (2.4)
非ヒスパニック／非ラテンアメリカ系	161 (92.5)	10 (100)	81 (96.4)
報告なし	1 (0.6)	0	1 (1.2)
国又は地理的領域、n（%）			
米国	22 (12.6)	0	4 (4.8)
日本	10 (5.7)	10 (100)	0
欧州	86 (49.4)	0	49 (58.3)
その他の地域	56 (32.2)	0	31 (36.9)

略語：N、各試験の安全性解析集団における被験者数；n、各基準に該当する被験者数；本剤、遺伝子組換え単鎖血液凝固第 VIII 因子

引用：

5.3.5.1 項、1001 試験 CSR、表 14.1.5.1、及び 5.3.5.1 項、表 14.1.5.1J

5.3.5.2 項、3002 試験 CSR、表 14.1.4.1

2.7.4.1.3.2　既往歴及び病歴

全体として、1001 試験及び 3002 試験における被験者集団の既往歴及び病歴は、血友病 A の一般患者集団に典型的なものであった［表 2.7.4-6（1001 試験）及び表 2.7.4-9（3002 試験）］。3002 試験の小児被験者では、既往歴及び病歴が異なっており、疾患の既往歴が短く、合併症が少ないこと、及び FVIII 製剤による治療期間が短いことを反映していた。1001 試験 CSR、11.2.2 項、3002 試験 CSR、11.2.2 項及び 11.2.3 項も参照。

2.7.4.1.3.2.1　1001 試験（12 歳以上 65 歳以下の被験者）

1001 試験におけるグローバル安全性解析集団［159 名（91.4%）］では、試験登録時に大多数の被験者で現病歴が報告された（表 2.7.4-6）。最も頻度が高かった現病歴は、器官別大分類（system organ class：SOC）の「筋骨格系および結合組織障害」［119 名（68.4%）］で、血友病性関節症［87 名（50.0%）］、関節可動域低下及び出血性関節症［いずれも 9 名（5.2%）］が見られた。

既往歴及び病歴には、日本人患者集団とグローバル患者集団との間に意味のある違いは認められなかった。日本人患者集団で最も高頻度の現病歴は、SOC の「筋骨格系および結合組織障害」（9 名、90%）で、血友病性関節症（9 名、90%）が最も多く見られた。

表 2.7.4-6　現病歴（安全性解析集団、1001 試験）

	被験者数（%）	
器官別大分類 **基本語**	**グローバル患者集団** **（N = 174）**	**日本人患者集団** **（N = 10）**
すべての医学的既往／外科手術歴	**159 (91.4)**	**10 (100)**
筋骨格系および結合組織障害 [a]	**119 (68.4)**	**9 (90.0)**
血友病性関節症	87 (50.0)	9 (90.0)
関節可動域低下	9 (5.2)	0
出血性関節症	9 (5.2)	0
関節痛	7 (4.0)	0
関節炎	5 (2.9)	0
筋萎縮	5 (2.9)	0
滑膜炎	4 (2.3)	0
関節摩擦音	4 (2.3)	0
関節障害	4 (2.3)	0
関節拘縮	4 (2.3)	0
腱障害	3 (1.7)	0
変形性関節症	3 (1.7)	0
関節強直	3 (1.7)	0

略語：N、安全性解析集団の被験者数

[a] 基本語は最も多く認められた器官別大分類において安全性解析集団の被験者 3 名以上で報告されたもの。

引用：5.3.5.1 項、1001 試験 CSR、表 14.1.6.1；5.3.5.1 項、表 14.1.6.2J

グローバル患者集団における既往歴又は現病歴で、ウイルス検査が陽性と報告された被験者は、ヒト免疫不全ウイルス（HIV）が 18 名（10.3%）、C 型肝炎ウイルスが 62 名（35.6%）、B 型肝炎ウイルスが 10 名（5.7%）であった。日本人患者集団でも同程度の割合で認められた（表 2.7.4-7）。

表 2.7.4-7　ウイルス感染歴（安全性解析集団、1001 試験）

器官別大分類 基本語	被験者数（%） グローバル患者集団 (N = 174)	 日本人患者集団 (N = 10)
ウイルス検査陽性（既往歴及び現病歴）	**65 (37.4)**	**3 (30.0)**
C 型肝炎	62 (35.6)	3 (30.0)
HIV 感染	18 (10.3)	2 (20.0)
B 型肝炎	10 (5.7)	0

略語：HIV、ヒト免疫不全ウイルス；N、安全性解析集団の被験者数
引用：5.3.5.1 項、1001 試験 CSR、表 14.1.6.3；5.3.5.1 項、表 14.1.6.3J

本試験では、腎機能障害又は肝機能障害の被験者を除外する規定は設けなかった（ただし、スクリーニング時にアスパラギン酸アミノトランスフェラーゼ又はアラニンアミノトランスフェラーゼが正常値上限の 5 倍を超える場合、又は血清クレアチニンが正常値上限の 2 倍を超える場合を除く）。

- グローバル患者集団：9 名の被験者が「肝胆道系障害」［胆石症（n = 2）、高ビリルビン血症（n = 2）、肝機能異常（n = 2）、脂肪肝（n = 1）、慢性胆嚢炎（n = 1）、慢性肝炎（n = 1）］で、5 名の被験者が「腎および尿路障害」［腎結石症（n = 3）、尿路結石（n = 2）］であった（1001 試験、表 14.1.6.1）。
- 日本人患者集団：1 名の日本人被験者で肝機能異常の肝胆道系障害が見られた。腎および尿路障害を認めた日本人被験者はいなかった（1001 試験、表 14.1.6.2J）。

1001 試験の組入れ基準として、すべての被験者が過去に FVIII による治療を受けていた。グローバル患者集団では、過去 12 箇月に血漿製剤［83 名（47.7%）］又は遺伝子組換え製剤［91 名（52.3%）］のいずれかによる治療を受けていた被験者の割合はほぼ同じで、オンデマンド療法［92 名（52.9%）］又は定期的な投与［86 名（49.4%）］を受けていた被験者の割合もほぼ同じであった。また、過去 12 箇月で両レジメンを受けていたと報告した被験者は 4 名であった（表 2.7.4-8；1001 試験、一覧表 16.2.4.6）。

日本人患者集団では、定期的な投与で遺伝子組換え製剤による治療を受けていた被験者の割合がグローバル患者集団より高かった。これは、日本における現在の FVIII 治療状況と一致している。

表 2.7.4-8　FVIII 治療歴（安全性解析集団、1001 試験）

	被験者数（%） グローバル患者集団 (N = 174)	 日本人患者集団 (N = 10)
製剤の種類		
血漿由来製剤	83 (47.7)	0
遺伝子組換え製剤	91 (52.3)	10 (100)
用法		
定期的な投与	86 (49.4)	9 (90.0)
オンデマンド療法	92 (52.9)	1 (10.0)

略語：FVIII、血液凝固第 VIII 因子；N、安全性解析集団の被験者数
注：被験者は、複数の用法を選択した可能性がある。
引用：5.3.5.1 項、1001 試験 CSR、表 14.1.8.1；5.3.5.1 項、表 14.1.8.1.J

2.7.4.1.3.2.2　3002 試験（0 歳以上 12 歳未満の被験者）

小児被験者で予測されるように、3002 試験で現病歴が報告された被験者の割合は低かった［33 名（39.3%）］。最も高い頻度で見られた現病歴は「筋骨格系および結合組織障害」［19 名（22.6%）］で、そのうち 3 名以上の被験者に認められた唯一の基本語（preferred term : PT）は、血友病性関節症［10 名（11.9%）］であった（表 2.7.4-9）。他に 3 名以上の被験者に認められた唯一の PT は、中心静脈カテーテル留置、喘息、及びアレルギー性鼻炎［各 3 名（3.6%）］であった。HIV 感染、B 型肝炎又は C 型肝炎感染の検査で陽性となった被験者はいなかった（3002 試験、表 14.1.5.2）。「肝胆道系障害」又は「腎および尿路障害」を認めた被験者はいなかった（3002 試験、表 14.1.5.1.1）。

表 2.7.4-9　2 名以上の被験者に認められた現病歴（安全性解析集団、3002 試験）

器官別大分類 基本語	被験者数（%） （N = 84）
すべての医学的既往／外科手術歴	**33 (39.3)**
外科および内科処置	**4 (4.8)**
中心静脈カテーテル留置	3 (3.6)
筋骨格系および結合組織障害	**19 (22.6)**
血友病性関節症	10 (11.9)
出血性関節症	2 (2.4)
関節拘縮	2 (2.4)
くる病	2 (2.4)
滑膜炎	2 (2.4)
先天性、家族性および遺伝性障害	**3 (3.6)**
血友病[a]	2 (2.4)
呼吸器、胸郭および縦隔障害	**6 (7.1)**
喘息	3 (3.6)
アレルギー性鼻炎	3 (3.6)
胃腸障害	**4 (4.8)**
齲歯	2 (2.4)
免疫系障害	**3 (3.6)**
複合アレルギー	2 (2.4)

略語：N、安全性解析集団の被験者数
[a]　この重度血友病（試験の選択基準）集団における特発性血腫及び外傷性血腫の発現は、血友病-出血障害としてコード化した。
引用：5.3.5.2 項、3002 試験 CSR、表 14.1.5.1.1

3002 試験の選択基準により、すべての被験者に FVIII 製剤による治療歴があった。遺伝子組換え FVIII 製剤による治療歴のある被験者の割合［49 名（58.3%）］は血漿由来 FVIII 製剤［33 名（39.3%）］と比較して高かった（表 2.7.4-10）。本試験開始前に、被験者の 71.4%が定期的な投与を受けていた。

表 2.7.4-10　FVIII 治療歴（安全性解析集団、3002 試験）

	被験者数（%） （N = 84）
製剤の種類	
遺伝子組換え FVIII 製剤	49 (58.3)
血漿由来 FVIII 製剤	33 (39.3)
不明	2 (2.4)
用法	
定期的な投与	60 (71.4)
オンデマンド療法	24 (28.6)

略語：FVIII、血液凝固第 VIII 因子；N、安全性解析集団の被験者数
注：本表では、登録前の最も新しい製剤及び用法のみを示す。
引用：5.3.5.2 項、3002 試験 CSR、表 14.1.7.1

2.7.4.1.3.3　併用薬

併用薬は、本試験中に本剤以外に投与されたすべての医薬品であり、本剤の初回投与前に投与を開始し、依然として継続中の医薬品も含まれる。基礎疾患である血友病 A とその合併症で予想される併用薬で、鎮痛薬、抗炎症薬、及び抗生剤などであった。

全体として、併用薬の使用には、日本人患者集団とグローバル患者集団との間に意味のある違いは認められなかった。

1001 試験で併用薬を使用した被験者は、グローバル患者集団で 123 名（70.7%）、日本人患者集団で 10 名（100%）であった（表 2.7.4-11 参照）。グローバル患者集団で最も高い頻度で用いられた併用薬は、paracetamol（被験者の 23.0%）、セレコキシブ（同 7.5%）、アモキシシリン（同 6.3%）、トラネキサム酸（同 6.3%）、及びイブプロフェン（同 5.7%）であった。日本人患者集団では、グローバル患者集団と同様に、最も高い頻度で用いられた薬物は、鎮痛薬［ロキソプロフェンナトリウム（被験者の 50%）及びケトプロフェン（同 40.0%）］であった。1 名の日本人被験者で、併用薬としてルリオクトコグアルファを用いたことが報告された。治験実施施設の追跡により、実際には被験者が登録前にルリオクトコグアルファの使用を中止していたことが明らかになった（1001 試験 CSR、11.2.2.4 項参照）。別の日本人以外の被験者で、臍ヘルニアの外科的修復に用いられた遺伝子組換え FVIII 製剤の併用が報告された。

表 2.7.4-11　日本人被験者 2 名以上又はグローバル患者集団の被験者 10 名以上で使用された併用薬（安全性解析集団、1001 試験）

	被験者数（%）	
	グローバル患者集団 (N = 174)	日本人患者集団 (N = 10)
すべての併用薬	**123 (70.7)**	**10 (100)**
paracetamol	40 (23.0)	1 (10.0)
セレコキシブ	13 (7.5)	1 (10.0)
アモキシシリン	11 (6.3)	0
トラネキサム酸	11 (6.3)	2 (20.0)
イブプロフェン	10 (5.7)	0
ケトプロフェン	5 (2.9)	4 (40.0)
ラミブジン	5 (2.9)	2 (20.0)
ロキソプロフェンナトリウム	5 (2.9)	5 (50.0)
カルボシステイン	2 (1.1)	2 (20.0)
セフジトレン　ピボキシル	2 (1.1)	2 (20.0)
フェキソフェナジン塩酸塩	2 (1.1)	2 (20.0)

略語：N、安全性解析集団の被験者数
引用：5.3.5.1 項、1001 試験 CSR、表 14.1.9.1；5.3.5.1 項、表 14.1.9.1.J

1001 試験の外科的 substudy 期間で、外科的解析集団の被験者 13 名はすべて併用薬を使用しており、その大多数が手術のための麻酔薬又は鎮痛薬であった。最も高い頻度で用いられた薬物は、プロポフォール（被験者の 76.9%）、paracetamol（同 61.5%）、フェンタニル（同 53.8%）、及びセファゾリンナトリウム（同 53.8%）であった（1001 試験、表 14.1.9.2）。

3002 試験で併用薬を使用した被験者は 66 名（78.6%）であった（3002 試験、表 14.1.9.1 参照）。最も高い頻度で用いられた薬物は、paracetamol（42.9%）、イブプロフェン（7.1%）、及びアモキシシリン（6.0%）であった。

2.7.4.2　有害事象

2.7.4.2.1　有害事象の解析

本項では、1001 試験及び 3002 試験の安全性解析集団を対象に TEAE（本剤の初回投与前に発現しており投与後に重症度が悪化した AE、又は初回投与前には見られなかったが、投与後に発現した AE）を要約している。1001 試験の外科的 substudy 期間中に発現が認められた AE は個別に解析している。

1001 試験及び 3002 試験では、TEAE、死亡、治験治療下で発現した SAE（TESAE）、及び投与中止に至った TEAE を SOC 及び PT 別に提示している。さらに、注目すべき有害事象（AESI）も提示している。AESI は、血栓塞栓事象（TEE）、過敏症、及びアナフィラキシー反応とし、あらかじめ定義した ICH 国際医薬用語集（Medical Dictionary for Regulatory Activities：MedDRA）の MedDRA 標準検索式（standardized MedDRA query：SMQ）を用いた検索により事前に特定したものを判定した。他の臨床的に重要な事象［FVIII に対するインヒビター産生及び免疫原性事象（非中和 ADA 及び CHO 細胞由来タンパク質に対する抗体の産生）］及び局所忍容性についても考察している。

関連のある TEAE 又は AE とは、治験責任医師により治験薬と関連ありと判定された事象である。

AE はすべて MedDRA（1001 試験ではバージョン 14.1、3002 試験ではバージョン 16.1）によりコード化した。

日本人患者集団（1001 試験で N = 10）では、同様な方法を用いてグローバル患者集団とおおむね同じ解析結果を示している（1001 試験の日本人患者集団の AE 表は 5.3.5.1 項参照）。日本人患者集団とグローバル患者集団を比較したその他の解析には以下のものが含まれる。

- 経時的な TEAE の要約：1001 試験：5.3.5.1 項、表 14.3.2.32J
- 基本語別の経時的な TEAE の発現率：1001 試験：5.3.5.1 項、表 14.3.2.33J
- 基本語別の経時的な投与当たりの TEAE の発現率：1001 試験：5.3.5.1 項、表 14.3.2.34J

2.7.4.2.1.1　一般的な有害事象

2.7.4.2.1.1.1　有害事象の全体的な要約

1001 試験及び 3002 試験で報告された TEAE の全体的な要約を表 2.7.4-12 に示す。

1001 試験の日本人患者集団とグローバル患者集団の全体的な TEAE/AE プロファイルに臨床的に意味のある違いは認められなかった。

0 歳以上 18 歳未満の被験者（1001 試験及び 3002 試験）と 18 歳以上 65 歳以下の被験者（1001 試験）の全体的な TEAE プロファイルにも臨床的に重要な差は認められなかった。1001 試験 CSR、12.2.1 項及び 3002 試験 CSR、12.2.1 項も参照。

1001 試験では、グローバル患者集団の被験者のうち 113 名（64.9%）で 292 件の TEAE が報告された。そのうち 6 件の TEAE を除くすべての TEAE が軽度又は中等度であった。治験薬と関連ありと判定された TEAE は、13 名（7.5%）の被験者で 19 件認められた。試験脱落に至った TEAE はなく、死亡例もなかった。TESAE は、7 名（4.0%）の被験者で 9 件報告され、1 名（0.6%）の被験者で治験薬と関連ありと判定された TESAE（過敏症）が認められた。

日本人患者集団の被験者のうち 8 名（80%）で計 20 件の TEAE が報告された。治験薬と関連ありと判定された TEAE は、1 例（10%）の被験者で 1 件認められた（浮動性めまい、軽度、発症当日に回復、治験薬の変更は不要であった）。日本人患者集団で、重度の TEAE、死亡、重篤な TEAE、又は試験脱落に至る TEAE は認められなかった。

3002 試験では、64 名（76.2%）の被験者で 183 件の TEAE が報告された。そのうち 4 件の TEAE を除くすべての TEAE が軽度又は中等度であった。1 件の TEAE（過敏症）が治験薬と関連ありと判定された。1 件の TEAE（関節痛、非重篤、治験薬と関連なし）により試験脱落に至った。死亡例はなかった。TESAE は、9 名（10.7%）の被験者で 11 件報告され、いずれも治験薬と関連なしと判定された。

表 2.7.4-12　TEAE の要約（安全性解析集団、1001 試験及び 3002 試験）

	1001 試験				3002 試験	
	グローバル患者集団 (N = 174)		日本人患者集団 (N = 10)		グローバル患者集団 (N = 84)	
AE の種類	**n（%）**	**E**	**n（%）**	**E**	**n（%）**	**E**
AE	121 (69.5)	325	8 (80.0)	20	64 (76.2)	193
TEAE	113 (64.9)	292	8 (80.0)	20	64 (76.2)	183
試験脱落に至った TEAE	0	0	0	0	1 (1.2)	1
TEAE の重症度						
軽度	94 (54.0)	225	8 (80.0)	18	52 (61.9)	137
中等度	43 (24.7)	61	2 (20.0)	2	25 (29.8)	42
重度	5 (2.9)	6	0	0	4 (4.8)	4
治験薬と関連ありと判定された TEAE	13 (7.5)	19	1 (10.0)	1	1 (1.2)	1
TEAE の転帰						
AE に関連する死亡	0	0	0	0	0	0
未回復	22 (12.6)	25	3 (30.0)	3	6 (7.1)	9
回復	104 (59.8)	256	8 (80.0)	17	61 (72.6)	168
回復したが後遺症あり	1 (0.6)	1	0	0	0	0
軽快	9 (5.2)	10	0	0	4 (4.8)	4
不明	0	0	0	0	2 (2.4)	2
SAE	8 (4.6)	10	0	0	9 (10.7)	12
TESAE	7 (4.0)	9	0	0	9 (10.7)	11
治験薬と関連ありと判定された TESAE	1 (0.6)	1	0	0	0	0

略語：AE、有害事象；E、事象数；N、各試験の安全性解析集団における被験者数；n、事象を認めた被験者数；SAE、重篤な有害事象；TEAE、治験治療下で発現した有害事象；TESAE、治験治療下で発現した重篤な有害事象

注：AE 及び SAE には、発現日が治験薬投与開始前の事象及び外科的 substudy 期間中に認められた事象が含まれる。

引用：

1001 試験 CSR、表 14.3.2.1、及び 5.3.5.1 項、表 14.3.2.1J

3002 試験 CSR、表 14.3.1.1

2.7.4.2.1.1.2　高頻度で報告された有害事象

2.7.4.2.1.1.2.1　1001 試験（12 歳以上 65 歳以下の被験者）

グローバル患者集団で最も多く（被験者の 5%超で）報告された TEAE は、鼻咽頭炎（被験者の 10.3%）、関節痛（同 9.8%）、及び頭痛（同 6.9%）であった（表 2.7.4-13）。1001 試験 CSR、12.2 項も参照。SOC 別の TEAE は、2.7.4.2.1.5.1 項に要約している。

日本人患者集団で最も多く報告された TEAE は、鼻咽頭炎（被験者の 40%）及びインフルエンザ（被験者の 20%）であり、その他の TEAE は、すべて 1 名の日本人被験者に発現した。TEAE プロファイルにおいて、日本人患者集団とグローバル患者集団との間に意味のある違いは認められなかった。

表 2.7.4-13　グローバル患者集団の 2%以上の被験者で発現し、基本語で頻度の高い順に示した TEAE（安全性解析集団、1001 試験）

	グローバル患者集団		日本人患者集団	
基本語	被験者数（%）（N = 174）	事象数	被験者数（%）（N = 10）	事象数
すべての TEAE	**113 (64.9)**	**292**	**8 (80.0)**	**20**
鼻咽頭炎	18 (10.3)	22	4 (40.0)	4
関節痛	17 (9.8)	19	0	0
頭痛	12 (6.9)	13	1 (10.0)	1
発疹	7 (4.0)	8	1 (10.0)	1
歯痛	6 (3.4)	8	0	0
上気道感染	6 (3.4)	6	0	0
背部痛	5 (2.9)	6	0	0
咳嗽	5 (2.9)	6	0	0
高血圧	5 (2.9)	5	0	0
浮動性めまい	4 (2.3)	5	1 (10.0)	1
発熱	4 (2.3)	5	0	0
インフルエンザ	4 (2.3)	4	2 (20.0)	2

略語：N、安全性解析集団の被験者数；TEAE、治験治療下で発現した有害事象
注：本要約では、発現日が外科的 substudy 期間中の事象を除外している。
引用：1001 試験 CSR、表 14.3.2.4；5.3.5.1 項、表 14.3.2.28J

重度の TEAE は、5 名（2.9%）の被験者（いずれも日本人ではない）で 6 件認められた。貧血及び血小板減少症が 1 名の被験者に認められ、血友病性関節症、過敏症（治験薬と関連ありと判定された TESAE でもあった；詳細は 2.7.4.2.1.3.1 項参照）、足関節部骨折、及び自殺念慮がそれぞれ 1 名の被験者に認められた。

本試験の PK パートで本剤の高含量製剤［3000 IU/バイアル（調製後 600 IU/mL）；2 名の日本人被験者を含む］又は低含量製剤［250 IU/バイアル（調製後 100 IU/mL）；6 名の日本人被験者を含む］を投与された被験者 17 名に、局所刺激性反応は認められなかった（1001 試験、一覧表 16.2.9.6.6 及び 1001 試験、一覧表 16.2.7.1 及び 1001 試験、表 14.2.15.17.1）。

2.7.4.2.1.1.2.2　3002 試験（0 歳以上 12 歳未満の被験者）

3002 試験で最も多く（被験者の 5%超で）報告された TEAE は、鼻咽頭炎［14 名（16.7%）、15 件］、関節痛［8 名（9.5%）、8 件］、咳嗽［7 名（8.3%）、10 件］、頭痛［7 名（8.3%）、9 件］、頭部損傷［5 名（6.0%）、6 件］、発熱［5 名（6.0%）、5 件］であった（表 2.7.4-14）。感染因子

伝播が疑われる TEAE、又はアスパラギン酸アミノトランスフェラーゼ若しくはアラニンアミノトランスフェラーゼ異常に関連した TEAE の報告はなかった。3002 試験 CSR、12.2.3.1 項も参照。SOC 別の TEAE は、2.7.4.2.1.5.2 項に要約している。

表 2.7.4-14　3%以上の被験者で発現し、基本語で頻度の高い順に示した TEAE
（安全性解析集団、3002 試験）

基本語	被験者数（%） (N = 84)	事象数
すべての TEAE	**64 (76.2)**	**183**
鼻咽頭炎	14 (16.7)	15
関節痛	8 (9.5)	8
咳嗽	7 (8.3)	10
頭痛	7 (8.3)	9
頭部損傷	5 (6.0)	6
発熱	5 (6.0)	5
上気道感染	4 (4.8)	5
転倒	4 (4.8)	4
四肢痛	4 (4.8)	4
鼻炎	4 (4.8)	4
挫傷	3 (3.6)	6
貧血	3 (3.6)	5
裂傷	3 (3.6)	4
耳感染	3 (3.6)	3
口腔咽頭痛	3 (3.6)	3
アレルギー性鼻炎	3 (3.6)	3

略語：N、安全性解析集団の被験者数；TEAE、治験治療下で発現した有害事象
引用：5.3.5.2 項、3002 試験 CSR、表 14.3.1.15

それぞれ 1 名の被験者で発現した肺炎、全身性炎症反応症候群、齲歯、及び脾破裂の 4 件の TEAE が重度であると報告され（3002 試験、表 14.3.1.10）、そのうち 3 件（肺炎、全身性炎症反応症候群、及び脾破裂）は重篤でもあったが、重度の TEAE のうち治験責任医師により本剤と関連ありと判定されたものはなかった（3002 試験、一覧表 16.2.7.1）。詳細については、2.7.4.2.1.3.2 項を参照。

2.7.4.2.1.1.3　治験薬と関連ありと判定された有害事象

2.7.4.2.1.1.3.1　1001 試験（12 歳以上 65 歳以下の被験者）

1001 試験では、治験責任医師により治験薬と関連ありと判定された TEAE がグローバル患者集団の被験者 13 名（7.5%）で 19 件認められた。治験薬と関連ありと判定された TEAE で複数の被験者に報告された PT は、浮動性めまい及び過敏症（各 2 名）のみであった（表 2.7.4-15）。過敏症の可能性が示唆される用語についての臨床データベースの検索で、治験薬と関連する TEAE が 4 名の被験者で明らかになり、過敏症の PT が 2 名（1 名はそう痒症も合併）、発疹が 1 名、紅斑が 1 名に認められた（1001 試験、一覧表 16.2.7.1）。これらの 4 名のうち非中和 ADA が陽性の被験者はいなかった（1001 試験、一覧表 16.2.8.3）。1001 試験 CSR、12.2.2.3 項も参照。被験者 6080002-1001 に見られた重度かつ TESAE であった過敏症の 1 件を除いて、本剤と関連する TEAE のすべてが軽度又は中等度であった。詳細については、2.7.4.2.1.3.1 項を参照。最終追跡時点ではまだ回復中であった TEAE の発疹の 1 件（被験者 8400154-1004）以外、本剤と関

連する TEAE のすべての転帰は「回復」と報告された（1001 試験、一覧表 16.2.7.1）。1001 試験 CSR、12.2.2.2 項も参照。

日本人患者集団の 1 名（10%）の被験者で、治験責任医師により治験薬と関連ありと判定された TEAE が 1 件認められた（浮動性めまい、軽度、発症日当日に回復、治験薬の変更は不要であった；表 2.7.4-15）。臨床データベースの検索では、過敏症の可能性が示唆される本剤と関連する TEAE を認めた日本人被験者はいなかった。

表 2.7.4-15　治験責任医師により治験薬と関連ありと判定された器官別大分類及び基本語別の TEAE（安全性解析集団、1001 試験）

器官別大分類 基本語	グローバル患者集団 （N = 174） 被験者数（%）	 事象数	日本人患者集団 （N = 10） 被験者数（%）	 事象数
治験薬と関連ありと判定されたすべての TEAE	**13 (7.5)**	**19**	1 (10.0)	1
一般・全身障害および投与部位の状態	**4 (2.3)**	**5**	0	0
悪寒	1 (0.6)	2	0	0
熱感	1 (0.6)	1	0	0
注射部位疼痛	1 (0.6)	1	0	0
発熱	1 (0.6)	1	0	0
神経系障害	**3 (1.7)**	**3**	1 (10.0)	1
浮動性めまい	2 (1.1)	2	1 (10.0)	1
錯感覚	1 (0.6)	1	0	0
皮膚および皮下組織障害	**3 (1.7)**	**3**	0	0
紅斑	1 (0.6)	1	0	0
そう痒症	1 (0.6)	1	0	0
発疹	1 (0.6)	1	0	0
免疫系障害	**2 (1.1)**	**3**	0	0
過敏症	2 (1.1)	3	0	0
筋骨格系および結合組織障害	**1 (0.6)**	**4**	0	0
関節痛	1 (0.6)	3	0	0
関節可動域低下	1 (0.6)	1	0	0
臨床検査	**1 (0.6)**	**1**	0	0
薬物特異性抗体陽性 [a]	1 (0.6)	1	0	0

略語：N、安全性解析集団の被験者数；TEAE、治験治療下で発現した有害事象
[a]　この被験者では、非中和抗薬物抗体（ADA）の存在を治験責任医師が誤って TEAE として記録した。ADA は、臨床検査値として収集されることになっていた。
注：本要約では、発現日が外科的 substudy 期間中の事象を除外している。
引用：5.3.5.1 項、1001 試験 CSR、表 14.3.2.5;5.3.5.1 項、表 14.3.2.5J

2.7.4.2.1.1.3.2　3002 試験（0 歳以上 12 歳未満の被験者）

3002 試験で、TEAE である過敏症（被験者 6080002-2004）の 1 件が治験責任医師により本剤と関連ありと判定された（3002 試験、表 14.3.1.5 及び一覧表 16.2.7.1）。本事象は軽度かつ非重篤であり、治験薬の変更を必要としなかった。本事象は孤発症例であり、発現日に回復した。この被験者では治験薬と関連なしと判定された SAE が 2 件認められ、叙述を 2.7.4.2.1.3.2 項に示している。

2.7.4.2.1.2　死亡

1001 試験及び 3002 試験において、死亡例はなかった（表 2.7.4-12 参照）。

2.7.4.2.1.3　その他の重篤な有害事象

2.7.4.2.1.3.1　1001 試験（12 歳以上 65 歳以下の被験者）

1001 試験では、グローバル患者集団の被験者 7 名（4.0%）で 9 件の TESAE が認められた。そのうち 5 件は重度で、うち 1 件（過敏症）は治験責任医師により治験薬と関連ありと判定された（表 2.7.4-16）。すべての被験者は完全に回復した。1001 試験 CSR、12.3.1.2 項も参照。本試験で TESAE が認められた日本人被験者はいなかった（5.3.5.1 項、表 14.3.2.1J）。

表 2.7.4-16　TESAE を認めた被験者の一覧表（安全性解析集団、1001 試験）

被験者番号	人種	年齢（歳）	割り付けられた本剤レジメンと用量（IU/kg）	有害事象（基本語）	開始日／終了日 試験開始日を起点とした発現日 持続期間	因果関係／ 重症度	処置[a]	転帰
2760066-1003	白人	3[redacted]	定期的な投与 週 3 回 50 IU/kg	扁桃出血	[redacted] 年 3 月 19 日／ #同 年 3 月 22 日 Day 148 4 日間	関連なし／ 中等度	用量変更なし	回復
3800022-1002	白人	4[redacted]	オンデマンド療法 35 IU/kg	貧血	[redacted] 年 12 月 24 日／ #翌 年 3 月 4 日 Day 428 71 日間	関連なし／ 重度	用量変更なし	回復
				血小板減少症	[redacted] 年 12 月 24 日／ #翌 年 1 月 29 日 Day 428 37 日間	関連なし／ 重度	用量変更なし	回復
6080002-1001	アジア人	1[redacted]	定期的な投与 週 2 回 43 IU/kg	過敏症	[redacted] 年 2 月 11 日／ #同 年 2 月 11 日 Day 22 1 日間	関連あり／ 重度	減量	回復
6160014-1009	白人	5[redacted]	定期的な投与 週 3 回 35 IU/kg	血中尿酸増加	[redacted] 年 3 月 25 日／ #同 年 3 月 28 日 Day 104 4 日間	関連なし／ 軽度	用量変更なし	回復
				食道静脈瘤	[redacted] 年 10 月 13 日／ #同 年 10 月 16 日 Day 306 4 日間	関連なし／ 軽度	用量変更なし	回復
6420030-1002	白人	5[redacted]	定期的な投与 週 3 回 28 IU/kg	ウイルス感染	[redacted] 年 11 月 20 日／ #同 年 11 月 28 日 Day 120 9 日間	関連なし／ 中等度	用量変更なし	回復
7240008-1001	白人	4[redacted]	定期的な投与 週 2 回 42 IU/kg	術後創感染[b]	[redacted] 年 1 月 28 日／ #同 年 2 月 27 日 Day 72 31 日間	関連なし／重度	用量変更なし	回復

#新薬承認情報提供時に置き換え

表 2.7.4-16　TESAE を認めた被験者の一覧表（安全性解析集団、1001 試験）（続き）

被験者番号	人種	年齢（歳）	割り付けられた本剤レジメンと用量（IU/kg）	有害事象（基本語）	開始日／終了日 試験開始日を起点とした発現日 持続期間	因果関係／ 重症度	処置[b]	転帰
8400204-1001	白人	2[redacted]	オンデマンド療法 42 IU/kg	足関節部骨折	[redacted]年 1 月 19 日／ #同 年 5 月 12 日 Day 404 114 日間	関連なし／ 重度	用量変更なし	回復
8400184-1006	白人	1[redacted]	定期的な投与 週 2 回 35 IU/kg	自殺念慮	[redacted]年 1 月 13 日／ #同 年 1 月 15 日 Day 113 3 日間	関連なし／ 重度	用量変更なし	回復

略語：TEAE、治験治療下で発現した有害事象
[a]　本剤に関して行った処置
[b]　外科的 substudy で発現した事象
引用：5.3.5.1 項、一覧表 16.2.7.2J

#新薬承認情報提供時に置き換え

日本人以外の被験者 6080002-1001 における重度かつ本剤と関連ありと判定された TESAE である過敏症、並びに日本人以外の被験者 3800022-1002 における重度かつ治験薬と関連なしと判定された TESAE である貧血及び血小板減少症の詳細を以下に示す（1001 試験 CSR、14.3.3 項及び一覧表 16.2.7.2 参照）。

- **被験者 6080002-1001**：本被験者は 1[redacted] 歳のフィリピンのアジア人男性で、[redacted] 年 2 月 11 日に過敏症反応による SAE が報告された。この重篤な過敏症反応の症例報告では、そう痒症、発熱、紅斑、頭痛、呼吸困難、胸部不快感、及び発疹の症状が記載されていた。本被験者は、43 IU/kg の用量で週 2 回の定期的な投与に割り付けられていた。

  本被験者の既往歴には、クリオプレシピテートに対する過敏症、絆創膏製品の Leucoplast®による局所過敏症、外因性喘息などがあった。急性扁桃咽頭炎（喉頭炎、咽頭炎、扁桃炎を伴う上気道感染）の既往歴も報告された。

  #同 年 2 月 11 日午前 1 時 00 分（治験薬最終投与の約 2.5 時間後）に、重度の過敏症反応（重度のそう痒症）が発現した。午前 9 時 30 分に、呼吸困難、両手及び両腕の皮膚発赤、重度の頭痛が報告された。#同 年 2 月 11 日に診療所へ来院し、入院した。入院時のバイタルサインはすべて正常であり、胸部は清澄で呼気性喘鳴又は吸気性喘鳴は認められず、両肺の呼吸も良好であった。上肢に紅斑が見られたが、下肢に発疹は見られなかった。救急治療室で、ステロイド及び抗ヒスタミン剤が投与された。約 17.5 時間後に過敏症反応は回復したと判定され、被験者は退院した。退院時に、5 日間で漸減するステロイドが処方された。治験薬の次回の投与では、治験実施施設で抗ヒスタミン剤を併用し用量を減量して監視下で投与した。監視下での投与後、治験薬に対する反応は認められず、その後の投与でも後遺症は見られなかったため、試験を継続した。

  本被験者は後遺症を認めずに回復し、本事象は治験薬と関連ありと判定された。前投薬を追加して試験を継続し、その後に AE の報告はなかった。

- **被験者 3800022-1002**：本被験者は 4[redacted] 歳のヒスパニック系／ラテンアメリカ系男性で、[redacted] 年 9 月 25 日に本剤（35 IU/kg）のオンデマンド療法に割り付けられた。本被験者の既往歴には輸血後の C 型肝炎ウイルス感染があり、リバビリン（ヌクレオシド阻害剤）、ペグインターフェロン α-2a（ペグ化インターフェロン）、及びテラプレビル（プロテアーゼ阻害剤）を併用した抗ウイルス療法を受けていた。

  #翌 年 12 月 24 日に、重度の貧血に加え、粘液性皮膚出血を伴う血小板減少症が認められた。これらの診断は臨床検査により確認され、#翌 年 12 月 24 日から #翌々年 1 月 3 日まで入院した。リバビリン、ペグインターフェロン α-2a、及びテラプレビルによる C 型肝炎治療は中断された。

  #翌々 年 1 月 29 日に血小板減少症から回復し #翌々 年 3 月 4 日に貧血から回復した。治験責任医師はいずれの事象も治験薬と関連なしと判定し、リバビリン／ペグインターフェロン α-2a／テラプレビルの併用療法に伴い溶血性貧血及び骨髄抑制が見られるため、むしろ C 型肝炎治療に関連ありと判定した。

2.7.4.2.1.3.2　3002 試験（0 歳以上 12 歳未満の被験者）

3002 試験では、9 名（10.7%）の被験者で 11 件の TESAE が認められ（表 2.7.4-17）、そのうち本剤と関連ありと判定されたものはなく、すべての被験者が完全に回復した。3002 試験 CSR、12.3.1.2 項も参照。

表 2.7.4-17　TESAE を認めた被験者の一覧表（安全性解析集団、3002 試験）

被験者番号	人種	年齢（歳）	割り付けられた本剤レジメンと用量（IU/kg）	有害事象（基本語）	開始日／終了日 試験開始日を起点とした発現日 持続期間	因果関係／ 重症度	処置[a]	転帰
0360014-2003	白人	[redacted]	定期的な投与 週 2 回 44 IU/kg	裂傷	[redacted] 年 5 月 17 日／ #同 年 5 月 17 日 Day 131 1 日間	関連なし／ 中等度	用量変更なし	回復
5280006-2001	白人	[redacted]	定期的な投与 週 2 回 20 IU/kg	医療機器閉塞	[redacted] 年 1 月 29 日／ #同 年 2 月 2 日 Day 42 5 日間	関連なし／ 軽度	増量	回復
5280007-2001	白人	[redacted]	定期的な投与 2 日ごと 40 IU/kg	貧血	[redacted] 年 9 月 23 日／ #同 年 9 月 25 日 Day 7 3 日間	関連なし／ 中等度	増量	回復
				貧血	[redacted] 年 9 月 27 日／ #同 年 10 月 14 日 Day 11 18 日間	関連なし／ 中等度	増量	回復
				貧血	[redacted] 年 11 月 1 日／ #同 年 11 月 14 日 Day 46 14 日間	関連なし／ 中等度	増量	回復
6080001-2004	アジア人	[redacted]	定期的な投与 週 3 回 43 IU/kg	消化不良	[redacted] 年 4 月 3 日／ #同 年 4 月 5 日 Day 14 3 日間	関連なし／ 軽度	用量変更なし	回復
6080002-2004	アジア人	[redacted]	定期的な投与 週 3 回 25 IU/kg	菌血症	[redacted] 年 4 月 8 日／ #同 年 4 月 20 日 Day 23 13 日間	関連なし／ 中等度	投与中断	回復
6420037-2001	白人	[redacted]	定期的な投与 週 2 回 38 IU/kg	肺炎	[redacted] 年 6 月 6 日／ #同 年 6 月 11 日 Day 181 6 日間	関連なし／ 重度	用量変更なし	回復
7640002-2001	アジア人	[redacted]	定期的な投与 週 3 回 34 IU/kg	全身性炎症反応症候群	[redacted] 年 8 月 18 日／ #同 年 9 月 1 日 Day 5 15 日間	関連なし／ 重度	用量変更なし	回復

#新薬承認情報提供時に置き換え

表 2.7.4-17　TESAE を認めた被験者の一覧表（安全性解析集団、3002 試験）（続き）

被験者番号	人種	年齢（歳）	割り付けられた本剤レジメンと用量（IU/kg）	有害事象（基本語）	開始日／終了日 試験開始日を起点とした発現日 持続期間	因果関係／ 重症度	処置[a]	転帰
7640003-2001	アジア人	[redacted]	定期的な投与 週 2 回 20 IU/kg	手骨折	[redacted] 年 2 月 27 日／＃同 年 3 月 6 日 Day 214 8 日間	関連なし／ 中等度	用量変更なし	回復
8400184-2001	白人	[redacted]	定期的な投与 週 2 回 50 IU/kg	脾破裂	[redacted] 年 3 月 2 日／＃同 年 4 月 25 日 Day 162 55 日間	関連なし／ 重度	増量	回復

略語：TESAE、治験治療下で発現した有害事象
[a]　本剤に関して行った処置
引用：5.3.5.2 項、一覧表 16.2.7.2J

＃新薬承認情報提供時に置き換え

医療機器閉塞、貧血、菌血症、及び全身性炎症反応症候群の TESAE に関する詳細を以下に示す（3002 試験 CSR、12.3.1.2 項も参照）。

- **被験者 5280006-2001**（医療機器閉塞）：[redacted] 歳の本被験者は、[redacted] 年 12 月に本試験の定期的投与群（週 2 回 20 IU/kg）に登録された。被験者の既往歴には、中心静脈カテーテル留置及び不安があった。＃同 年 12 月 19 日に本剤（20 IU/kg）による治療を開始した。

  ＃翌 年 1 月 29 日に、閉塞した Port-a-Cath（医療機器閉塞）を抜去するために待機的に入院した。装置自体の閉塞であり、血管内血栓又は血管内での血塊形成は認められなかった。＃3年前の 8 月から in situ で Port-a-Cath が留置されていた。＃翌 年 1 月 30 日の午前 11 時 45 分から午後 12 時 12 分まで手術を実施し、合併症又は出血は見られなかった。新たな機器の植え込みは実施しなかった。手術前に本剤 1072 IU を追加投与し、手術後の夜に 2018 IU を投与した。手術の翌日には、朝に 2018 IU を投与し、夜に 1072 IU を投与した。手術の 2 日後には、朝に 1545 IU を投与し、夜に 1072 IU を投与した後、通常の定期的な投与に戻った。Port-a-Cath の抜去は、軽微な手術（主要な体腔を開放せず、生命を脅かす可能性のない手術）に分類された。＃翌 年 2 月 2 日に、被験者は回復したと判定され、退院した。本事象は孤発的な医療機器閉塞であることから、TEE に相当しない。
- **被験者 5280007-2001**（貧血）：[redacted] 歳の本被験者は、[redacted] 年 9 月に定期的投与群（2 日ごと 40 IU/kg）に登録され、TESAE である貧血が 3 回認められた。数箇月前に被験者にポートが留置され、母親は治験実施施設で在宅治療の訓練及び試験に合格していた。試験登録後 6 日以内に母親からメレナが報告され、2 日間入院した。入院中にメレナは確認されなかったが、ヘモグロビンが 4.2 g/dL と低値（貧血）であったことから、輸血を行った。2 日後に、ヘモグロビンが再び 4.9 g/dL に減少し、母親から再びメレナの報告があったことから、再び入院した。このときは 17 日間入院し、溶血検査、テクネチウム - 99m（Meckel）シンチグラフィー、及び胃内視鏡を含め、診断を目的とした一連の精密検査を実施したが、いずれでも病理所見は認められなかった。退院して 2 週間後に、自宅で小児が発熱した旨の連絡が母親からあり、退院して 16 日後に、母親からメレナが報告されたことから再入院し、ヘモグロビンの進行性減少が 4.6 g/dL に達したため再輸血が必要であった。この時点で、セカンドオピニオンを受けるため別の医療施設に搬送された。治験責任医師は、心配した家族から、その症状の原因が母親にある可能性を示唆する自発的な電話を受けたことを報告した。地域の当局は、治験責任医師から代理人によるミュンヒハウゼン症候群／小児疾患偽装の疑いがあるという通知を受け、小児は里親による養育に移された。本被験者は試験から除外した（家庭問題による医師の決定に基づく）。本被験者のデータで解析に用いたものは、医療従事者により観察されたもののみであった。
- **被験者 6080002-2004**（菌血症）：本症例は 1[redacted] 歳の被験者（登録時[redacted] 歳）で、[redacted] 年 3 月に定期的投与群に登録された。本試験への登録前に、オンデマンド療法のみによる様々な血漿由来 FVIII 濃縮製剤による治療を受けていた。登録前 12 箇月に FVIII 製剤

を約 27 ED 投与されており、全体で約 100 ED に達していた。＃同 年 3 月 17 日に本剤（週 3 回 25 IU/kg）による治療を開始した。

スクリーニング時の ADA 検査では、非中和性免疫グロブリン G（IgG）の ADA が陽性であったが、中央検査機関でのインヒビター検査では、最初は陰性（0.4 BU/mL 未満）であると報告された。

＃同 年 3 月 19 日に、治験薬と関連ありと判定された TEAE の過敏症が認められ、抗ヒスタミン薬による治療を必要としたが、軽度であり、発現日に回復した。＃同 年 4 月 8 日に、数日前に留置したヘパリンロック式末梢血管カテーテルを介して本剤を投与した後、治験薬と関連なしと判定された TESAE の発熱及び悪寒を伴う菌血症が認められた。その後、末梢血管カテーテルを抜去し、抗生剤による治療を実施した。＃同 年 4 月 20 日に菌血症から回復した。

＃同 年 4 月 9 日の Month 1 来院時に、インヒビター検査用血液検体をルーチンで採取した。この検体では、中央検査機関で実施したベセスダ／ナイメゲン検査により 0.90 BU/mL の低力価インヒビターが検出された（PT：抑制抗体陽性；軽度）。確認用の血液検体が必要とされたため、初回検体採取から 18 日後に血液検体を採取した。2 つの検体採取間に 7 ED の投与を受けていた。中央検査機関で実施したベセスダ／ナイメゲン検査により、この検体でも低力価インヒビターが確認された。

治験依頼者のプログラムディレクター、独立データ安全性モニタリング委員会の医学専門家、及び治験責任医師が参加して、本被験者の治療及び追跡について協議した。インヒビターの月 1 回の検査及び週 3 回投与の 25 IU/kg から 50 IU/kg への増量が推奨された。＃同 年 5 月 14 日の Month 2 来院時にインヒビター追跡用検体を採取した。この検体を中央検査機関で分析したところ、1.2 BU/mL の低力価インヒビターが検出された。同時に、臨床検査データの再検証によりスクリーニング時に採取した投与前検体で 3.46 BU/mL の低力価インヒビターが検出されたことが明らかになった。臨床検査の手順ミスのため、このスクリーニング検体は最初に陰性であると報告されていた。スクリーニング検体の再検査を数回実施したところ、この検体は陽性で、既存のインヒビターであることが確認された。そのため、このデータでデータベース及び重篤未知の副作用（Suspected Unexpected Serious Adverse Reaction：SUSAR）報告を更新し、試験での新規（de-novo）のインヒビター産生からスクリーニング時の既存のインヒビターに記述を変更した。因果関係の評価は、治験薬と「関連あり」から「関連なし」に変更し、規制当局、独立データ安全性モニタリング委員会、倫理委員会、及び治験責任医師に、その旨を通知した。本事象との関連で、遺伝子検査を実施したところ、イントロン 22 の逆位（高リスクのヌル変異）が明らかになった。

3002 試験で、本被験者は出血エピソードに対する治療を 7 回受けており、そのほとんどは、口腔粘膜出血であった。すべての出血は、本剤により良好に管理された。追跡調査のインヒビター検体採取では、インヒビター力価の減少が認められた（下表参照）。＃同 年 7 月 14 日（被験者の Month 4 来院）に、インヒビターは陽性カットオフ値未満（0.6 BU/mL 未満）に低下し、＃同 年 8 月 11 日の試験終了来院まで陰性を持続していた。被験者は同日中に継続投与試験である 3001 試験に移行し、IR は

1.3 (IU/dL)/(IU/kg)であった。本剤による定期的な投与は継続した。

日付	インヒビター力価（BU/mL）
[redacted]年2月21日（スクリーニング）	3.46
#同 年4月9日	0.90
#同 年4月27日	0.65
#同 年5月14日	1.20
#同 年6月16日	0.83
#同 年7月14日	0.55
#同 年8月11日（試験終了）	0.47

- **被験者 7640002-2001**（全身性炎症反応症候群）：[redacted]歳の本被験者（16 kg、108 cm）は、[redacted]年8月に3002試験の定期的な投与（週3回34 IU/kg）に登録された。過去12箇月間に23回の外傷性出血エピソードの既往があり、自然出血エピソードはなかった。本試験への登録前の#前々年10月から血漿由来FVIII製剤による治療歴があった　#同年8月14日に本剤 33 IU/kgによる治療を開始した。

　#同 年8月17日に、左肘に外傷性出血エピソードが見られ、自宅で本剤 500 IUを投与した。疼痛が持続したため、初回投与の15.5時間後に2回目の投与が行われた。本剤 500 IUの3回目の投与は（疼痛は安定しているが、重度なため）、2回目の投与の13.25時間後に行われた。両親は、注射セットのラインにまだ残存している治験薬を投与しようとして、滅菌していない生理食塩水でラインをフラッシュした。この生理食塩水は、糖尿病合併症により下肢を切断した祖母の切断端の創傷感染に対して適用されていた包帯の洗浄を目的とした生理食塩水で、数日間にわたり開放されていた瓶から吸引したものであった。

　この生理食塩水投与の30分以内に、高熱及び戦慄が発現した。両親は治験責任医師に連絡し、直ちに病院で診察を受けるよう指示された。約30分後に病院に到着し、本事象発現から約120分後に病棟に入院した。入院直後は、血圧94 mmHg/54 mmHg、心拍数160回／分、呼吸数26回／分、体温40.4°Cであった。被験者の臨床徴候は、病院スタッフによる解釈で低血圧及び頻脈と判定された。全身性炎症反応症候群の事象（重度であるが、治験責任医師により治験薬と関連なしと判定された）であることが確認された。輸液の静脈内ボーラス投与による大量輸液療法を実施し、低血圧による敗血症性ショックを想定して、施設内プロトコールに従い持続点滴としてドパミン及びノルアドレナリンによる治療を実施した。病状が安定したため、強心剤を漸減し、48時間後に中止した。14日間の抗生剤静脈内投与［メロペネム（60 mg/kg/日）、クロキサシリン（100 mg/kg/日）、及びアミカシン（15 mg/kg/日）］を開始した。しかし、血液培養検体はすべて陰性であった。

　左肘の出血性関節症の治療として、本剤を出血性関節症の発現から6回投与した（31 IU/kgを12時間ごとに投与）。その後、被験者が退院するまで、定期的な投与として本剤を週3回投与した。

　退院前に、治験責任医師及び治験実施施設の治験チームにより被験者の両親に対して良好な無菌操作及び注射方法に従うよう再教育と再評価を実施した。敗血症の転帰は、#同 年9月1日に回復したことが報告された。被験者は試験を継続しており、本

剤の用量は変更していない。

2.7.4.2.1.4　その他の重要な有害事象

2.7.4.2.1.4.1　中止に至った有害事象

1001 試験では試験中止に至った TEAE は見られなかった。3002 試験では 1 件の TEAE により 1 名の被験者が試験を中止した（表 2.7.4-12 及び以下の簡潔な叙述を参照）。

3002 試験では、[redacted] 年 3 月 7 日に定期的投与群の 1[redacted] 歳の被験者（7920008-2002）に中等度の股関節痛が認められた。MRI 検査により出血エピソードは除外された。氷冷及び安静で対処した。＃同 年 3 月 23 日に、本剤の最終投与を実施し（計 9 ED）、＃同 年 3 月 24 日に、股関節痛により試験を中止した。＃同 年 5 月 27 日に完全に回復した。本事象は、非重篤で治験薬と関連なしと判定された。詳細については、3002 試験 CSR、12.3.1.3 項を参照。

2.7.4.2.1.4.2　経時的な有害事象の発現率

1001 試験では、TEAE の頻度、重篤な TEAE の頻度、又は理由を問わない中止の頻度に本剤の使用に伴う経時的な増加は認められなかった。さらに、日本人安全性解析集団で各 6 箇月間に最も多く報告された TEAE の頻度は、グローバル安全性解析集団で報告された頻度と同程度であった（表 2.7.4-18 及び表 2.7.4-19）。

#新薬承認情報提供時に置き換え

表 2.7.4-18　治験治療下で発現した有害事象の期間ごとの要約（日本人患者集団及びグローバル安全性解析集団、1001 試験）

AE カテゴリー	解析集団	被験者数（%）					
		0～6 箇月	6～12 箇月	12～18 箇月	18～24 箇月	24～30 箇月	全体
すべての TEAE	日本人（N = 10）	6 (60.0)	4 (44.4)	1 (33.3)	0	0	8 (80.0)
	グローバル（N = 174）	101 (58.0)	24 (23.8)	6 (20.0)	2 (16.7)	0	113 (64.9)
治験薬と関連ありと判定された TEAE	日本人	1 (10.0)	0	0	0	0	1 (10.0)
	グローバル	12 (6.9)	2 (2.0)	0	0	0	13 (7.5)
重篤な TEAE	日本人	0	0	0	0	0	0
	グローバル	5 (2.9)	1 (1.0)	2 (6.7)	0	0	7 (4.0)
TEAE による中止	日本人	0	0	0	0	0	0
	グローバル	0	0	0	0	0	0

注：
本表では各期間で規定事象が 1 件以上認められた被験者の数及び割合［n（%）］を示している。割合は所定の期間における各解析集団の被験者数に基づく。
発現日が外科的 substudy 期間中の TEAE は、本要約表から除外している。
引用：5.3.5.1 項、表 14.3.2.32J

表 2.7.4-19　グローバル安全性解析集団の 2%以上の被験者で認められた、治験治療下で発現した有害事象の期間ごとの要約
（日本人患者集団及びグローバル安全性解析集団、1001 試験）

基本語	解析集団	被験者数（%）					
		0～6 箇月	6～12 箇月	12～18 箇月	18～24 箇月	24～30 箇月	全体
鼻咽頭炎	日本人（N = 10）	2 (20.0)	2 (22.2)	0	0	0	4 (40.0)
	グローバル（N = 174）	14 (8.0)	5 (5.0)	0	0	0	18 (10.3)
関節痛	日本人	0	0	0	0	0	0
	グローバル	15 (8.6)	2 (2.0)	0	0	0	17 (9.8)
頭痛	日本人	1 (10.0)	0	0	0	0	1 (10.0)
	グローバル	10 (5.7)	2 (2.0)	0	0	0	12 (6.9)
発疹	日本人	1 (10.0)	0	0	0	0	1 (10.0)
	グローバル	4 (2.3)	1 (1.0)	0	0	0	7 (4.0)
歯痛	日本人	0	0	0	0	0	0
	グローバル	5 (2.9)	1 (1.0)	0	0	0	6 (3.4)
上気道感染	日本人	0	0	0	0	0	0
	グローバル	6 (3.4)	0	0	0	0	6 (3.4)
背部痛	日本人	0	0	0	0	0	0
	グローバル	5 (2.9)	1 (1.0)	0	0	0	5 (2.9)
咳嗽	日本人	0	0	0	0	0	0
	グローバル	3 (1.7)	0	3 (10.0)	0	0	5 (2.9)
高血圧	日本人	0	0	0	0	0	0
	グローバル	5 (2.9)	0	0	0	0	5 (2.9)
浮動性めまい	日本人	1 (10.0)	0	0	0	0	1 (10.0)
	グローバル	4 (2.3)	0	0	0	0	4 (2.3)
発熱	日本人	0	0	0	0	0	0
	グローバル	4 (2.3)	0	0	0	0	4 (2.3)
インフルエンザ	日本人	2 (20.0)	0	0	0	0	2 (20.0)
	グローバル	3 (1.7)	0	0	0	0	4 (2.3)

注：本表では各期間で規定事象が 1 件以上認められた被験者の数及び割合［n（%）］を示している。割合は所定の期間における各解析集団の被験者数に基づく。発症日が外科的 substudy 期間の TEAE は、本表から除外している。
引用：5.3.5.1 項、表 14.3.2.33J

2.7.4.2.1.4.3　臨床的に重要な事象及び注目すべき有害事象

2.7.4.2.1.4.3.1　FVIII に対するインヒビター産生

1001 試験及び 3002 試験では、本剤への曝露下で FVIII に対するインヒビター産生が認められた被験者はいなかった（1001 試験、表 14.3.1.1 並びに 3002 試験、表 14.3.3.1.1 及び表 14.3.3.1.2 参照）。1001 試験では、グローバル安全性解析集団のすべての被験者で 95%信頼区間（0.0%～2.1%）の上限が許容上限の 6.8%を下回っていたことから、本試験における主要安全性評価項目は十分に達成された。

3002 試験では、被験者 1 名（6080002-2004）に低力価インヒビターが認められ（PT：抑制抗体陽性）、臨床検査の誤りにより当初 TEAE として記録された。しかし、その後に低力価インヒビターが以前から存在していた（スクリーニング時に既に存在していた）ことが特定され、本剤への曝露下で発現した新規（de-novo）インヒビターでないことが判明した。詳細については、2.7.4.2.1.3.2 項を参照。

実施中の継続投与試験である 3001 試験では、登録された 12 例の PUP のうち 5 例にインヒビターの産生が認められた。20[redacted] 年[redacted] 月[redacted] 日時点での症例の概要を以下に示す。

被験者 3800023-3001

イントロン 22 逆位の遺伝子異常、インヒビター発現前の 3 度の出血事象、発熱及び咳嗽を伴う[redacted]歳のイタリア白人男児 PUP 症例であった。[redacted] 年 10 月 18 日、最初のインヒビター検体が採取され、力価は 0.93 BU/mL であった。＃同 年 11 月 2 日、確認のための検体が採取され、力価は 1.35 BU/mL であった。そのため、患者は本剤への 13 ED 後、インヒビターが発現したと診断された。＃同 年 12 月 5 日、力価のピークは 2.58 BU/mL に達し、#翌 年 1 月 18 日時点での力価は 0.95 BU/mL であった。インヒビター発現以降は、＃同 年 11 月 27 日に外傷性口腔内出血を発現し、本剤及び第 VIIa 因子の 9 回の投与が必要であった。

- 本剤の投与：＃同 年 8 月 1 日、治験責任医師は本患者におけるすべての出血エピソードに対し、40 IU/kg のオンデマンド療法を選択した。＃同 年 10 月 4 日、治験責任医師は治療を 38 IU/kg（週 1 回）の定期投与に変更した ＃同 年 11 月 15 日、治験責任医師は投与量を 40 IU/kg（週 2 回）、さらに 50 IU/kg（週 3 回）へと調整し、＃同 年 11 月 29 日以降、患者は 50 IU/kg（週 3 回）の強化定期投与療法を施行されている。
- インヒビター発現のリスク因子：イントロン 22 逆位、C2 ドメイン、ヌル変異、インヒビター発現前の 3 度の出血事象、発熱及び咳嗽、重度の血友病、若年、及び PUP であること

被験者 3800023-3002

イントロン 22 逆位の遺伝子変異を有し、インヒビター発現前に 1 度の出血事象を呈した[redacted]歳のイタリア白人男児 PUP 症例であった。[redacted] 年 11 月 21 日、最初のインヒビター検体が採取され、力価は 0.79 BU/mL であった。＃同 年 12 月 1 日、確認のためのインヒビター検体が採取され、力価は 1.18 BU/mL であった。そのため、患者は本剤への 17 ED 後、インヒビターが発現したと診断された。＃同 年 12 月 15 日、力価のピークは 9.7 BU/mL に達し、＃翌 年 2 月 8 日時点での力価は 5.88 BU/mL であった。＃翌 年 2 月 21 日時点において、インヒビターと診断されて以降、患者は出血事象を発現していない。

- 本剤の投与：＃同 年 10 月 6 日の試験開始時、治験責任医師は 30 IU/kg（週 1 回）の定期投与療法を選択した。＃同 年 10 月 12 日、治験責任医師は投与量を 40 IU/kg（週 1 回）に調整した。＃同 年 12 月 17 日、治験責任医師は投与量を 30 IU/kg（週 2 回）に調整した。
- インヒビター発現のリスク因子：イントロン 22 逆位、C2 ドメイン、ヌル変異、インヒビター発現前の 1 度の出血事象、重度の血友病、若年、及び PUP であること

被験者 5280007-3001

C209_212de 1 p.の第 VIII 因子遺伝子異常（Phe70；フレームシフト突然変異（小欠失））、インヒビター発現前に治療された 2 度の出血、複数回の転倒及び発熱歴を有する[redacted]歳のオランダ白人男児 PUP 症例であった。[redacted]年 1 月 25 日、最初のインヒビター検体が採取され、検査結果は 0.83 BU/mL であった。＃同 年 2 月 16 日、確認のためのインヒビター検体が採取され、検査結果は 0.72 BU/mL であり、これが最も直近の力価であった。患者は本剤への 20 ED 後、インヒビターが発現したと診断された。インヒビター発現後の＃前 年 2 月 8 日、本患者は 1 度の外傷性出血を呈したが、これはまだ評価は行われていない。

- 本剤の投与：＃前々年 8 月 26 日、治験責任医師は本臨床試験開始時にオンデマンド療法を選択し、関節出血に対し 29 IU/kg 及びその他の出血事象に対し 56 IU/kg を投与。＃前々年 12 月 23 日、回復状態及び体重増加を考慮して外傷性出血に対する増量を行うため投与量の調整が行われ、外傷に対して 77 IU/kg が投与された。＃前 年 11 月 29 日、治療法が 21 IU/kg/週の予防投与に調整された。
- インヒビター発現のリスク因子：フレームシフト突然変異（小欠失）、A1 ドメイン、ヌル変異の可能性（ポリ A 範囲内の小欠失は非ヌル変異と思われる）、2 度の治療を受けた出血、複数回の転倒及び発熱、オンデマンド療法、若年、重度の血友病、及び PUP であること

被験者 5280007-3002

イントロン 22 逆位の遺伝子変異を有し、インヒビター発現前に 2 度の出血事象、膿痂疹、事象発現前の手足口病を含む多重感染を呈した[redacted]歳のオランダ白人男児 PUP 症例であった。[redacted]年 6 月 17 日、最初のインヒビター検体が採取され、力価は 0.61 BU/mL であった。＃同 年 7 月 15 日、確認のための検体が採取され、力価は 4.02 BU/mL であった。そのため患者は本剤への 32 ED 後、インヒビターが発現したと診断された ＃同 年 9 月 14 日、力価のピークは 5.9 BU/mL に達した。＃翌 年 1 月 9 日時点の力価は 0.93 BU/mL であった。最初にインヒビターの結果が出て以降、患者は 3 度の出血を発現した。＃同 年 9 月 19 日に始まった出血事象は、本剤及び第 VIIa 因子の 3 回の投与が必要であった。その他の出血事象はすべて本剤のみにより治療された。

- 本剤の投与：＃前 年 12 月 18 日の登録時、治験責任医師は関節に対して 26 IU/kg、筋肉に対して 51 IU/kg、深部筋肉及び外傷性出血に対して 77 IU/kg の処方用量を選択した。＃同 年 3 月 30 日、治験責任医師は治療を 27 IU/kg（週 1 回）の定期投与療法に変更した。＃同 年 5 月 18 日、レジメンは 23 IU/kg（週 2 回）に増量された ＃同 年 7 月 19 日、レジメンは 42 IU/kg（週 3 回）に増量された。＃同 年 9 月 20 日、レジメンは 59 IU/kg（2 日おき）に増量された。
- インヒビター発現のリスク因子：イントロン 22 逆位、C2 ドメイン、ヌル変異、2 度の出血事象、インヒビター発現前の多重感染、若年、重度の血友病、及び PUP であること

被験者 7100001-3003

c.453_459delinsGGAAGG, pSer152Glufs*9 in exon 4 の第 VIII 因子遺伝子異常、フレームシフト突然変異（小欠失）及びインヒビター診断の約 5 週間前の左前腕の特発性出血歴を有する[redacted]歳の南アフリカ黒人男児 PUP 症例であった。[redacted]年 12 月 21 日、最初のインヒビター検体が採取され、結果は 1.77 BU/mL であった。＃翌 年 1 月 11 日、確認のためのインヒビター検体が採取され、結果は 8.5 BU/mL であった。そのため患者は本剤への 8 ED 後にインヒビターが発現したと診断された。診断時に高力価（例：5 BU/mL を超える）の患者は試験を中止しなければならない旨の記述が実施計画書にあるため、患者は試験を中止した。患者の最後のインヒビター力価（試験中止時に採取）は 12.9 BU/mL であった。

- 本剤の投与：＃同 年 11 月 16 日、治験責任医師は 30 IU/kg（週 1 回）の定期投与療法を割り当てた。
- インヒビター発現のリスク因子:フレームシフト突然変異（小欠失）（c.453_459delinsGGAAGG, pSer152Glufs*9 in exon 4）、ヌル変異、A2 ドメイン、黒色人種、重度の血友病、若年、及び PUP であること

上記のとおり、実施中の 3001 試験における PUP でのインヒビター発現率（41.7%：5 例/12 例）が、SIPPET 等の公表された研究（Peyvandi, Mannucci, Garagiola et al. 2016）にて報告されているインヒビター発現率からの真の上昇を示すものなのか、または被験者のインヒビター発現のリスクが高かったのかについては、エビデンスが不足しているため結論づけることは困難である。インヒビターを発現した 5 例の PUP のうち 4 例が試験を継続しており、インヒビター力価は低力価となっている。また、臨床試験及び製造販売開始後に本剤の投与を受けた PTP において、インヒビター発現は報告されていない。したがって、本剤においてベネフィットがリスクを上回ることに変わりはない。

2.7.4.2.1.4.3.2　非中和抗薬物抗体

非中和 ADA 及び CHO 細胞由来タンパク質に対する抗体について、1001 試験及び 3002 試験でベースライン時又はその後のいずれかの時点で検査が陽性となった被験者の数及び割合を要約した。ADA 検査の結果が陽性で、かつ IgG 又は免疫グロブリン M（IgM）の検査結果も陽性であった場合に、当該被験者の検査結果を陽性とみなし、それ以外の場合は陰性とみなした。詳細については、1001 試験 CSR、12.3.1.3.3 項及び 12.3.1.3.4 項並びに 3002 試験 CSR、12.5 項及び 12.6 項を参照。

1001 試験

1001 試験では、グローバル患者集団の被験者 8 名が本剤投与前に非中和 ADA（FVIII に対する IgG 及び／又は IgM 抗体）の検査が陽性で、試験を開始した（表 2.7.4-20）。これらの被験者 8 名のうち、7 名が試験終了まで陽性のままで、1 名は IgG 抗体陽性で試験を開始したが、試験終了来院までに陰性となった。別の被験者 4 名が試験中に IgG 及び／又は IgM 抗体が陽性となった。これらの被験者 4 名のうち、2 名は試験終了来院時に抗体検査の結果が陰性で、2 名は陽性であった。これらの被験者のいずれにも治験薬と関連ありと判定された TEAE は見られず（1001 試験、一覧表 16.2.7.1 参照）、試験中のいずれかの時点で検査が陽性であった被験者

で、治験依頼者のメディカルレビューにより、報告された非中和 ADA のいずれかと関係していると判定された TEAE が認められた被験者はいなかった。

日本人患者集団で 2 名の被験者が本剤投与前に非中和 ADA の検査が陽性で、試験を開始した（表 2.7.4-20）。いずれの被験者も試験終了まで陽性のままであった。試験中に IgG 及び／又は IgM 抗体が陽性となった日本人被験者はいなかった。試験中のいずれかの時点で検査が陽性であった日本人被験者で、治験依頼者のメディカルレビューにより、報告された非中和 ADA のいずれかと関係していると判定された TEAE が認められた被験者はいなかった。

表 2.7.4-20　非中和抗薬物抗体（安全性解析集団、1001 試験）

	被験者数（%）	
抗薬物抗体の状態	**グローバル患者集団 (N = 174)**	**日本人患者集団 (N = 10)**
試験中のいずれかの時点で陽性 [a,b]	12 (6.9)	2 (20.0)
ベースライン時に陽性	8 (4.6)	2 (20.0)
ベースライン時に陽性で、その後のいずれかの時点で陽性 [b]	8 (4.6)	2 (20.0)
ベースライン時に陽性で、試験終了時に陽性	6 (3.4)[c]	2 (20.0)
ベースライン時に陰性で、その後のいずれかの時点で陽性 [b]	4 (2.3)	0
ベースライン時に陰性で、試験終了時に陽性	2 (1.1)	0

略語：N、安全性解析集団の被験者数

[a] 抗薬物抗体の結果が陽性で、かつ免疫グロブリン G 及び免疫グロブリン M の検査結果のいずれかが陽性であれば、当該被験者の検査結果を陽性とみなし、それ以外では陰性とみなした。

[b] ベースライン後の検査結果で 1 回以上陽性であれば、当該被験者の検査結果を陽性とみなした。スクリーニングから検査結果がすべて陰性であれば、当該被験者の検査結果を陰性とみなした。

[c] これに加え、別の被験者 1 名（7100002-1001）では、「試験終了来院」としては記録されなかったものの、当該被験者で記録されている最後の来院時に陽性であった。そのため、ベースライン時に陽性で、本試験への参加終了時に陽性であった被験者は 7 名である。

引用：5.3.5.1 項、1001 試験 CSR、表 14.3.1.4;5.3.5.1 項、表 14.3.1.4J

3002 試験

3002 試験で、非中和 ADA の検査結果が陽性で試験に登録された被験者は 10 名であった（表 2.7.4-21）。試験中に非中和 ADA が発現した被験者は 10 名であった。これらの 10 名のうち、試験終了来院時に検査結果が陰性であった被験者が 3 名、陽性であった被験者が 7 名であった。年齢群間で ADA に意味のある違いは認められなかった（3002 試験、表 14.3.3.2.2 及び表 14.3.3.2.3）。

表 2.7.4-21　非中和抗薬物抗体（安全性解析集団、3002 試験）

	被験者数（%）
抗薬物抗体の状態	**(N = 84)**
試験中のいずれかの時点で陽性 [a,b]	20 (23.8)
ベースライン時に陽性	10 (11.9)
ベースライン時に陽性で、その後のいずれかの時点で陽性 [b]	10 (11.9)
ベースライン時に陽性で、試験終了時に陽性	8 (9.5) [c]
ベースライン時に陰性で、その後のいずれかの時点で陽性 [b]	10 (11.9)
ベースライン時に陰性で、試験終了時に陽性	7 (8.3)

略語：N、安全性解析集団の被験者数

[a] 抗薬物抗体の結果が陽性で、かつ免疫グロブリン G 及び免疫グロブリン M の検査結果のいずれかが陽性であれば、被験者の検査結果を陽性とみなし、それ以外では陰性とみなした。

[b] ベースライン後の検査結果で 1 回以上陽性であれば、被験者の検査結果を陽性とみなした。スクリーニングから検査結果がすべて陰性であれば、被験者の検査結果を陰性とみなした。
[c] この中には、試験終了時の結果が得られなかったが、試験を通して以前の来院のいずれも陽性であった別の 1 名の被験者（0400002-2002）は含まれていない。
引用：5.3.5.2 項、3002 試験 CSR、表 14.3.3.4 及び一覧表 16.2.8.3

試験中のいずれかの時点で検査結果が陽性であり、治験依頼者によるメディカルレビューで、報告された非中和 ADA のいずれかと関係していると評価された TEAE が認められた被験者はいなかった（3002 試験、一覧表 16.2.7.1 及び一覧表 16.2.8.3）。さらに、3002 試験の年間出血率は、ADA の検査結果が陽性であった定期的与群の被験者部分集団と、有効性解析集団に含まれる定期的な投与を受けた全被験者との間で同程度であった（3002 試験 CSR、11.5.2.2.2 項参照）。

非中和 ADA 産生の臨床的意義は、FVIII 補充療法に対する反応と同様、系統的に検討されていない。文献の公表データでは、FVIII の回復及び／又は半減期に対する影響は見られないことが示されている（Batlle et al., 1996, Ling et al., 2003, Dazzi et al., 1996）。しかし、一部の研究では、FVIII の安定性及び PK に対する影響の可能性を認めている（Ling et al., 2003, Reipert et al., 2007, Lavigne-Lissalde et al., 2007）。1001 試験及び 3002 試験で非中和 ADA の検査結果が陽性であった PK 解析集団の被験者 14 名（2 名の日本人被験者を含む）では、ADA が陰性であった被験者と比較して、FVIII 活性プロファイル又は PK パラメーターに意味のある違いは認められなかった（2.7.2.4 項参照）。注目すべきことに、Algiman らは、健康被験者から採取した 500 血漿検体中 85 検体（17%）で、生来の FVIII 中和活性の存在を報告している（Algiman et al., 1992）。

2.7.4.2.1.4.3.3　CHO 細胞由来タンパク質に対する抗体

1001 試験及び 3002 試験では、CHO 細胞由来タンパク質に対する抗体の検査はすべて陰性であった［2.7.6.1 項（1001 試験）；2.7.6.2 項（3002 試験）］。

2.7.4.2.1.4.3.4　血栓塞栓事象

1001 試験及び 3002 試験では、血管内 TEE は認められなかった［2.7.6.1 項（1001 試験）；2.7.6.2 項（3002 試験）］。3002 試験では、日本人以外の被験者 1 名（5280006-2001）に医療機器閉塞の TESAE が認められた。これは、SMQ を「塞栓性及び血栓性イベント」とした検索により特定された。本事象は SMQ 検索により特定されたが、投与器具に限定された合併症であり、血管内血栓形成を伴うものではなかった。本事象は、治験責任医師及び治験依頼者により治験薬と関連なしと判定された。この被験者の簡潔な叙述は、2.7.4.2.1.3.2 項に示している。

2.7.4.2.1.4.3.5　過敏症及びアナフィラキシー反応

1001 試験

1001 試験では、全体で過敏症反応が認められた被験者の割合は低かった（グローバル患者集団 1.1%、日本人患者集団 0%）。事前に定義した SMQ による検索（2.7.4.2.1 項に記述）により、過敏症又はアナフィラキシー反応の症状又は徴候と判断できる事象が認められた被験者の割合は低かった（10%未満）。その個々の事象は、表 2.7.4-22 に示している。これらの事象のうち日本人被験者で発現したものは 1 件（発疹）で、他の事象はすべて日本人以外の被験者で発現し

たものである。治験依頼者のメディカルレビューにより、咳嗽及びくしゃみの事象は、過敏症反応と関連なしと判定された。他の事象は、メディカルレビューにより過敏症反応の可能性を除外できなかった。特定された事象で、メディカルレビュー後にアナフィラキシー反応と判定されたものはなかった。1001 試験、12.3.1.4 項を参照。

これらの TEAE は、過敏症を示す 6 件の事象が認められた以下の被験者 4 名で治験薬と関連ありと判定された（1001 試験、一覧表 16.2.7.4 参照）。

- **被験者 6080002-1001**（日本人以外の被験者）では、治験薬と関連ありと判定された TESAE として 1 件の過敏症に加え、非重篤の治験薬と関連ありと判定された TEAE として 1 件のそう痒症が認められた。詳細は 2.7.4.2.1.3.1 項に示している。
- **被験者 6080001-1002**（日本人以外の被験者）では、非重篤の治験薬と関連ありと判定された TEAE として 2 件の過敏症が認められた。いずれの事象に対しても治験薬の用量は変更しなかった。治験薬投与前日の夜にセチリジンを 1 錠服用するよう指示し、2 回目の事象発現後には、治験薬投与後 1 時間にわたり院内にとどまるよう指示し、観察した。いずれの事象も回復した。
- **被験者 6080001-1003**（日本人以外の被験者）では、非重篤の治験薬と関連ありと判定された TEAE として 1 件の紅斑が認められた。治験薬の用量は変更せず、他の治療を行うことなく回復した。
- **被験者 8400154-1004**（日本人以外の被験者）では、非重篤の治験薬と関連ありと判定された TEAE として 1 件の発疹が認められた。この事象により治験薬の投与を中断したが、他の措置は行わず、報告時点では回復中であった。発疹以外の TEAE は認められなかった。

表 2.7.4-22　過敏症及びアナフィラキシー反応の可能性がある TEAE
（安全性解析集団、1001 試験）

カテゴリー 器官別大分類 基本語	被験者数（%） (N = 174)	事象数
過敏症又はアナフィラキシー反応の可能性があるすべての TEAE	**15 (8.6)**	**20**
SMQ：アナフィラキシー反応（広義）	**14 (8.0)**	**17**
皮膚および皮下組織障害	9 (5.2)	10
発疹	7 (4.0)	8
紅斑	1 (0.6)	1
そう痒症	1 (0.6)	1
呼吸器、胸郭および縦隔障害	5 (2.9)	7
咳嗽	5 (2.9)	6
くしゃみ	1 (0.6)	1
PT：過敏症	**2 (1.1)**	**3**
免疫系障害	2 (1.1)	3
過敏症	2 (1.1)	3

略語：N、安全性解析集団の被験者数；PT、基本語；SMQ、MedDRA 標準検索式；TEAE、治験治療下で発現した有害事象
注:被験者に複数の AE が発現した場合、それぞれの被験者数として 1 回のみカウントする。外科的 substudy 期間中に生じた有害事象は、TEAE の要約から除外している。検索基準は、SMQ のアナフィラキシー反応（広義）及び PT の「過敏症」であった。
引用：5.3.5.1 項、1001 試験 CSR、表 14.3.2.30

3002 試験

3002 試験では、事前に定義した SMQ による検索（2.7.4.2.1 項に記述）により、過敏症又はアナフィラキシー反応の症状又は徴候と判断できる事象が認められた被験者は 13 名であった。その個々の事象は、表 2.7.4-23 に示している。これらの事象のうち 1 件（被験者 6080002-2004 の過敏症）を除くすべてが治験責任医師及び治験依頼者により治験薬と関連なしと判定された（3002 試験、一覧表 16.2.7.5）。治験薬と関連ありと判定された過敏症の事象は軽度であり、この事象による本剤の用量変更は行わなかった。この被験者の叙述は、2.7.4.2.1.3.2 項に示している。

特定された事象のうち、治験依頼者のメディカルレビューによりアナフィラキシー反応と判定されたものはなかった。咳嗽、喘息、湿疹、アレルギー性鼻炎、及び結膜炎の事象は、過敏症反応と関係がなく、むしろ感冒又は基礎疾患と関係していると判定された。ただし、紅斑性皮疹は、治験依頼者により過敏症反応の症状である可能性を除外できないと判定されたが、治験責任医師は治験薬と関連なしと判定した。

表 2.7.4-23　過敏症及びアナフィラキシー反応の可能性がある TEAE
（安全性解析集団、3002 試験）

カテゴリー 器官別大分類 基本語	被験者数（%） (N = 84)	事象数
過敏症又はアナフィラキシー反応の可能性があるすべての TEAE	**13 (15.5)**	**19**
SMQ：アナフィラキシー反応（広義）	**9 (10.7)**	**13**
呼吸器、胸郭および縦隔障害	8 (9.5)	12
咳嗽	7 (8.3)	10
喘息	1 (1.2)	2
皮膚および皮下組織障害	1 (1.2)	1
紅斑性皮疹	1 (1.2)	1
SMQ：過敏症（広義）	**7 (8.3)**	**9**
眼障害	1 (1.2)	1
結膜炎	1 (1.2)	1
免疫系障害	1 (1.2)	1
過敏症	1 (1.2)	1
呼吸器、胸郭および縦隔障害	3 (3.6)	5
アレルギー性鼻炎	3 (3.6)	3
喘息	1 (1.2)	2
皮膚および皮下組織障害	2 (2.4)	2
湿疹	1 (1.2)	1
紅斑性皮疹	1 (1.2)	1

略語：N、安全性解析集団の被験者数；TEAE、治験治療下で発現した有害事象；SMQ、MedDRA 標準検索式
注：検索基準は、SMQ のアナフィラキシー反応（広義）及び SMQ の過敏症（広義）であった。
引用：5.3.5.2 項、3002 試験 CSR、表 14.3.1.13.1

2.7.4.2.1.4.4　局所忍容性

注射部位の局所忍容性は、被験者が 5 点スケールで評価するとともに、治験責任医師が紅斑に対して 5 点スケールを、また掻痒、局所疼痛又は局所熱感に対して別の 5 点スケールを用いて、浮腫又は硬結のサイズを計測することにより評価した。

2.7.4.2.1.4.4.1　1001 試験（12 歳以上 65 歳以下の被験者）

全体として、グローバル患者集団で評価した投与の 99.3%及び日本人患者集団で評価した投与の 100%で、被験者による反応の評価は「なし」（局所反応は見られない）であった。これらの被験者による評価と一致して、グローバル患者集団で治験責任医師が評価した投与の 99.8%及び日本人患者集団で治験責任医師が評価した投与の 100%で評価は「なし」（局所反応は見られない）であった。1001 試験 CSR、12.2.3.1 項も参照。

表 2.7.4-24　局所忍容性（安全性解析集団、1001 試験）

評価	グローバル患者集団（N = 174） 被験者数（%）	グローバル患者集団（N = 174） 事象数（%）	日本人患者集団（N = 10） 被験者数（%）	日本人患者集団（N = 10） 事象数（%）
被験者による忍容性評価				
1 回以上の評価	172 (98.9)	13580	10 (100)	651
反応				
なし	172 (100)	13491 (99.3)	10 (100)	650 (98.8)
ほとんどなし	15 (8.7)	65 (0.5)	1 (10)	1 (0.2)
わずか	7 (4.1)	17 (0.1)	0	0
ある程度	4 (2.3)	7 (0.1)	0	0
耐え難い	0	0	0	0
治験責任医師による忍容性評価				
1 回以上の評価	153 (87.9)	553	10 (100)	65
紅斑の評価				
なし	153 (100)	552 (99.8)	10 (100)	65 (100)
非常にわずか（ほとんど気付かれない）	1 (0.7)	1 (0.2)	0	0
軽度	0	0	0	0
中等度～重度	0	0	0	0
重度（発赤）～わずかな痂皮形成	0	0	0	0

略語：N、安全性解析集団の被験者数
注：すべての評価で浮腫／硬結の最大サイズを要約している。
引用：5.3.5.1 項、1001 試験 CSR、表 14.3.3.1.1 及び 14.3.3.2-1; 5.3.5.1 項、表 14.3.3.1.1J 及び表 14.3.3.2.1J

注目すべきことに、本剤の高含量［3000 IU/バイアル（調製後 600 IU/mL）］及び低含量［250 IU/バイアル（調製後 100 IU/mL）］製剤の PK 比較に含まれる被験者で、局所反応が認められた被験者はいなかった（1001 試験、一覧表 16.2.9.6.6、一覧表 16.2.7.5、及び一覧表 16.2.7.6）。

2.7.4.2.1.4.4.2　3002 試験（0 歳以上 12 歳未満の被験者）

3002 試験では、計 5,313 回の注射を行った（3002 試験、表 14.1.8.5.1）。そのうち局所忍容性を被験者が評価したのは 4,774 回で、治験責任医師が評価したのは 309 回であった（表 2.7.4-25）。これらの投与のうち 4,747 回（99.4%）で被験者による反応の評価が「なし」（局所反応は見られない）であった。5 名（6.0%）の被験者における 12 回（0.3%）の投与では、被験者による局所反応評価が「ある程度」であり、別の 15 回（0.3%）の投与では、被験者による局所反応評価が「わずか」又は「ほとんどなし」であった。これらの被験者による評価と一致して、治験責任医師が評価した投与のうち 307 回（99.4%）では、局所反応の評価が「なし」であった。被験者 2 名（2.4%）に見られた 2 件（0.6%）の紅斑の事象（被験者 0360014-2002 で Infusaport 上方の皮膚に発現した 1 件及び被験者 6080002-2004 で耳に発現したと報告された 1 件）のみが治験責任医師により「軽度」と判定された。3002 試験 CSR、12.2.3.5 項も参照。

表 2.7.4-25　局所忍容性（安全性解析集団、3002 試験）

評価	被験者数（%） (N = 84)	事象数 （%）
被験者による忍容性評価		
1 回以上の評価	83 (98.8)	4774
反応		
なし	83 (100)	4747 (99.4)
ほとんどなし	4 (4.8)	10 (0.2)
わずか	1 (1.2)	5 (0.1)
ある程度	5 (6.0)	12 (0.3)
耐え難い	0	0
治験責任医師による忍容性評価		
1 回以上の評価	84 (100)	309
紅斑の評価		
なし	83 (98.8)	307 (99.4)
非常にわずか（ほとんど気付かれない）	0	0
軽度	2 (2.4)	2 (0.6)
中等度～重度	0	0
重度（発赤）～わずかな痂皮形成	0	0

略語：N、安全性解析集団の被験者数
注：すべての評価で浮腫／硬結の最大サイズを要約している。
引用：5.3.5.2 項、3002 試験 CSR、表 14.3.2.1.1 及び 14.3.2.2.1

2.7.4.2.1.5　器官系又は症候群別有害事象の解析

2.7.4.2.1.5.1　1001 試験（12 歳以上 65 歳以下の被験者）

グローバル患者集団で、TEAE の発現率が最も高い（被験者の 10%超）SOC は、「感染症および寄生虫症」［45 名（25.9%）］並びに「筋骨格系および結合組織障害」［26 名（14.9%）］であった（表 2.7.4-26）。

日本人患者集団でも、これらは TEAE の発現率が最も高い SOC であった。他の SOC における TEAE の分布では、日本人患者集団とグローバル患者集団で臨床的に重要な違いは認められなかった。

表 2.7.4-26　グローバル患者集団における被験者の 2%以上に発現した TEAE の器官別大分類及び基本語（安全性解析集団、1001 試験）

	グローバル患者集団 (N = 174)		日本人患者集団 (N = 10)	
器官別大分類 基本語	被験者数（%）	事象数	被験者数（%）	事象数
すべての TEAE	**113 (64.9)**	**292**	**8 (80.0)**	**20**
感染症および寄生虫症	**45 (25.9)**	**61**	**6 (60.0)**	**9**
鼻咽頭炎	18 (10.3)	22	4 (40.0)	4
上気道感染	6 (3.4)	6	0	0
インフルエンザ	4 (2.3)	4	2 (20.0)	2
筋骨格系および結合組織障害	**26 (14.9)**	**46**	**0**	**0**
関節痛	17 (9.8)	19	0	0
背部痛	5 (2.9)	6	0	0
神経系障害	**19 (10.9)**	**25**	**2 (20.0)**	**2**
頭痛	12 (6.9)	13	1 (10.0)	1
浮動性めまい	4 (2.3)	5	1 (10.0)	1
胃腸障害	**17 (9.8)**	**23**	**0**	**0**
歯痛	6 (3.4)	8	0	0
皮膚および皮下組織障害	**17 (9.8)**	**21**	**3 (30.0)**	**4**
発疹	7 (4.0)	8	1 (10.0)	1
一般・全身障害および投与部位の状態	**17 (9.8)**	**20**	**0**	**0**
発熱	4 (2.3)	5	0	0
呼吸器、胸郭および縦隔障害	**9 (5.2)**	**17**	**0**	**0**
咳嗽	5 (2.9)	6	0	0
血管障害	**7 (4.0)**	**7**	**0**	**0**
高血圧	5 (2.9)	5	0	0

略語：N、安全性解析集団の被験者数；TEAE、治験治療下で発現した有害事象
注：本要約では、発現日が外科的 substudy 期間中の事象を除外している。器官別大分類で提示している被験者及び事象の数は、器官別大分類全体で報告された合計を表す（表に示した基本語のみではない）。
引用：5.3.5.1 項、1001 試験 CSR、表 14.3.2.4;5.3.5.1 項、表 14.3.2.4J

2.7.4.2.1.5.2　3002 試験（0 歳以上 12 歳未満の被験者）

小児集団で典型的で、3002 試験で TEAE の発現率が最も高かった SOC は「感染症および寄生虫症」［38 名（45.2%）］であった（表 2.7.4-27）。

表 2.7.4-27　グローバル患者集団における被験者の 2%以上で発現した TEAE の器官別大分類及び基本語（安全性解析集団、3002 試験）

器官別大分類 基本語	被験者数（%） (N = 84)	事象数
すべての TEAE	**64 (76.2)**	**183**
感染症および寄生虫症	**38 (45.2)**	**60**
鼻咽頭炎	14 (16.7)	15
上気道感染	4 (4.8)	5
鼻炎	4 (4.8)	4
耳感染	3 (3.6)	3
下気道感染	2 (2.4)	3
医療機器関連感染	2 (2.4)	2
胃腸炎	2 (2.4)	2
咽頭炎	2 (2.4)	2
皮膚感染	2 (2.4)	2
ウイルス感染	2 (2.4)	2
傷害、中毒および処置合併症	**20 (23.8)**	**32**
頭部損傷	5 (6.0)	6
転倒	4 (4.8)	4
挫傷	3 (3.6)	6
裂傷	3 (3.6)	4
靭帯捻挫	2 (2.4)	2
四肢損傷	2 (2.4)	2
筋骨格系および結合組織障害	**15 (17.9)**	**18**
関節痛	8 (9.5)	8
四肢痛	4 (4.8)	4
筋骨格痛	2 (2.4)	2
呼吸器、胸郭および縦隔障害	**12 (14.3)**	**19**
咳嗽	7 (8.3)	10
口腔咽頭痛	3 (3.6)	3
アレルギー性鼻炎	3 (3.6)	3
神経系障害	**8 (9.5)**	**14**
頭痛	7 (8.3)	9
一般・全身障害および投与部位の状態	**8 (9.5)**	**8**
発熱	5 (6.0)	5
胃腸障害	**7 (8.3)**	**8**
齲歯	2 (2.4)	2
嘔吐	2 (2.4)	2
血液およびリンパ系障害	**6 (7.1)**	**8**
貧血	3 (3.6)	5
鉄欠乏性貧血	2 (2.4)	2
耳および迷路障害	**3 (3.6)**	**3**
耳痛	2 (2.4)	2

略語：N、安全性解析集団の被験者数；TEAE、治験治療下で発現した有害事象
引用：5.3.5.2 項、3002 試験 CSR、表 14.3.1.4.1

2.7.4.2.1.6　外科処置を受けた被験者における有害事象

2.7.4.2.1.6.1　1001 試験（12 歳以上 65 歳以下の被験者）

1001 試験で、被験者 13 名（すべて日本人以外の被験者）に対して 16 回の手術を施行した（2.7.6.1 項参照）。これら 13 名のうち、8 名（61.5%）の被験者で外科的 substudy 期間中に 15 件の AE が報告された（表 2.7.4-28）。1 件の AE（術後創感染）のみが重篤であった（1001 試験、一覧表 16.2.7.2 参照）。AE は、一般に外科処置に関連する事象と一致しており、処置によ

る疼痛が最も高い頻度で報告された事象であった［5 名（38.5%）で各 1 件］。治験責任医師により治験薬と関連ありと判定された PT はなかった。

表 2.7.4-28　外科的 substudy 期間中に発現した AE（外科的解析集団、1001 試験）

器官別大分類 基本語	被験者数（%） (N = 13)	事象数
外科的 substudy 期間中に発現したすべての AE	**8 (61.5)**	**15**
傷害、中毒および処置合併症	**6 (46.2)**	**6**
処置による疼痛	5 (38.5)	5
術後創合併症	1 (7.7)	1
胃腸障害	**2 (15.4)**	**3**
悪心	2 (15.4)	2
嘔吐	1 (7.7)	1
血液およびリンパ系障害	**2 (15.4)**	**2**
貧血	1 (7.7)	1
鉄欠乏性貧血	1 (7.7)	1
感染症および寄生虫症	**1 (7.7)**	**1**
術後創感染	1 (7.7)	1
筋骨格系および結合組織障害	**1 (7.7)**	**1**
関節痛	1 (7.7)	1
神経系障害	**1 (7.7)**	**1**
失神寸前の状態	1 (7.7)	1
腎および尿路障害	**1 (7.7)**	**1**
急性腎不全	1 (7.7)	1

略語：AE、有害事象；N、外科的解析集団の被験者数
引用：5.3.5.1 項、1001 試験 CSR、表 14.3.2.27

2.7.4.2.1.7　副作用

治験責任医師及び治験依頼者による AE と本剤との因果関係の評価は、本剤投与と AE 発現との間の時間的関連性、本剤の作用機序に基づく病態生理学的に妥当と思われる説明、FVIII 補充製剤として分類される薬剤で既知の安全性プロファイル、AE の頻度及び可能であれば再投与試験の結果など、いくつかの因子を考慮に入れて実施した。

表 2.7.4-29 に示す PT は、1001 試験及び 3002 試験で認められた ADR である。表 2.7.4-29 のデータはさらに詳細なものを表 2.7.4-32 に示す。

表 2.7.4-29　器官別大分類及び基本語別の副作用（安全性解析集団、1001 試験及び 3002 試験）

	発現頻度	
器官別大分類	**1%未満**	**1%以上**
神経系障害	浮動性めまい 錯感覚	
免疫系障害		過敏症
皮膚および皮下組織障害	紅斑 そう痒症 発疹	
一般・全身障害および投与部位の状態	悪寒 熱感 注射部位疼痛 発熱	

注：頻度は、規定の副作用が認められた被験者の割合（%）で、1001 試験及び 3002 試験の計 258 名の被験者を母数としている。
MedDRA の基本語「薬物過敏症」は基本語「過敏症」に含めている。
引用：表 2.7.4-32

注：他に 3 つの PT（関節痛、関節可動域低下、薬物特異性抗体陽性）があり、それに対して 1 つ以上の事象が治験責任医師により本剤と関連ありと判定された。治験依頼者は以下の理由によりこれらの 3 つの PT を表 2.7.4-29 から除外している。

- 関節痛（1001 試験の被験者 17 名で 19 件の事象、3002 試験の被験者 8 名で 8 件の事象）：関節痛の事象は被験者の基礎疾患である血友病性関節症に関係している可能性があり、これら事象は、1001 試験の 1 名の被験者を除いて治験責任医師により本剤と関連なしと判定され、さらに本剤の有効性とは無関係とみなされた。
- 関節可動域低下（1001 試験の被験者 1 名で 1 件の事象）：本事象は被験者の基礎疾患である血友病性関節症に関係している可能性が極めて高いと考えられる。
- 薬物特異性抗体陽性（1001 試験の被験者 1 名で 1 件の事象）：この 1 名の被験者における ADA の存在は、治験責任医師の誤りにより TEAE として記録された。ADA は臨床検査として収集されたにすぎない。この臨床検査所見に伴う AE は認められていない。

2.7.4.2.2　個別有害事象の文章による説明

TESAE 及びその他の重要な AE が認められた被験者の叙述は、1001 試験（1001 試験 CSR、付録 14.3.3）及び 3002 試験［3002 試験 CSR、12.3.1.2 項（TESAE）、12.3.1.3 項（中止に至った TEAE）］の各 CSR に示している。

2.7.4.3　臨床検査値の評価

2.7.4.3.1　血液学的検査及び生化学検査

血液学的検査及び生化学検査のデータは、1001 試験及び 3002 試験についてのみ提示している。1001 試験及び 3002 試験で測定した血液学的検査パラメーター及び生化学検査パラメーターの一覧を表 2.7.4-30 に示す。分析は、治験実施施設の臨床検査室で標準のバリデーション済みの測定法を用いて実施した。

表 2.7.4-30　1001 試験及び 3002 試験で測定した臨床検査項目

血液学的検査	生化学検査
ヘモグロビン、ヘマトクリット、赤血球、平均赤血球容積、白血球、好中球、リンパ球、単球、好酸球、好塩基球、及び血小板、CD4 陽性リンパ球数（HIV 陽性が確認された被験者が対象）	ナトリウム、カリウム、クロール、血中尿素窒素、クレアチニン、γ-グルタミルトランスフェラーゼ、アルカリホスファターゼ、アラニンアミノトランスフェラーゼ、アスパラギン酸アミノトランスフェラーゼ、乳酸脱水素酵素、アルブミン、総ビリルビン、総蛋白、ブドウ糖、カルシウム、及び尿素

略語：HIV、ヒト免疫不全ウイルス
引用：5.3.5.1 項、1001 試験 CSR、付録 16.1.1、8.3.2.3 項、及び 5.3.5.2 項、3002 試験 CSR、付録 16.1.1、8.3.2.3 項

臨床検査（血液学的検査及び生化学検査）の結果は、ベースラインからの変化に加え、パラメーター別及び予定来院別に要約している。本剤の初回投与後のいずれかの来院時に測定値が基準範囲を外れており、治験責任医師が臨床的に重要と判断した場合は、いずれも TEAE として記録するものとした。ベースライン後のいずれかの時点で、治験治療下で発現した血液学的検査及び生化学検査値異常が認められた被験者の数及び割合を表に要約している。治験治療下で発現した臨床検査値異常は、ベースラインの値が正常で、その後に異常になったものである。

2.7.4.3.1.1　血液学的検査

1001 試験及び 3002 試験では、すべての血液学的検査パラメーターのベースラインから試験終了来院までの平均変化量、及びベースラインからその後に最高値又は最低値になるまでの平均変化量はともに小さかった（1001 試験、表 14.3.4.1 及び表 14.3.4.3、3002 試験、表 14.3.4.1 及び表 14.3.4.3 参照）。

所定のパラメーターのいずれについても、いずれかの来院時に臨床的に重要な異常値が報告された被験者は、1001 試験で 2 名（1.1%）以下、3002 試験で 2 名（2.4%）以下であった（1001 試験、表 14.3.4.5、及び 3002 試験、表 14.3.4.5）。1001 試験 CSR、12.4.2.1 項、及び 3002 試験 CSR、12.9.2.1 項も参照。

1001 試験では、被験者 3 名（いずれも日本人以外の被験者）に貧血の TEAE が認められ、そのうち治験責任医師により本剤と関連ありと判定されたものはなかった（1001 試験、一覧表 16.2.7.1）。これら被験者のうち 2 名では、貧血が非重篤かつ軽度であり、回復していないと報告された。このうち 1 名の被験者（8400184-1003）では、既往歴で貧血が既に認められており、他の 1 名の被験者では鉄補充療法が行われた（1001 試験、一覧表 16.2.4.8）。もう 1 名の被験者（3800022-1002）では、貧血が重篤かつ重度で入院に至ったが、回復したと報告された。この被験者の叙述は 2.7.4.2.1.3.1 項に示している。

1001 試験の日本人被験者では、臨床的に重大な生化学検査異常値又は SOC の「臨床検査」に分類される TEAE は認められなかった（1001 試験、一覧表 16.2.8.6）。

3002 試験では、被験者 6 名で貧血の TEAE が認められ、そのうち治験責任医師により本剤と関連ありと判定されたものはなかった。6 名のうち 5 名の被験者では、貧血の TEAE が非重篤かつ軽度又は中等度であった。これらの事象のうち 2 件が鉄欠乏性貧血であり、3 件の事象に対して鉄補充療法が行われた。2 件の事象（1 件は回復中、もう 1 件は未回復）を除くすべての

貧血の TEAE が最後に得られた評価で回復したと報告された（3002 試験、一覧表 16.2.7.1 及び一覧表 16.2.4.9）。残りの被験者（5280007-2001）では、貧血の TESAE が個別に 3 件報告された（本人以外によるミュンヒハウゼン症候群）。この症例の詳細な叙述は、2.7.4.2.1.3.2 項に示している。

2.7.4.3.1.2　生化学検査

1001 試験及び 3002 試験では、すべての生化学検査パラメーターのベースラインから試験終了来院までの平均変化量、及びベースラインからその後に最高値又は最低値になるまでの平均変化量はともに小さかった（1001 試験、表 14.3.4.2 及び表 14.3.4.4、3002 試験、表 14.3.4.2 及び表 14.3.4.4 参照）。

1001 試験では、所定のパラメーターのいずれにおいても臨床的に重要な異常値が報告された被験者は 2 名（1.1%）以下であった（1001 試験、表 14.3.4.6）。SOC の「臨床検査」では、計 9 名（5.2%）の被験者で 13 件の TEAE が認められた（1001 試験、表 14.3.2.4 参照）。これには、薬物特異的抗体の TEAE が認められた日本人以外の被験者 1 名が含まれていたが、抗体所見を AE として報告する必要はなかったので、本事象は誤って TEAE として報告されたものである。その他の 8 名の被験者では、肝機能検査異常［2 名（1.1%）で各 1 件］以外に、複数の被験者で発現した臨床検査の PT はなかった。また、治験責任医師により治験薬と関連ありと判定された TEAE もなかった（1001 試験、表 14.3.2.5 参照）。1001 試験 CSR、12.4.2.2 項も参照。
1001 試験の日本人被験者のうち、生化学検査結果で臨床的に重要な異常又は臨床検査の SOC に分類される TEAE が認められた被験者はいなかった（1001 試験、一覧表 16.2.8.6）。

3002 試験では、治験責任医師により臨床的に重要と判定された治験治療下で発現した異常値が報告された被験者はいなかった（3002 試験、表 14.3.4.6）。腎臓又は肝臓のパラメーターの変化／異常値に関して、一貫した傾向又はパターンは確認されなかった。境界値に近い肝酵素増加又はビリルビン増加の症例は、主にスクリーニング／Day 1 に既に高値であった被験者、又は再発を認めない孤発症例であった。3002 試験 CSR、12.9.2.2 項も参照。

2.7.4.3.2　ウイルス安全性

本剤の最終製品におけるウイルス安全性は、発現系のウイルス検査、細胞培養処理における動物由来生物不含培地の使用、及び専用のウイルス除去／不活化工程の採用を組み合わせることによって確保している。この総合戦略により、ウイルス安全性レベルの高い最終製品が得られた（これらの方法の簡潔な概要については、2.7.1.1.2 項を参照）。

ウイルス感染が疑われる場合にのみ、ウイルス安全性検査用保存検体を検査した。1001 試験及び 3002 試験に参加した被験者では、ウイルスマーカーの有無を調べるために保存血液検体の検査が必要になった事象は発現しなかった（1001 試験、一覧表 16.2.8.5 及び 3002 試験、一覧表 16.2.8.6）。

2.7.4.4　バイタルサイン、身体的所見及び安全性に関連する他の観察項目

2.7.4.4.1　バイタルサイン及び身体所見

1001 試験及び 3002 試験でのバイタルサイン及び身体所見のデータを提示する。バイタルサインの結果は、ベースラインからの変化とともに、各パラメーターについて予定試験来院別に要約している。治験治療下で発現した臨床的に重要な可能性があるバイタルサイン値（5.3.5.1 項、1001 試験 CSR、付録 16.1.9、6.16.5 項、及び 5.3.5.2 項、3002 試験 CSR、付録 16.1.9、表 1 で定義）が認められた被験者の数及び割合は、試験来院別に表に要約している。治験責任医師により臨床的に重要なベースラインからの変化と判定された好ましくない身体所見があれば、AE として報告した。

1001 試験では、バイタルサインに意味のある変化は観察されなかった［高含量及び低含量の製剤で PK を比較した Part 3 又は 3002 試験を含む（1001 試験 CSR、12.5 項及び 1001 試験、表 14.3.5.2、並びに 3002 試験 CSR、12.10 項及び 3002 試験、表 14.3.5.2 参照）］。1001 試験の終了時に臨床的に重要な可能性があるバイタルサイン値の変化が被験者 2 名（1.1%）で報告された（拡張期血圧が高い日本人以外の被験者 1 名、拡張期血圧が低い日本人被験者 1 名；1001 試験、表 14.3.5.2 及び 1001 試験、一覧表 16.2.9.1）。

3002 試験では、臨床的に重要な可能性がある値のほとんどが孤発症例であり、臨床的に重要な可能性があるバイタルサイン値が特定の年齢群又は治療方法に集中する傾向は認められなかった（3002 試験、表 14.3.5.2、3002 試験、一覧表 16.2.9.1、及び 3002 試験、一覧表 16.2.9.2）。

2.7.4.5　特定の患者集団及び状況下における安全性

2.7.4.5.1　内因性要因

部分集団で評価した唯一の内因性要因は年齢であった。インヒビター産生が見られなかったため、部分集団解析は、1001 試験及び 3002 試験での TEAE 並びに局所忍容性データについてのみ実施した。これらの解析は、1001 試験及び 3002 試験のグローバル安全性解析集団で登録患者集団を対象に以下の年齢群で実施した。

- 1001 試験：12 歳以上 18 歳未満（N = 14）及び 18 歳以上 65 歳以下（N = 160）
- 3002 試験：0 歳以上 6 歳未満（N = 35）及び 6 歳以上 12 歳未満（N = 49）

日本人被験者の例数が少ないことを考慮して、日本人患者集団を対象とした AE の年齢群別の部分集団解析は実施していない。

2.7.4.5.1.1　年齢別の有害事象

有害事象の全発現率

グローバル患者集団における TEAE の発現率は、1001 試験で 12 歳以上 18 歳未満［10 名（71.4%）］及び 18 歳以上 65 歳以下［103 名（64.4%）］、3002 試験で 0 歳以上 6 歳未満［28 名（80.0%）］及び 6 歳以上 12 歳未満［36 名（73.5%）］の被験者で同程度であった（表 2.7.4-31）。治験薬と関連ありと判定された TEAE の割合も、1001 試験の両年齢群［12 歳以上 18 歳未満で 1 名（7.1%）、18 歳以上 65 歳以下で 12 名（7.5%）］（1001 試験、表 14.3.2.18）、及び 3002 試験の両年齢群［0 歳以上 6 歳未満で 0 名、6 歳以上 12 歳未満で 1 名（2.0%）］（3002 試験、表 14.3.1.1）で同程度であった。

表 2.7.4-31　TEAE の年齢別要約（安全性解析集団、1001 試験及び 3002 試験）

AE の種類	**被験者数（%）**			
	3002 試験		**1001 試験**	
	0 歳以上 6 歳未満（N = 35）	**6 歳以上 12 歳未満（N = 49）**	**12 歳以上 18 歳未満（N = 14）**	**18 歳以上 65 歳以下（N = 160）**
AE	28 (80.0)	36 (73.5)	10 (71.4)	111 (69.4)
TEAE	28 (80.0)	36 (73.5)	10 (71.4)	103 (64.4)
試験脱落に至った TEAE	0	1 (2.0)	0	0
TEAE の重症度				
軽度	22 (62.9)	30 (61.2)	7 (50.0)	87 (54.4)
中等度	11 (31.4)	14 (28.6)	3 (21.4)	40 (25.0)
重度	3 (8.6)	1 (2.0)	2 (14.3)	3 (1.9)
治験薬と関連ありと判定された TEAE	0	1 (2.0)	1 (7.1)	12 (7.5)
TEAE の転帰				
AE に伴う死亡	0	0	0	0
未回復	3 (8.6)	3 (6.1)	3 (21.4)	19 (11.9)
回復	26 (74.3)	35 (71.4)	10 (71.4)	94 (58.8)
回復したが後遺症あり	0	0	0	1 (0.6)
軽快	1 (2.9)	3 (6.1)	0	9 (5.6)
不明	1 (2.9)	1 (2.0)	0	0
SAE	4 (11.4)	5 (10.2)	2 (14.3)	6 (3.8)
TESAE	4 (11.4)	5 (10.2)	2 (14.3)	5 (3.1)
治験薬と関連ありと判定された TESAE	0	0	1 (7.1)	0

略語 : AE、有害事象 ; N、各試験の安全性解析集団における各年齢群内の被験者数 ; SAE、重篤な有害事象 ; TEAE、治験治療下で発現した有害事象 ; TESAE、治験治療下で発現した重篤な有害事象

注：1001 試験の AE 及び SAE には、発現日が治験薬投与開始日前及び外科的 substudy 期間中の事象を含めている。

引用：5.3.5.1 項、1001 試験 CSR、表 14.3.2.14、及び 5.3.5.2 項、3002 試験 CSR、表 14.3.1.1

器官別大分類別の有害事象

1001 試験及び 3002 試験で TEAE の発現率が最も高かった SOC は、全年齢群で「感染症および寄生虫症」であり、18 歳未満の被験者［3002 試験の 0 歳以上 6 歳未満で 18 名（51.4%）及び 6 歳以上 12 歳未満で 20 名（40.8%）、1001 試験の 12 歳以上 18 歳未満で 6 名（42.9%）］では 18 歳以上 65 歳以下の被験者［1001 試験で 39 名（24.4%）］より発現率が高かった（1001 試験、表 14.3.2.17、及び 3002 試験、表 14.3.1.4.1）。

基本語別の有害事象

PT レベルで最も頻度が高い TEAE は、18 歳未満の全年齢群では鼻咽頭炎［3002 試験の 0 歳以上 6 歳未満で 6 名（17.1%）、6 歳以上 12 歳未満で 8 名（16.3%）、1001 試験の 12 歳以上 18 歳未満で 2 名（14.3%）］、12 歳以上 18 歳未満の被験者ではインフルエンザ［1001 試験で 2 名（14.3%）］、18 歳以上 65 歳以下の被験者では関節痛［1001 試験で 17 名（10.6%）］であった（1001 試験、表 14.3.2.17、及び 3002 試験、表 14.3.1.15）。

2.7.4.5.1.2　年齢別の局所忍容性

局所忍容性の評価では、被験者による評価又は治験責任医師による評価のいずれにおいても、年齢群間で注目すべき差は見られず、すべての年齢群にわたり投与の 99%超で局所反応は報告されなかった。

1001 試験における被験者による局所忍容性の評価では、12 歳以上 18 歳未満の被験者で発現した事象の 99.7%、18 歳以上 65 歳以下の被験者で発現した事象の 99.3%で「なし」（局所反応は認められない）であった（1001 試験、表 14.3.3.1.2）。3002 試験における被験者による局所忍容性の評価では、0 歳以上 6 歳未満の被験者で発現した事象の 99.6%、6 歳以上 12 歳未満の被験者で発現した事象の 99.4%で「なし」であった（3002 試験、表 14.3.2.1.1）。

1001 試験における治験責任医師による局所忍容性の評価では、12 歳以上 18 歳未満の被験者で発現した事象の 100%、18 歳以上 65 歳以下の被験者で発現した事象の 99.8%で「なし」であった（1001 試験、表 14.3.3.2.2）。3002 試験では、0 歳以上 6 歳未満の被験者で発現した事象の 99.4%、6 歳以上 12 歳未満の被験者で発現した事象の 99.3%で「なし」であった（3002 試験 CSR、表 14.3.2.2.1）。

日本人被験者の例数が少ないことを考慮して、日本人患者集団を対象とした局所忍容性の年齢群別の部分集団解析は実施していない。

2.7.4.5.2　外因性要因

外因性要因の解析は実施していない。

2.7.4.5.3　薬物相互作用

本剤の代謝では、産生されたペプチド断片及びアミノ酸が比較的少なかったことから、本剤が代謝による薬物間相互作用に関与している可能性は低い。本剤は静脈内投与されるため、食物との相互作用が生じる可能性はない。

2.7.4.5.4　妊娠及び授乳時の使用

血友病 A は、主に男性に発生する疾患であり、FVIII が内因性タンパク質であることから、FVIII による胎児毒性作用は考えられない。したがって、構造異常、胚・胎児及び／又は乳児死亡、機能障害、成長異常などの発生毒性のリスクは評価できない。

1001 試験及び 3002 試験では、すべての被験者が男性であったことから、妊婦又は授乳婦に対して本剤を投与したデータは得られておらず、本剤の母乳への移行又は乳汁分泌に対する影響は不明である。

妊婦又は授乳婦に対する本剤の投与は、明らかに必要な場合のみに限定すべきである。

本剤のタンパク質（ヒト FVIII）は、その構造及び機能が十分に明らかにされている、天然に存在するタンパク質であるため生殖毒性試験は不要であった。さらに、単回投与毒性試験及び反復投与毒性試験中にリプロダクティブ・ヘルスへの影響を示唆する、あるいは生殖毒性、発生毒性、胚毒性又は若年毒性を検討する特殊な機構的毒性学試験の実施が必要となるような安全性シグナルは認められなかった（2.6.6.5 項を参照）。

2.7.4.5.5　過量投与

指示された本剤用量の 2 倍以上を投与したことに伴う TEAE が発現した場合は、過量投与とみなし、電子症例報告書に記録するとともに、72 時間以内に治験依頼者に報告するものとした（5.3.5.1 項、1001 試験 CSR、付録 16.1.1 の治験実施計画書 6.8 項参照）。

1001 試験では、指示された本剤用量の 2 倍以上を投与したことに伴う TEAE が日本人以外の被験者 1 名で報告された。この被験者では、出血エピソードに対して 35～50 IU/kg が指示されたが、ロット 10180841M（6054 IU）6 バイアルが投与され、111.3 IU/kg となった。被験者は、治験薬及びトラマドール塩酸塩（Tramal™）が投与された後に浮動性めまい、熱感、及びそう痒を訴えた。これらの事象はまとめて PT の「医薬品副作用」にコード化された。本事象は軽度かつ非重篤で、治験責任医師により治験薬と関連なし（むしろ Tramal™に起因する）と判定された（1001 試験、表 14.3.2.13 及び一覧表 16.2.7.1 参照）。

3002 試験では、指示された本剤用量の 2 倍以上を投与したことに伴う事象は見られなかった（3002 試験、表 14.3.6）。

2.7.4.5.6　薬物乱用

本剤を投与した被験者で、乱用、誤用、多幸症、又は嗜癖の報告はなかった。非合法目的での本剤の使用は確認されていない。そのため、非合法目的で本剤が誤用される可能性は小さいと考えられる。

2.7.4.5.7　離脱症状及び反跳現象

離脱症状及び反跳現象に関する安全性データは得られていない。

2.7.4.5.8　自動車運転及び機械操作に対する影響及び精神機能の障害

自動車運転及び機械操作の能力に対する本剤の影響に関する試験は実施していない。

2.7.4.6　市販後データ

現時点までに得られている市販後の情報では、新たな安全性の懸念は特定されていない。

2.7.4.7　結論

全体として、1001 試験及び 3002 試験から得られたデータでは、本剤が重度血友病 A の被験者に対して安全かつ忍容性は良好であることが示され、日本人とグローバル患者集団との間で安全性及び忍容性プロファイルに意味のある違いは見られなかった。成人被験者 174 名及び小児被験者 84 名での本剤の累積投与日数は、成人被験者では平均 8.5 箇月の試験期間（最大 25 箇月間で 395 ED）、小児被験者では平均 6.0 箇月の試験期間（最大 11 箇月間で 142 ED）で 19,000 ED を超えた。合計 185 名の被験者が 50 ED 以上を達成し、EMA 2011 ガイドラインによる PTP に対する全曝露量の要件は満たされ、すべての年齢群でそれを上回った。PTP では、本剤の投与中に（100 ED 以上に達した被験者 60 名においても）、FVIII に対するインヒビター産生が認められた症例はなく、CHO 細胞由来タンパク質に対する抗体産生が認められた症例もなかった。1001 試験及び 3002 試験で認められた非中和 ADA の発現率は、文献で公表された血友病患者及び一般集団における発現率を上回らなかった（Lavigne-Lissalde et al., 2007; Batlle et al., 1996; Klintman et al., 2013）。概して、ADA の臨床的意義は依然として不明である（Lavigne-Lissalde et al., 2007; Batlle et al., 1996; Lebreton et al., 2011）。1001 試験及び 3002 試験期間中のいずれかの時点で検査結果が陽性となった被験者のうち、治験依頼者のメディカルレビューにより、報告された非中和 ADA のいずれかと関係していると判定された TEAE が認められた被験者はいなかった。

試験の中止に至った AE の全発現率は、被験者の 1%未満（1001 試験 0%、3002 試験 1.2%）であった。事前に規定した SMQ 検索により特定された AESI（過敏症／アナフィラキシー反応及び TEE）に関する治験依頼者のメディカルレビューにより、アナフィラキシー反応又は TEE であると判定された事象はなく、1001 試験及び 3002 試験で過敏症反応に関係している可能性があると判定された TEAE の発現率は低かった（1001 試験 4.5%、3002 試験 1.1%）。

1001 試験及び 3002 試験における TEAE の大多数が軽度又は中等度であり、本剤の投与と関連ありと判定されたものは少なかった。1001 試験及び 3002 試験で TESAE 又は 3001 試験で SAE が報告された被験者は少なかった（被験者全体での約 6%）。死亡例はなかった。これらの試験で観察された安全性プロファイルは、検討した各年齢群で一致しており、予測されていない安全性所見は認められなかった。

さらに、TEAE、治験薬と関連のある TEAE 及び TESAE の経時的発現率の解析では、1001 試験の最大 25 箇月の曝露期間で遅発性の TEAE の所見は認められなかった。

局所反応が見られなかった投与の割合は 99%を超えていた。

結論として、本剤では、検討したすべての年齢群で優れた安全性プロファイルが認められた。さらに、日本人患者集団とグローバル患者集団との間で本剤の安全性プロファイルに意味のある違いは認められなかった。1001 試験及び 3002 試験では、0～65 歳の PTP の累積投与日数は 19,000 ED を超えていたが、インヒビター産生が記録された症例は無く、最大 25 箇月の投与期間を通して遅発性 AE の徴候も認められなかった。全体で、TEAE 及び TESAE の数は少なく、本剤を投与した 258 名の被験者で、治験薬と関連ありと判定された TESAE は 1 件のみ（過敏症）であった。1001 試験及び 3002 試験で観察された AE／SAE のプロファイルは、定期的な投与及び出血エピソードに対するオンデマンド療法に関しても（Valentino et al., 2012; Mahlangu et al., 2014; Shapiro, 2007; Klukowska et al., 2015; Young et al., 2015; Kulkarni et al., 2013）、外科処置に関しても（Mahlangu et al., 2014; Shapiro, 2007）、現在利用可能な他の製品で明らかにされたプロファイルと一致している。

なお、実施中の 3001 試験では、本剤を投与された PUP 12 例中 5 例でインヒビターが発現した（粗発現率：41.7%、信頼区間：13.8%～69.6%）。本試験での 5 例のインヒビター発現が、公表文献にて報告されているインヒビター発現率からの真の上昇を示すものなのか、または被験者のインヒビター発現のリスクが高かったのかについては、エビデンスが不足しているため結論づけることは困難である。また、臨床試験及び製造販売開始後に本剤の投与を受けた PTP において、インヒビター発現は報告されていない。したがって、本剤においてベネフィットがリスクを上回ることに変わりはない。

2.7.4.8　付録

表 2.7.4-32　潜在的副作用の頻度（グローバル安全性解析集団、1001 試験及び 3002 試験）

		被験者数（%） 事象数	
		グローバル患者集団	
器官別大分類	基本語	（N = 258）	
神経系障害	浮動性めまい	2 (0.8)	2
	錯感覚	1 (0.4)	1
免疫系障害	過敏症	3 (1.2)	4
皮膚および皮下組織障害	紅斑	1 (0.4)	1
	そう痒症	1 (0.4)	1
	発疹	1 (0.4)	1
一般・全身障害および投与部位の状態	悪寒	1 (0.4)	2
	熱感	1 (0.4)	1
	注射部位疼痛	1 (0.4)	1
	発熱	1 (0.4)	1

注：
本表は、規定の事象が 1 件以上認められた被験者の数及び割合を示している。
MedDRA の基本語「薬物過敏症」（1 名の被験者で 1 件）は基本語「過敏症」に含めている。

1001 試験 CSR、表 14.1.6.1: Medical/Surgical History

1001 試験 CSR、表 14.1.9.2: Medications Taken During the Surgical Period

1001 試験 CSR、表 14.1.13: Preventive and Additional Doses

1001 試験 CSR、表 14.2.15.17.1: Part 3 – FVIII activities of CSL627, 3000 and 250 IU/vial strengths CS baseline uncorrected; initial PK

1001 試験 CSR、表 14.3.1.1: Inhibitors

1001 試験 CSR、表 14.3.2.4: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

1001 試験 CSR、表 14.3.2.5: Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

1001 試験 CSR、表 14.3.2.13: Non-Serious Medical Events of Special Interest

1001 試験 CSR、表 14.3.2.17: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age

1001 試験 CSR、表 14.3.2.18: Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age

1001 試験 CSR、表 14.3.3.1.2: Local Tolerability – Subject Assessment by Age

1001 試験 CSR、表 14.3.3.2.2: Local Tolerability – Investigator Assessment by Age

1001 試験 CSR、表 14.3.4.1: Hematology Results and Changes from Baseline at Each Visit

1001 試験 CSR、表 14.3.4.2: Biochemistry Results and Changes from Baseline at Each Visit

1001 試験 CSR、表 14.3.4.3: Hematology Changes from Baseline to Lowest, Highest and Final Value

1001 試験 CSR、表 14.3.4.4: Biochemistry Changes from Baseline to Lowest, Highest and Final Value

1001 試験 CSR、表 14.3.4.5: Hematology Treatment-Emergent Clinically Significant Abnormal Results

1001 試験 CSR、表 14.3.4.6: Biochemistry Treatment-Emergent Clinically Significant Abnormal Results

1001 試験 CSR、表 14.3.5.2: Vital Signs Treatment-Emergent Potentially Clinically Significant Results

1001 試験、表 14.1.5.1J: Japanese Demographics

1001 試験、表 14.1.6.2J: Japanese Medical/Surgical History

1001 試験、表 14.1.13J: Japanese Preventive and Additional Doses

1001 試験、表 14.3.2.1J: Summary of Adverse Events

1001 試験、表 14.3.2.32J: Summary of Treatment-Emergent Adverse Event Over Time

1001 試験、表 14.3.2.33J: Incidence of Treatment-Emergent Adverse Events by Preferred Term Over Time

1001 試験、表 14.3.2.34J: Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time

3002 試験 CSR、表 14.1.5.1.1: Medical/Surgical History

3002 試験 CSR、表 14.1.5.2: Medical/Surgical History Related to Viral Diseases

3002 試験 CSR、表 14.1.8.5.1: Extent of Exposure to CSL627

3002 試験 CSR、表 14.1.8.7.1: Preventive and Additional Doses

3002 試験 CSR、表 14.1.9.1: Concomitant Medications

3002 試験 CSR、表 14.3.1.1: Summary of Adverse Events

3002 試験 CSR、表 14.3.1.4.1: Treatment Emergent Adverse Events by System Organ Class and Preferred Term

3002 試験 CSR、表 14.3.1.5: Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term

3002 試験 CSR、表 14.3.1.10: Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

3002 試験 CSR、表 14.3.1.15: Treatment Emergnet Adverse Events in Decreasing Frequency of Preferred Term

3002 試験 CSR、表 14.3.2.1.1: Local Tolerability – Subject Assessment

3002 試験 CSR、表 14.3.2.2.1: Local Tolerability – Investigator Assessment

3002 試験 CSR、表 14.3.3.1.1: Summary of Inhibitors Verified Upon Re-Testing (Excluding Subjects with Inhibitors at Baseline)

3002 試験 CSR、表 14.3.3.1.2: Summary of Inhibitor Assay Tests by Visit

3002 試験 CSR、表 14.3.3.2.2: Summary of Anti-rFVIII Antibodies (Age 0 to <6 Years)

3002 試験 CSR、表 14.3.3.2.3: Summary of Anti-rFVIII Antibodies (Age ≥6 to <12 Years)

3002 試験 CSR、表 14.3.4.1: Hematology Results and Changes from Baseline at Each Visit

3002 試験 CSR、表 14.3.4.2: Biochemistry Results and Changes from Baseline at Each Visit

3002 試験 CSR、表 14.3.4.3: Hematology Changes from Baseline to Lowest, Highest and Final Value

3002 試験 CSR、表 14.3.4.4: Biochemistry Changes from Baseline to Lowest, Highest and Final Value

3002 試験 CSR、表 14.3.4.5: Hematology Treatment-Emergent Clinically Significant Abnormal Results

3002 試験 CSR、表 14.3.4.6: Biochemistry Treatment-Emergent Clinically Significant Abnormal Results

3002 試験 CSR、表 14.3.5.2: Vital Signs Treatment-Emergent Potentially Clinically Significant Results

3002 試験 CSR、表 14.3.6: Medical Events of Special Interest

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Any Medical/Surgical History	124 (71.3)	159 (91.4)
Musculoskeletal and connective tissue disorders	15 (8.6)	119 (68.4)
Haemophilic arthropathy	4 (2.3)	87 (50.0)
Joint range of motion decreased	0	9 (5.2)
Haemarthrosis	0	9 (5.2)
Arthralgia	1 (0.6)	7 (4.0)
Synovitis	3 (1.7)	4 (2.3)
Muscle atrophy	0	5 (2.9)
Joint crepitation	1 (0.6)	4 (2.3)
Arthritis	0	5 (2.9)
Arthropathy	1 (0.6)	4 (2.3)
Tendon disorder	1 (0.6)	3 (1.7)
Joint contracture	0	4 (2.3)
Muscle haemorrhage	4 (2.3)	0
Osteoarthritis	1 (0.6)	3 (1.7)
Joint ankylosis	0	3 (1.7)
Back pain	2 (1.1)	1 (0.6)
Joint swelling	0	2 (1.1)
Osteoporosis	0	2 (1.1)
Spinal osteoarthritis	0	2 (1.1)

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Musculoskeletal and connective tissue disorders (continued)		
Amyotrophy	0	1 (0.6)
Bone cyst	0	1 (0.6)
Bone deformity	0	1 (0.6)
Elbow deformity	0	1 (0.6)
Epiphyseal disorder	1 (0.6)	0
Exostosis	0	1 (0.6)
Intervertebral disc protrusion	0	1 (0.6)
Joint stiffness	1 (0.6)	0
Knee deformity	1 (0.6)	0
Limb asymmetry	0	1 (0.6)
Muscle spasms	0	1 (0.6)
Osteoarthropathy	0	1 (0.6)
Osteochondrosis	0	1 (0.6)
Osteonecrosis	0	1 (0.6)
Osteopenia	0	1 (0.6)
Pathological fracture	0	1 (0.6)
Polyarthritis	0	1 (0.6)
Soft tissue haemorrhage	0	1 (0.6)
Synovial cyst	0	1 (0.6)
Tendonitis	0	1 (0.6)
Trigger finger	0	1 (0.6)

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Congenital, familial and genetic disorders	1 (0.6)	103 (59.2)
Factor VIII deficiency	0	101 (58.0)
Glucose-6-phosphate dehydrogenase deficiency	0	2 (1.1)
Thalassaemia alpha	0	2 (1.1)
Gilbert's syndrome	0	1 (0.6)
Pectus excavatum	1 (0.6)	0
Thalassaemia trait	0	1 (0.6)
Surgical and medical procedures	94 (54.0)	7 (4.0)
Knee arthroplasty	21 (12.1)	2 (1.1)
Synovectomy	18 (10.3)	0
Synoviorthesis	12 (6.9)	0
Tooth extraction	9 (5.2)	0
Appendicectomy	8 (4.6)	0
Knee operation	7 (4.0)	0
Circumcision	5 (2.9)	2 (1.1)
Cholecystectomy	6 (3.4)	0
Hip arthroplasty	4 (2.3)	1 (0.6)
Arthrodesis	5 (2.9)	1 (0.6)
Central venous catheter removal	4 (2.3)	0
Central venous catheterisation	3 (1.7)	0
Elbow operation	3 (1.7)	0

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Surgical and medical procedures (continued)		
Joint arthroplasty	3 (1.7)	0
Ankle arthroplasty	3 (1.7)	0
Wisdom teeth removal	2 (1.1)	0
Catheter placement	2 (1.1)	0
Adenoidectomy	2 (1.1)	0
Inguinal hernia repair	2 (1.1)	0
Removal of internal fixation	2 (1.1)	0
Tendon operation	2 (1.1)	0
Tonsillectomy	2 (1.1)	0
Cataract operation	1 (0.6)	0
Corneal transplant	1 (0.6)	0
Fracture treatment	1 (0.6)	0
Tenotomy	1 (0.6)	0
Abscess drainage	1 (0.6)	0
Ankle operation	1 (0.6)	0
Bone lesion excision	1 (0.6)	0
Cholelithotomy	1 (0.6)	0
Cyst removal	1 (0.6)	0
Debridement	1 (0.6)	0
Dental operation	1 (0.6)	0
Epiphyseal surgery	1 (0.6)	0

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Surgical and medical procedures (continued)		
External fixation of fracture	1 (0.6)	0
Eyeglasses therapy	0	1 (0.6)
Finger repair operation	1 (0.6)	0
Gastric polypectomy	1 (0.6)	0
Hepatitis B immunisation	0	1 (0.6)
Internal fixation of fracture	1 (0.6)	0
Laparotomy	1 (0.6)	0
Lithotripsy	1 (0.6)	0
Mastectomy	1 (0.6)	0
Medical device removal	1 (0.6)	0
Meniscus operation	1 (0.6)	0
Mole excision	1 (0.6)	0
Orchidectomy	1 (0.6)	0
Pilonidal sinus repair	1 (0.6)	0
Polypectomy	1 (0.6)	0
Removal of epiphyseal fixation	1 (0.6)	0
Renal stone removal	1 (0.6)	0
Spermatocele excision	1 (0.6)	0
Spinal laminectomy	1 (0.6)	0
Suture insertion	1 (0.6)	0
Thoracic operation	1 (0.6)	0

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Surgical and medical procedures (continued)		
Tongue tie operation	1 (0.6)	0
Vasectomy	1 (0.6)	0
Infections and infestations	38 (21.8)	54 (31.0)
Hepatitis C	17 (9.8)	41 (23.6)
HIV infection	0	18 (10.3)
Hepatitis B	6 (3.4)	4 (2.3)
Tonsillitis	3 (1.7)	0
Herpes zoster	2 (1.1)	0
Subcutaneous abscess	2 (1.1)	0
Upper respiratory tract infection	2 (1.1)	0
Urinary tract infection	1 (0.6)	1 (0.6)
Skin infection	1 (0.6)	0
Anal abscess	1 (0.6)	0
Appendicitis	1 (0.6)	0
Arthritis bacterial	1 (0.6)	0
Cellulitis orbital	1 (0.6)	0
Chronic sinusitis	0	1 (0.6)
Diverticulitis	0	1 (0.6)
Gonorrhoea	1 (0.6)	0
Hepatitis A	1 (0.6)	0

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Infections and infestations (continued)		
Hepatitis G	0	1 (0.6)
Hepatitis post transfusion	0	1 (0.6)
Herpes simplex	0	1 (0.6)
Lower respiratory tract infection	1 (0.6)	0
Mumps	1 (0.6)	0
Oesophageal candidiasis	0	1 (0.6)
Otitis externa	1 (0.6)	0
Pharyngitis	1 (0.6)	0
Pharyngotonsillitis	1 (0.6)	0
Pilonidal cyst	1 (0.6)	0
Pneumonia	1 (0.6)	0
Pulmonary tuberculosis	1 (0.6)	0
Sepsis	1 (0.6)	0
Sinusitis	0	1 (0.6)
Trichophytosis	1 (0.6)	0
Varicella	1 (0.6)	0
Gastrointestinal disorders	12 (6.9)	20 (11.5)
Abdominal pain	3 (1.7)	0
Constipation	1 (0.6)	2 (1.1)
Dental caries	0	3 (1.7)

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Gastrointestinal disorders (continued)		
Duodenal ulcer	2 (1.1)	1 (0.6)
Diarrhoea	2 (1.1)	0
Gingivitis	1 (0.6)	1 (0.6)
Haemorrhoids	0	2 (1.1)
Retroperitoneal haematoma	2 (1.1)	0
Abdominal hernia	0	1 (0.6)
Abdominal tenderness	0	1 (0.6)
Crohn's disease	0	1 (0.6)
Dyspepsia	0	1 (0.6)
Dysphagia	1 (0.6)	0
Gastric ulcer	0	1 (0.6)
Gastritis	0	1 (0.6)
Gastrointestinal haemorrhage	1 (0.6)	0
Gastrooesophageal reflux disease	0	1 (0.6)
Haemorrhoidal haemorrhage	0	1 (0.6)
Inguinal hernia	1 (0.6)	0
Irritable bowel syndrome	0	1 (0.6)
Lip swelling	1 (0.6)	0
Mallory-Weiss syndrome	0	1 (0.6)
Nausea	0	1 (0.6)
Pancreatitis	1 (0.6)	0

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Gastrointestinal disorders (continued)		
Pancreatitis chronic	0	1 (0.6)
Peptic ulcer perforation	1 (0.6)	0
Periodontitis	0	1 (0.6)
Tooth disorder	0	1 (0.6)
Vomiting	0	1 (0.6)
Vascular disorders	3 (1.7)	20 (11.5)
Hypertension	0	18 (10.3)
Haematoma	3 (1.7)	0
Phlebitis superficial	0	1 (0.6)
Varicose vein	0	1 (0.6)
Injury, poisoning and procedural complications	17 (9.8)	5 (2.9)
Femur fracture	5 (2.9)	1 (0.6)
Concussion	5 (2.9)	0
Hand fracture	2 (1.1)	1 (0.6)
Clavicle fracture	2 (1.1)	0
Extradural haematoma	2 (1.1)	0
Multiple fractures	2 (1.1)	0
Post-traumatic neck syndrome	1 (0.6)	0
Contusion	0	1 (0.6)

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Injury, poisoning and procedural complications (continued)		
Femoral neck fracture	1 (0.6)	0
Humerus fracture	0	1 (0.6)
Joint dislocation	0	1 (0.6)
Joint injury	1 (0.6)	0
Laceration	1 (0.6)	0
Ligament rupture	0	1 (0.6)
Ligament sprain	1 (0.6)	0
Lower limb fracture	1 (0.6)	0
Tibia fracture	1 (0.6)	0
Traumatic haematoma	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders	6 (3.4)	16 (9.2)
Asthma	1 (0.6)	6 (3.4)
Epistaxis	1 (0.6)	3 (1.7)
Rhinitis allergic	0	3 (1.7)
Bronchitis chronic	0	2 (1.1)
Cough	1 (0.6)	0
Dyspnoea	1 (0.6)	0
Haemothorax	1 (0.6)	0
Nasal dryness	0	1 (0.6)
Pharyngeal haematoma	1 (0.6)	0

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Respiratory, thoracic and mediastinal disorders (continued)		
Rhinorrhoea	0	1 (0.6)
Sleep apnoea syndrome	0	1 (0.6)
Throat tightness	1 (0.6)	0
Investigations	11 (6.3)	7 (4.0)
Arthroscopy	6 (3.4)	0
Blood creatinine increased	0	2 (1.1)
Hepatitis C antibody positive	1 (0.6)	1 (0.6)
Aspiration joint	1 (0.6)	0
Aspiration pleural cavity	1 (0.6)	0
Blood bilirubin increased	0	1 (0.6)
Blood cholesterol increased	0	1 (0.6)
Bronchoscopy	1 (0.6)	0
Chlamydia test positive	1 (0.6)	0
Colonoscopy	1 (0.6)	0
Hepatic enzyme increased	0	1 (0.6)
Hepatitis C virus test positive	0	1 (0.6)
Platelet count decreased	0	1 (0.6)
Weight increased	1 (0.6)	0

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Nervous system disorders	6 (3.4)	14 (8.0)
Headache	0	6 (3.4)
Epilepsy	1 (0.6)	1 (0.6)
Haemorrhage intracranial	2 (1.1)	0
Migraine	0	2 (1.1)
Cerebral haemorrhage	1 (0.6)	0
Autonomic nervous system imbalance	0	1 (0.6)
Carpal tunnel syndrome	1 (0.6)	0
Hypotonia	0	1 (0.6)
Lumbar radiculopathy	0	1 (0.6)
Nystagmus	0	1 (0.6)
Syringomyelia	0	1 (0.6)
VIIth nerve paralysis	1 (0.6)	0
Immune system disorders	0	17 (9.8)
Drug hypersensitivity	0	7 (4.0)
Seasonal allergy	0	7 (4.0)
Multiple allergies	0	2 (1.1)
House dust allergy	0	1 (0.6)

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n	 (%)	Active History (N=174) n	 (%)
Metabolism and nutrition disorders	2	(1.1)	14	(8.0)
Hypercholesterolaemia	0		4	(2.3)
Vitamin D deficiency	0		3	(1.7)
Diabetes mellitus	0		2	(1.1)
Gout	0		2	(1.1)
Obesity	0		2	(1.1)
Central obesity	0		1	(0.6)
Dyslipidaemia	0		1	(0.6)
Hyperhomocysteinaemia	0		1	(0.6)
Hypertriglyceridaemia	0		1	(0.6)
Hyperuricaemia	1	(0.6)	0	
Vitamin K deficiency	1	(0.6)	0	
Skin and subcutaneous tissue disorders	4	(2.3)	11	(6.3)
Acne	2	(1.1)	3	(1.7)
Scar	0		2	(1.1)
Alopecia	0		1	(0.6)
Dermal cyst	1	(0.6)	0	
Dermatitis atopic	0		1	(0.6)
Drug eruption	1	(0.6)	0	
Dry skin	1	(0.6)	0	
Hyperkeratosis	0		1	(0.6)

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Skin and subcutaneous tissue disorders (continued)		
Leukoderma	0	1 (0.6)
Neurodermatitis	0	1 (0.6)
Pruritus	1 (0.6)	0
Psoriasis	0	1 (0.6)
Rash	0	1 (0.6)
Skin discolouration	0	1 (0.6)
Hepatobiliary disorders	4 (2.3)	9 (5.2)
Cholelithiasis	2 (1.1)	2 (1.1)
Hepatic function abnormal	0	2 (1.1)
Hepatic steatosis	1 (0.6)	1 (0.6)
Hyperbilirubinaemia	0	2 (1.1)
Cholecystitis	1 (0.6)	0
Cholecystitis chronic	0	1 (0.6)
Chronic hepatitis	0	1 (0.6)
Renal and urinary disorders	7 (4.0)	5 (2.9)
Nephrolithiasis	2 (1.1)	3 (1.7)
Calculus urinary	2 (1.1)	2 (1.1)
Haematuria	2 (1.1)	0
Calculus bladder	1 (0.6)	0
Renal haemorrhage	1 (0.6)	0

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Psychiatric disorders	0	10 (5.7)
Insomnia	0	3 (1.7)
Anxiety	0	2 (1.1)
Depression	0	2 (1.1)
Attention deficit/hyperactivity disorder	0	1 (0.6)
Neurosis	0	1 (0.6)
Seasonal affective disorder	0	1 (0.6)
Eye disorders	4 (2.3)	6 (3.4)
Cataract	1 (0.6)	1 (0.6)
Conjunctivitis allergic	0	2 (1.1)
Blindness unilateral	0	1 (0.6)
Eye pruritus	1 (0.6)	0
Keratoconus	0	1 (0.6)
Myopia	0	1 (0.6)
Optic atrophy	0	1 (0.6)
Retinopathy	1 (0.6)	0
Strabismus	1 (0.6)	0

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Blood and lymphatic system disorders	3 (1.7)	5 (2.9)
Iron deficiency anaemia	1 (0.6)	2 (1.1)
Anaemia	1 (0.6)	0
Anaemia haemolytic autoimmune	1 (0.6)	0
Haemorrhagic anaemia	0	1 (0.6)
Pancytopenia	0	1 (0.6)
Thrombocytopenia	0	1 (0.6)
Reproductive system and breast disorders	4 (2.3)	2 (1.1)
Erectile dysfunction	0	1 (0.6)
Gynaecomastia	1 (0.6)	0
Monorchidism	1 (0.6)	0
Pelvic haematoma	1 (0.6)	0
Sexual dysfunction	1 (0.6)	0
Testicular atrophy	0	1 (0.6)
Cardiac disorders	3 (1.7)	2 (1.1)
Angina pectoris	2 (1.1)	0
Atrial fibrillation	0	1 (0.6)
Bundle branch block left	0	1 (0.6)
Cardiac failure chronic	0	1 (0.6)
Cardiomyopathy	1 (0.6)	0
Palpitations	1 (0.6)	0

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Social circumstances	0	5 (2.9)
Tattoo	0	3 (1.7)
Cosmetic body piercing	0	1 (0.6)
Tobacco user	0	1 (0.6)
Endocrine disorders	0	3 (1.7)
Goitre	0	2 (1.1)
Hypothyroidism	0	1 (0.6)
General disorders and administration site conditions	1 (0.6)	2 (1.1)
Fatigue	0	1 (0.6)
Oedema peripheral	1 (0.6)	0
Pain	0	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.7)	0
Angiofibroma	1 (0.6)	0
Gastrointestinal tract adenoma	1 (0.6)	0
Melanocytic naevus	1 (0.6)	0

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.6.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History (N=174) n (%)	Active History (N=174) n (%)
Ear and labyrinth disorders	0	1 (0.6)
Hearing impaired	0	1 (0.6)
Pregnancy, puerperium and perinatal conditions	0	1 (0.6)
Premature baby	0	1 (0.6)

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the respective group
[3] Medical/Surgical histories were coded using MedDRA Version 14.1

Table 14.1.9.2 Medications Taken During the Surgical Period
(Surgical Population)

ATC Class Preferred Drug Name	Total (N=13) n (%)
Any Surgical Period Medication	13 (100.0)
OTHER GENERAL ANESTHETICS	10 (76.9)
PROPOFOL	10 (76.9)
KETAMINE HYDROCHLORIDE	1 (7.7)
FIRST-GENERATION CEPHALOSPORINS	9 (69.2)
CEFAZOLIN SODIUM	7 (53.8)
CEFAZOLIN	2 (15.4)
ANILIDES	8 (61.5)
PARACETAMOL	8 (61.5)
PHENYLPIPERIDINE DERIVATIVES	8 (61.5)
FENTANYL	7 (53.8)
PETHIDINE	2 (15.4)
FENTANYL CITRATE	1 (7.7)

Source: Listing 16.2.4.8
Notes: [1] Surgical Period medications are all medications that started during the surgical period of the study
[2] Table presents number and percentage of subjects [(n (%)]
[3] Percentages are based on the number of subjects in the respective group.
[4] Medications were coded using the WHO drug dictionary September 2011

Table 14.1.9.2 Medications Taken During the Surgical Period
(Surgical Population)

ATC Class Preferred Drug Name	Total (N=13) n (%)
NATURAL OPIUM ALKALOIDS	7 (53.8)
MORPHINE	6 (46.2)
HYDROMORPHONE	1 (7.7)
OXYCODONE	1 (7.7)
TYLOX /00446701/	1 (7.7)
OTHER OPIOIDS	7 (53.8)
TRAMADOL HYDROCHLORIDE	3 (23.1)
TRAMADOL	3 (23.1)
ULTRACET	1 (7.7)
PROTON PUMP INHIBITORS	6 (46.2)
OMEPRAZOLE	4 (30.8)
PANTOPRAZOLE SODIUM SESQUIHYDRATE	1 (7.7)
ESOMEPRAZOLE	1 (7.7)
RABEPRAZOLE	1 (7.7)
AMIDES	5 (38.5)
BUPIVACAINE HYDROCHLORIDE	3 (23.1)
LIDOCAINE	2 (15.4)
BUPIVACAINE	1 (7.7)

Source: Listing 16.2.4.8
Notes: [1] Surgical Period medications are all medications that started during the surgical period of the study
[2] Table presents number and percentage of subjects [(n (%)]
[3] Percentages are based on the number of subjects in the respective group.
[4] Medications were coded using the WHO drug dictionary September 2011

Table 14.1.9.2 Medications Taken During the Surgical Period
(Surgical Population)

ATC Class Preferred Drug Name	Total (N=13) n (%)
SEROTONIN (5HT3) ANTAGONISTS	5 (38.5)
ONDANSETRON	5 (38.5)
GLUCOCORTICOIDS	5 (38.5)
DEXAMETHASONE	5 (38.5)
HEPARIN GROUP	4 (30.8)
ENOXAPARIN	3 (23.1)
TINZAPARIN	1 (7.7)
OTHER QUATERNARY AMMONIUM COMPOUNDS	4 (30.8)
ROCURONIUM BROMIDE	2 (15.4)
CISATRACURIUM BESILATE	1 (7.7)
ROCURONIUM	1 (7.7)
BENZODIAZEPINE DERIVATIVES	3 (23.1)
MIDAZOLAM	2 (15.4)
OXAZEPAM	1 (7.7)

Source: Listing 16.2.4.8
Notes: [1] Surgical Period medications are all medications that started during the surgical period of the study
[2] Table presents number and percentage of subjects [(n (%)]
[3] Percentages are based on the number of subjects in the respective group.
[4] Medications were coded using the WHO drug dictionary September 2011

Table 14.1.9.2 Medications Taken During the Surgical Period
(Surgical Population)

ATC Class Preferred Drug Name	Total (N=13) n (%)
PROPULSIVES	3 (23.1)
METOCLOPRAMIDE	2 (15.4)
METOCLOPRAMIDE HYDROCHLORIDE	1 (7.7)
SALT SOLUTIONS	2 (15.4)
SODIUM CHLORIDE	2 (15.4)
SECOND-GENERATION CEPHALOSPORINS	2 (15.4)
CEFUROXIME	2 (15.4)
ANTICHOLINESTERASES	2 (15.4)
NEOSTIGMINE	1 (7.7)
NEOSTIGMINE BROMIDE	1 (7.7)
COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE	2 (15.4)
AUGMENTIN /00756801/	1 (7.7)
SPEKTRAMOX	1 (7.7)
H2-RECEPTOR ANTAGONISTS	2 (15.4)
RANITIDINE HYDROCHLORIDE	2 (15.4)

Source: Listing 16.2.4.8
Notes: [1] Surgical Period medications are all medications that started during the surgical period of the study
[2] Table presents number and percentage of subjects [(n (%)]
[3] Percentages are based on the number of subjects in the respective group.
[4] Medications were coded using the WHO drug dictionary September 2011

Table 14.1.9.2 Medications Taken During the Surgical Period
(Surgical Population)

ATC Class Preferred Drug Name	Total (N=13) n (%)
OTHER ANALGESICS AND ANTIPYRETICS	2 (15.4)
NEFOPAM	2 (15.4)
PROPIONIC ACID DERIVATIVES	2 (15.4)
DEXKETOPROFEN TROMETAMOL	1 (7.7)
KETOPROFEN	1 (7.7)
PYRAZOLONES	1 (7.7)
METAMIZOLE SODIUM	1 (7.7)
INSULINS AND ANALOGUES FOR INJECTION, INTERMEDIATE-ACTING COMBINED WITH FAST-ACTING	1 (7.7)
NOVOMIX	1 (7.7)
IRON PREPARATIONS	1 (7.7)
IRON	1 (7.7)
OTHER AMINOGLYCOSIDES	1 (7.7)
GENTAMICIN	1 (7.7)

Source: Listing 16.2.4.8
Notes: [1] Surgical Period medications are all medications that started during the surgical period of the study
[2] Table presents number and percentage of subjects [(n (%)]
[3] Percentages are based on the number of subjects in the respective group.
[4] Medications were coded using the WHO drug dictionary September 2011

Table 14.1.9.2 Medications Taken During the Surgical Period
(Surgical Population)

ATC Class Preferred Drug Name	Total (N=13) n	 (%)
OTHER ANTIBIOTICS FOR TOPICAL USE	1	(7.7)
BACITRACIN	1	(7.7)
ACE INHIBITORS, PLAIN	1	(7.7)
PERINDOPRIL ARGININE	1	(7.7)
ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	1	(7.7)
NEODOLPASSE	1	(7.7)
AMINO ACIDS	1	(7.7)
TRANEXAMIC ACID	1	(7.7)
ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREATMENT	1	(7.7)
CHLORHEXIDINE GLUCONATE	1	(7.7)
BARBITURATES, PLAIN	1	(7.7)
METHOHEXITAL	1	(7.7)
BELLADONNA ALKALOIDS, TERTIARY AMINES	1	(7.7)
ATROPINE	1	(7.7)

Source: Listing 16.2.4.8
Notes: [1] Surgical Period medications are all medications that started during the surgical period of the study
[2] Table presents number and percentage of subjects [(n (%)]
[3] Percentages are based on the number of subjects in the respective group.
[4] Medications were coded using the WHO drug dictionary September 2011

Table 14.1.9.2 Medications Taken During the Surgical Period
(Surgical Population)

ATC Class Preferred Drug Name	Total (N=13) n	 (%)
BETA-LACTAMASE INHIBITORS	1	(7.7)
CLAVULANIC ACID	1	(7.7)
CHOLINE DERIVATIVES	1	(7.7)
SUXAMETHONIUM CHLORIDE	1	(7.7)
CONTACT LAXATIVES	1	(7.7)
COLOXYL WITH SENNA	1	(7.7)
COXIBS	1	(7.7)
CELECOXIB	1	(7.7)
DIHYDROPYRIDINE DERIVATIVES	1	(7.7)
NIFEDIPINE	1	(7.7)
DIPHENYLMETHANE DERIVATIVES	1	(7.7)
HYDROXYZINE	1	(7.7)
DIPHENYLPROPYLAMINE DERIVATIVES	1	(7.7)
PIRITRAMIDE	1	(7.7)

Source: Listing 16.2.4.8
Notes: [1] Surgical Period medications are all medications that started during the surgical period of the study
[2] Table presents number and percentage of subjects [(n (%)]
[3] Percentages are based on the number of subjects in the respective group.
[4] Medications were coded using the WHO drug dictionary September 2011

Table 14.1.9.2 Medications Taken During the Surgical Period
(Surgical Population)

ATC Class Preferred Drug Name	Total (N=13) n	 (%)
IMIDAZOLINE RECEPTOR AGONISTS	1	(7.7)
CLONIDINE HYDROCHLORIDE	1	(7.7)
INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	1	(7.7)
INSULIN PORCINE	1	(7.7)
INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING	1	(7.7)
INSULIN GLARGINE	1	(7.7)
IRON BIVALENT, ORAL PREPARATIONS	1	(7.7)
FERROUS SULFATE	1	(7.7)
OPIOID ANESTHETICS	1	(7.7)
REMIFENTANIL HYDROCHLORIDE	1	(7.7)
OSMOTICALLY ACTING LAXATIVES	1	(7.7)
MACROGOL 3350	1	(7.7)
OTHER ANTIDEPRESSANTS	1	(7.7)
MIRTAZAPINE	1	(7.7)

Source: Listing 16.2.4.8
Notes: [1] Surgical Period medications are all medications that started during the surgical period of the study
[2] Table presents number and percentage of subjects [(n (%)]
[3] Percentages are based on the number of subjects in the respective group.
[4] Medications were coded using the WHO drug dictionary September 2011

Table 14.1.9.2 Medications Taken During the Surgical Period
(Surgical Population)

ATC Class Preferred Drug Name	Total (N=13) n (%)
PENICILLINS WITH EXTENDED SPECTRUM	1 (7.7)
AMOXICILLIN	1 (7.7)
POTASSIUM	1 (7.7)
POTASSIUM CHLORIDE	1 (7.7)
SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	1 (7.7)
LACTEC /00490001/	1 (7.7)
SULFONAMIDES, PLAIN	1 (7.7)
FUROSEMIDE	1 (7.7)
SYNTHETIC ANTICHOLINERGICS, QUATERNARY AMMONIUM COMPOUNDS	1 (7.7)
GLYCOPYRRONIUM BROMIDE	1 (7.7)
THIAZIDES, PLAIN	1 (7.7)
HYDROCHLOROTHIAZIDE	1 (7.7)

Source: Listing 16.2.4.8
Notes: [1] Surgical Period medications are all medications that started during the surgical period of the study
[2] Table presents number and percentage of subjects [(n (%)]
[3] Percentages are based on the number of subjects in the respective group.
[4] Medications were coded using the WHO drug dictionary September 2011

Table 14.1.13 Preventive and Additional Doses
(Efficacy Population)

	On-demand (N=27)	Prophylaxis (N=146)	Total (N=173)
Preventative Doses			
Any Preventative Doses [n (%)]	21 (77.8)	24 (16.4)	45 (26.0)
Total Number of Preventative Doses			
n	21	24	45
Mean (SD)	15.0 (19.34)	9.3 (33.24)	12.0 (27.50)
Median	6.0	2.0	2.0
Min, Max	1, 73	1, 165	1, 165
Number of Preventative Doses	316	223	539
Additional Doses			
Any Additional Doses [n (%)]	15 (55.6)	18 (12.3)	33 (19.1)
Total Number of Additional Doses			
n	15	18	33
Mean (SD)	5.5 (7.16)	2.3 (2.66)	3.8 (5.36)
Median	3.0	1.0	1.0
Min, Max	1, 28	1, 11	1, 28
Number of Additional Doses	82	42	124

Source: Listing 16.2.5.4
Notes: [1] Where indicated, table presents number and percentage of subjects [(n(%)]
[2] Percentages are based on the number of subjects in the respective group.

Table 14.1.13 Preventive and Additional Doses
(Efficacy Population)

	On-demand (N=27)	Prophylaxis (N=146)	Total (N=173)
Preventative or Additional Doses			
Any Preventative or Additional Doses [n (%)]	25 (92.6)	39 (26.7)	64 (37.0)
Total Number of Preventative or Additional Doses			
n	25	39	64
Mean (SD)	15.9 (18.44)	6.8 (26.11)	10.4 (23.68)
Median	10.0	2.0	2.0
Min, Max	1, 73	1, 165	1, 165
Number of Preventative or Additional Doses	398	265	663

Source: Listing 16.2.5.4
Notes: [1] Where indicated, table presents number and percentage of subjects [(n(%)]
[2] Percentages are based on the number of subjects in the respective group.

Table 14.2.15.17.1 Part 3 - FVIII activities of CSL627, 3000 and 250 IU/vial strengths CS baseline uncorrected; initial PK (PK Population)

Subject/ Statistic	Pre-Infusion	10-15 mins	30 mins	1 hour	3 hours	6 hours	9 hours	24 hours	28 hours	32 hours	48 hours	72 hours	96 hours
Dose Group: 3000 IU/vial													
0360031-1003	3.78	137	128	137	110	99.4	94.3	61.1	53.7	47.2	28.4	12.6	5.87
2760034-1006	<1.00	84.6	80.9	82.2	67.6	65.3	54.6	29.7	27.5	22.6	11.7	3.36	<1.00
3480007-1002	<1.00	111	118	114	99.1	82.4	66.5	33.6	27.1	20.8	9.22	2.21	<1.00
3800023-1004	<1.00	102	99.4	88.4	82.8	68.0	55.3	ND	16.3	15.5	6.05	1.21	<1.00
3920025-1001	<1.00	120	119	112	94.7	79.6	57.2	19.9	15.6	12.4	4.44	<1.00	<1.00
3920028-1001	<1.00	132	115	114	105	87.2	73.5	31.9	30.1	22.2	9.24	2.98	<1.00
3920064-1001	<1.00	101	95.5	86.5	83.3	66.6	61.7	35.5	31.5	25.4	16.0	6.66	2.78
8400184-1008	<1.00	71.2	68.2	64.8	63.7	51.8	45.9	22.8	19.5	16.2	8.61	2.92	1.14
8400184-1009	<1.00	65.0	58.6	72.2	65.0	46.9	40.7	13.5	10.3	8.30	1.79	<1.00	<1.00
n	9	9	9	9	9	9	9	8	9	9	9	7	3
Mean	0.420	103	98.0	96.7	85.6	71.9	61.1	31.0	25.7	21.2	10.6	4.56	3.26
SD	1.26	25.4	24.4	23.5	17.5	16.9	15.9	14.3	12.8	11.2	7.84	3.92	2.40
CV (%)	300	24.8	24.9	24.3	20.5	23.5	26.0	46.1	49.7	52.7	73.9	86.0	73.6
Median	0.00	102	99.4	88.4	83.3	68.0	57.2	30.8	27.1	20.8	9.22	2.98	2.78
Min	0.00	65.0	58.6	64.8	63.7	46.9	40.7	13.5	10.3	8.30	1.79	1.21	1.14
Max	3.78	137	128	137	110	99.4	94.3	61.1	53.7	47.2	28.4	12.6	5.87
Geometric Mean	3.78	99.7	95.0	94.2	84.0	70.1	59.4	28.4	23.2	19.0	8.30	3.51	2.65

Source: Listing 16.2.9.6.5
Notes: [1] All values in IU/dL; Lower Limit of Quantification (LLOQ): 1.00 IU/dL.
[2] SD=Standard Deviation; CV=Coefficient of Variation.
[3] ND=Not Done (see listing).

Table 14.2.15.17.1 Part 3 - FVIII activities of CSL627, 3000 and 250 IU/vial strengths CS baseline uncorrected; initial PK (PK Population)

Subject/ Statistic	Pre-Infusion	10-15 mins	30 mins	1 hour	3 hours	6 hours	9 hours	24 hours	28 hours	32 hours	48 hours	72 hours	96 hours
Dose Group: 250 IU/vial													
2760034-1005	<1.00	107	108	101	88.4	68.9	59.3	27.8	23.6	19.0	8.71	2.52	<1.00
3920027-1001	1.39	104	100	95.7	82.3	65.9	61.5	29.6	22.7	20.1	10.4	4.56	2.45
3920029-1001	<1.00	89.1	87.8	79.9	67.2	56.8	47.8	27.4	23.1	19.6	12.3	4.75	1.57
3920030-1001	<1.00	114	110	103	86.0	58.3	51.1	21.4	16.3	13.1	5.71	1.05	<1.00
3920031-1001	1.45	117	115	105	95.8	82.0	67.7	37.2	32.9	25.2	15.4	6.22	2.91
3920031-1002	<1.00	118	112	111	97.4	83.6	68.3	31.9	25.7	18.4	6.32	1.24	<1.00
3920033-1001	2.76	104	93.7	76.6	69.7	58.6	50.3	29.4	24.3	21.9	12.8	5.99	3.66
8400184-1006	<1.00	96.5	91.8	89.4	75.9	52.9	35.9	21.0	14.2	12.8	3.95	<1.00	<1.00
n	8	8	8	8	8	8	8	8	8	8	8	7	4
Mean	0.700	106	102	95.1	82.8	65.9	55.2	28.2	22.9	18.8	9.45	3.76	2.65
SD	1.05	10.1	10.3	12.2	11.3	11.6	11.0	5.30	5.73	4.17	3.97	2.16	0.874
CV (%)	150	9.55	10.1	12.8	13.6	17.6	20.0	18.8	25.1	22.2	42.0	57.3	33.0
Median	0.00	106	104	98.2	84.2	62.3	55.2	28.6	23.4	19.3	9.56	4.56	2.68
Min	0.00	89.1	87.8	76.6	67.2	52.9	35.9	21.0	14.2	12.8	3.95	1.05	1.57
Max	2.76	118	115	111	97.4	83.6	68.3	37.2	32.9	25.2	15.4	6.22	3.66
Geometric Mean	1.77	106	102	94.4	82.2	65.0	54.2	27.8	22.2	18.3	8.65	3.08	2.53

Source: Listing 16.2.9.6.5
Notes: [1] All values in IU/dL; Lower Limit of Quantification (LLOQ): 1.00 IU/dL.
[2] SD=Standard Deviation; CV=Coefficient of Variation.
[3] ND=Not Done (see listing).

Table 14.3.1.1 Inhibitors
(Safety Population)

	Total (N=174) n (%)	95% CI [1] (N=120)	95% CI [2] (N=174)
Inhibitors to FVIII			
Positive	0	(0.0,3.0)	(0.0,2.1)
Negative	174 (100.0)		

Source: Listing 16.2.8.3
Notes: [1] Exact Clopper-Pearson 95% CI based on subjects with >=50 EDs from all CSL studies.
[2] Exact Clopper-Pearson 95% CI based on subjects in the Safety Population.

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Any Treatment-Emergent Adverse Events	113	(64.9)	292
Infections and infestations	45	(25.9)	61
Nasopharyngitis	18	(10.3)	22
Upper respiratory tract infection	6	(3.4)	6
Influenza	4	(2.3)	4
Viral infection	3	(1.7)	4
Sinusitis	3	(1.7)	3
Gastroenteritis	2	(1.1)	2
Gastroenteritis viral	2	(1.1)	2
Pharyngitis	2	(1.1)	2
Viral upper respiratory tract infection	2	(1.1)	2
Bronchitis	1	(0.6)	1
Ear infection	1	(0.6)	1
Fungal skin infection	1	(0.6)	1
Furuncle	1	(0.6)	1
Lower respiratory tract infection	1	(0.6)	1
Oral fungal infection	1	(0.6)	1
Oral herpes	1	(0.6)	1
Otitis media	1	(0.6)	1
Perirectal abscess	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Infections and infestations (continued)			
Respiratory tract infection	1	(0.6)	1
Rhinitis	1	(0.6)	1
Tonsillitis	1	(0.6)	1
Tooth abscess	1	(0.6)	1
Urinary tract infection	1	(0.6)	1
Musculoskeletal and connective tissue disorders	26	(14.9)	46
Arthralgia	17	(9.8)	19
Back pain	5	(2.9)	6
Haemophilic arthropathy	3	(1.7)	11
Pain in extremity	2	(1.1)	3
Groin pain	1	(0.6)	1
Joint range of motion decreased	1	(0.6)	1
Joint swelling	1	(0.6)	1
Lumbar spinal stenosis	1	(0.6)	1
Muscle spasms	1	(0.6)	1
Neck pain	1	(0.6)	1
Synovial cyst	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Injury, poisoning and procedural complications	26	(14.9)	34
Joint injury	3	(1.7)	4
Fall	3	(1.7)	3
Limb injury	2	(1.1)	3
Contusion	2	(1.1)	2
Laceration	2	(1.1)	2
Ligament sprain	2	(1.1)	2
Post-traumatic pain	2	(1.1)	2
Thermal burn	2	(1.1)	2
Wound	2	(1.1)	2
Ankle fracture	1	(0.6)	1
Arthropod bite	1	(0.6)	1
Chillblains	1	(0.6)	1
Conjunctival abrasion	1	(0.6)	1
Hand fracture	1	(0.6)	1
Muscle strain	1	(0.6)	1
Road traffic accident	1	(0.6)	1
Sunburn	1	(0.6)	1
Tendon rupture	1	(0.6)	1
Tongue injury	1	(0.6)	1
Traumatic haematoma	1	(0.6)	1
Wound haemorrhage	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Nervous system disorders	19	(10.9)	25
Headache	12	(6.9)	13
Dizziness	4	(2.3)	5
Paraesthesia	2	(1.1)	2
Somnolence	1	(0.6)	3
Hypoaesthesia	1	(0.6)	1
Migraine	1	(0.6)	1
Gastrointestinal disorders	17	(9.8)	23
Toothache	6	(3.4)	8
Dental caries	3	(1.7)	3
Abdominal pain	2	(1.1)	3
Constipation	1	(0.6)	1
Diarrhoea	1	(0.6)	1
Gastritis	1	(0.6)	1
Haematochezia	1	(0.6)	1
Haemorrhoidal haemorrhage	1	(0.6)	1
Loose tooth	1	(0.6)	1
Oesophagitis	1	(0.6)	1
Umbilical hernia	1	(0.6)	1
Varices oesophageal	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Skin and subcutaneous tissue disorders	17	(9.8)	21
Rash	7	(4.0)	8
Acne	2	(1.1)	2
Actinic keratosis	1	(0.6)	1
Dermatitis	1	(0.6)	1
Dermatitis allergic	1	(0.6)	1
Dermatitis atopic	1	(0.6)	1
Dermatitis contact	1	(0.6)	1
Dyshidrosis	1	(0.6)	1
Ecchymosis	1	(0.6)	1
Erythema	1	(0.6)	1
Heat rash	1	(0.6)	1
Petechiae	1	(0.6)	1
Pruritus	1	(0.6)	1
General disorders and administration site conditions	17	(9.8)	20
Pyrexia	4	(2.3)	5
Asthenia	2	(1.1)	2
Chest pain	2	(1.1)	2
Injection site pain	2	(1.1)	2
Chills	1	(0.6)	2

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
General disorders and administration site conditions (continued)			
Adverse drug reaction	1	(0.6)	1
Feeling hot	1	(0.6)	1
Local swelling	1	(0.6)	1
Localised oedema	1	(0.6)	1
Malaise	1	(0.6)	1
Oedema peripheral	1	(0.6)	1
Pain	1	(0.6)	1
Respiratory, thoracic and mediastinal disorders	9	(5.2)	17
Cough	5	(2.9)	6
Oropharyngeal pain	3	(1.7)	3
Nasal congestion	2	(1.1)	2
Rhinorrhoea	2	(1.1)	2
Nasal mucosal disorder	1	(0.6)	1
Pharyngeal erythema	1	(0.6)	1
Sneezing	1	(0.6)	1
Tonsillar haemorrhage	1	(0.6)	1
Investigations	9	(5.2)	13

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Investigations (continued)			
Liver function test abnormal	2	(1.1)	2
Blood uric acid increased	1	(0.6)	3
Blood glucose increased	1	(0.6)	2
Blood lactate dehydrogenase increased	1	(0.6)	1
Blood triglycerides increased	1	(0.6)	1
Blood urea increased	1	(0.6)	1
C-reactive protein increased	1	(0.6)	1
Drug specific antibody present	1	(0.6)	1
Gamma-glutamyltransferase increased	1	(0.6)	1
Vascular disorders	7	(4.0)	7
Hypertension	5	(2.9)	5
Capillary fragility	1	(0.6)	1
Haematoma	1	(0.6)	1
Blood and lymphatic system disorders	6	(3.4)	7
Anaemia	2	(1.1)	2
Leukocytosis	2	(1.1)	2
Eosinophilia	1	(0.6)	1
Iron deficiency anaemia	1	(0.6)	1
Thrombocytopenia	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Immune system disorders	3	(1.7)	4
Hypersensitivity	2	(1.1)	3
Seasonal allergy	1	(0.6)	1
Renal and urinary disorders	3	(1.7)	3
Haematuria	1	(0.6)	1
Pollakiuria	1	(0.6)	1
Renal colic	1	(0.6)	1
Eye disorders	2	(1.1)	2
Conjunctivitis	2	(1.1)	2
Metabolism and nutrition disorders	2	(1.1)	2
Hyperuricaemia	1	(0.6)	1
Iron deficiency	1	(0.6)	1
Surgical and medical procedures	1	(0.6)	2
Tooth extraction	1	(0.6)	2
Cardiac disorders	1	(0.6)	1
Arrhythmia	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Ear and labyrinth disorders	1	(0.6)	1
Ear pain	1	(0.6)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.6)	1
Gastrointestinal tract adenoma	1	(0.6)	1
Psychiatric disorders	1	(0.6)	1
Suicidal ideation	1	(0.6)	1
Reproductive system and breast disorders	1	(0.6)	1
Penile discharge	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.5 Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Any Related Treatment-Emergent Adverse Events	13	(7.5)	19
General disorders and administration site conditions	4	(2.3)	5
Chills	1	(0.6)	2
Feeling hot	1	(0.6)	1
Injection site pain	1	(0.6)	1
Pyrexia	1	(0.6)	1
Nervous system disorders	3	(1.7)	3
Dizziness	2	(1.1)	2
Paraesthesia	1	(0.6)	1
Skin and subcutaneous tissue disorders	3	(1.7)	3
Erythema	1	(0.6)	1
Pruritus	1	(0.6)	1
Rash	1	(0.6)	1
Immune system disorders	2	(1.1)	3
Hypersensitivity	2	(1.1)	3

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.5 Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Musculoskeletal and connective tissue disorders	1	(0.6)	4
Arthralgia	1	(0.6)	3
Joint range of motion decreased	1	(0.6)	1
Investigations	1	(0.6)	1
Drug specific antibody present	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.13 Non-Serious Medical Events of Special Interest
(Safety Population)

	Total (N=174) n	(%)	E
Any Non-Serious Medical Events of Special Interest	8	(4.6)	10
Minor Surgery	4	(2.3)	5
Toothache	2	(1.1)	2
Dental caries	1	(0.6)	1
Tooth extraction	1	(0.6)	2
Hospital admission for less than 24 hours for events not considered as SAEs	1	(0.6)	1
Joint injury	1	(0.6)	1
Any AE related to CSL627 associated with double or higher dose than prescribed	1	(0.6)	1
Adverse drug reaction	1	(0.6)	1
Hypersensitive Reactions	2	(1.1)	3
Hypersensitivity	2	(1.1)	3
Thrombotic Events	0		0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] and number of events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] AEs during the surgical period are excluded from the TEAE summaries
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.17 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age (Safety Population)

System Organ Class Preferred Term	12 to <18 Years (N=14) n	(%)	E	>=18 to <=65 Years (N=160) n	(%)	E	Total (N=174) n	(%)	E
Any Treatment-Emergent Adverse Events	10	(71.4)	26	103	(64.4)	266	113	(64.9)	292
Infections and infestations	6	(42.9)	7	39	(24.4)	54	45	(25.9)	61
Nasopharyngitis	2	(14.3)	2	16	(10.0)	20	18	(10.3)	22
Upper respiratory tract infection	1	(7.1)	1	5	(3.1)	5	6	(3.4)	6
Influenza	2	(14.3)	2	2	(1.3)	2	4	(2.3)	4
Viral infection	1	(7.1)	1	2	(1.3)	3	3	(1.7)	4
Sinusitis	0			3	(1.9)	3	3	(1.7)	3
Gastroenteritis	0			2	(1.3)	2	2	(1.1)	2
Gastroenteritis viral	1	(7.1)	1	1	(0.6)	1	2	(1.1)	2
Pharyngitis	0			2	(1.3)	2	2	(1.1)	2
Viral upper respiratory tract infection	0			2	(1.3)	2	2	(1.1)	2
Bronchitis	0			1	(0.6)	1	1	(0.6)	1
Ear infection	0			1	(0.6)	1	1	(0.6)	1
Fungal skin infection	0			1	(0.6)	1	1	(0.6)	1
Furuncle	0			1	(0.6)	1	1	(0.6)	1
Lower respiratory tract infection	0			1	(0.6)	1	1	(0.6)	1
Oral fungal infection	0			1	(0.6)	1	1	(0.6)	1
Oral herpes	0			1	(0.6)	1	1	(0.6)	1
Otitis media	0			1	(0.6)	1	1	(0.6)	1
Perirectal abscess	0			1	(0.6)	1	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.17 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age (Safety Population)

System Organ Class Preferred Term	12 to <18 Years (N=14) n (%)	E	>=18 to <=65 Years (N=160) n (%)	E	Total (N=174) n (%)	E
Infections and infestations (continued)						
Respiratory tract infection	0		1 (0.6)	1	1 (0.6)	1
Rhinitis	0		1 (0.6)	1	1 (0.6)	1
Tonsillitis	0		1 (0.6)	1	1 (0.6)	1
Tooth abscess	0		1 (0.6)	1	1 (0.6)	1
Urinary tract infection	0		1 (0.6)	1	1 (0.6)	1
Musculoskeletal and connective tissue disorders	0		26 (16.3)	46	26 (14.9)	46
Arthralgia	0		17 (10.6)	19	17 (9.8)	19
Back pain	0		5 (3.1)	6	5 (2.9)	6
Haemophilic arthropathy	0		3 (1.9)	11	3 (1.7)	11
Pain in extremity	0		2 (1.3)	3	2 (1.1)	3
Groin pain	0		1 (0.6)	1	1 (0.6)	1
Joint range of motion decreased	0		1 (0.6)	1	1 (0.6)	1
Joint swelling	0		1 (0.6)	1	1 (0.6)	1
Lumbar spinal stenosis	0		1 (0.6)	1	1 (0.6)	1
Muscle spasms	0		1 (0.6)	1	1 (0.6)	1
Neck pain	0		1 (0.6)	1	1 (0.6)	1
Synovial cyst	0		1 (0.6)	1	1 (0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.17 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age (Safety Population)

System Organ Class Preferred Term	12 to <18 Years (N=14) n (%) E	>=18 to <=65 Years (N=160) n (%) E	Total (N=174) n (%) E
Injury, poisoning and procedural complications	4 (28.6) 7	22 (13.8) 27	26 (14.9) 34
Joint injury	1 (7.1) 1	2 (1.3) 3	3 (1.7) 4
Fall	0	3 (1.9) 3	3 (1.7) 3
Limb injury	0	2 (1.3) 3	2 (1.1) 3
Contusion	0	2 (1.3) 2	2 (1.1) 2
Laceration	1 (7.1) 1	1 (0.6) 1	2 (1.1) 2
Ligament sprain	0	2 (1.3) 2	2 (1.1) 2
Post-traumatic pain	0	2 (1.3) 2	2 (1.1) 2
Thermal burn	0	2 (1.3) 2	2 (1.1) 2
Wound	0	2 (1.3) 2	2 (1.1) 2
Ankle fracture	0	1 (0.6) 1	1 (0.6) 1
Arthropod bite	0	1 (0.6) 1	1 (0.6) 1
Chillblains	0	1 (0.6) 1	1 (0.6) 1
Conjunctival abrasion	0	1 (0.6) 1	1 (0.6) 1
Hand fracture	1 (7.1) 1	0	1 (0.6) 1
Muscle strain	0	1 (0.6) 1	1 (0.6) 1
Road traffic accident	1 (7.1) 1	0	1 (0.6) 1
Sunburn	0	1 (0.6) 1	1 (0.6) 1
Tendon rupture	1 (7.1) 1	0	1 (0.6) 1
Tongue injury	0	1 (0.6) 1	1 (0.6) 1
Traumatic haematoma	1 (7.1) 1	0	1 (0.6) 1
Wound haemorrhage	1 (7.1) 1	0	1 (0.6) 1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.17 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age (Safety Population)

System Organ Class Preferred Term	12 to <18 Years (N=14) n	(%)	E	>=18 to <=65 Years (N=160) n	(%)	E	Total (N=174) n	(%)	E
Nervous system disorders	1	(7.1)	1	18	(11.3)	24	19	(10.9)	25
Headache	1	(7.1)	1	11	(6.9)	12	12	(6.9)	13
Dizziness	0			4	(2.5)	5	4	(2.3)	5
Paraesthesia	0			2	(1.3)	2	2	(1.1)	2
Somnolence	0			1	(0.6)	3	1	(0.6)	3
Hypoaesthesia	0			1	(0.6)	1	1	(0.6)	1
Migraine	0			1	(0.6)	1	1	(0.6)	1
Gastrointestinal disorders	1	(7.1)	1	16	(10.0)	22	17	(9.8)	23
Toothache	0			6	(3.8)	8	6	(3.4)	8
Dental caries	1	(7.1)	1	2	(1.3)	2	3	(1.7)	3
Abdominal pain	0			2	(1.3)	3	2	(1.1)	3
Constipation	0			1	(0.6)	1	1	(0.6)	1
Diarrhoea	0			1	(0.6)	1	1	(0.6)	1
Gastritis	0			1	(0.6)	1	1	(0.6)	1
Haematochezia	0			1	(0.6)	1	1	(0.6)	1
Haemorrhoidal haemorrhage	0			1	(0.6)	1	1	(0.6)	1
Loose tooth	0			1	(0.6)	1	1	(0.6)	1
Oesophagitis	0			1	(0.6)	1	1	(0.6)	1
Umbilical hernia	0			1	(0.6)	1	1	(0.6)	1
Varices oesophageal	0			1	(0.6)	1	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.17 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age (Safety Population)

System Organ Class Preferred Term	12 to <18 Years (N=14) n	(%)	E	>=18 to <=65 Years (N=160) n	(%)	E	Total (N=174) n	(%)	E
Skin and subcutaneous tissue disorders	3	(21.4)	4	14	(8.8)	17	17	(9.8)	21
Rash	0			7	(4.4)	8	7	(4.0)	8
Acne	1	(7.1)	1	1	(0.6)	1	2	(1.1)	2
Actinic keratosis	0			1	(0.6)	1	1	(0.6)	1
Dermatitis	0			1	(0.6)	1	1	(0.6)	1
Dermatitis allergic	0			1	(0.6)	1	1	(0.6)	1
Dermatitis atopic	0			1	(0.6)	1	1	(0.6)	1
Dermatitis contact	0			1	(0.6)	1	1	(0.6)	1
Dyshidrosis	1	(7.1)	1	0			1	(0.6)	1
Ecchymosis	0			1	(0.6)	1	1	(0.6)	1
Erythema	0			1	(0.6)	1	1	(0.6)	1
Heat rash	1	(7.1)	1	0			1	(0.6)	1
Petechiae	0			1	(0.6)	1	1	(0.6)	1
Pruritus	1	(7.1)	1	0			1	(0.6)	1
General disorders and administration site conditions	1	(7.1)	1	16	(10.0)	19	17	(9.8)	20
Pyrexia	0			4	(2.5)	5	4	(2.3)	5
Asthenia	0			2	(1.3)	2	2	(1.1)	2
Chest pain	0			2	(1.3)	2	2	(1.1)	2
Injection site pain	0			2	(1.3)	2	2	(1.1)	2
Chills	0			1	(0.6)	2	1	(0.6)	2

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.17 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age (Safety Population)

System Organ Class Preferred Term	12 to <18 Years (N=14) n	(%)	E	>=18 to <=65 Years (N=160) n	(%)	E	Total (N=174) n	(%)	E
General disorders and administration site conditions (continued)									
Adverse drug reaction	0			1	(0.6)	1	1	(0.6)	1
Feeling hot	0			1	(0.6)	1	1	(0.6)	1
Local swelling	0			1	(0.6)	1	1	(0.6)	1
Localised oedema	0			1	(0.6)	1	1	(0.6)	1
Malaise	1	(7.1)	1	0			1	(0.6)	1
Oedema peripheral	0			1	(0.6)	1	1	(0.6)	1
Pain	0			1	(0.6)	1	1	(0.6)	1
Respiratory, thoracic and mediastinal disorders	0			9	(5.6)	17	9	(5.2)	17
Cough	0			5	(3.1)	6	5	(2.9)	6
Oropharyngeal pain	0			3	(1.9)	3	3	(1.7)	3
Nasal congestion	0			2	(1.3)	2	2	(1.1)	2
Rhinorrhoea	0			2	(1.3)	2	2	(1.1)	2
Nasal mucosal disorder	0			1	(0.6)	1	1	(0.6)	1
Pharyngeal erythema	0			1	(0.6)	1	1	(0.6)	1
Sneezing	0			1	(0.6)	1	1	(0.6)	1
Tonsillar haemorrhage	0			1	(0.6)	1	1	(0.6)	1
Investigations	0			9	(5.6)	13	9	(5.2)	13

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.17 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age (Safety Population)

System Organ Class Preferred Term	12 to <18 Years (N=14) n	(%)	E	>=18 to <=65 Years (N=160) n	(%)	E	Total (N=174) n	(%)	E
Investigations (continued)									
Liver function test abnormal	0			2	(1.3)	2	2	(1.1)	2
Blood uric acid increased	0			1	(0.6)	3	1	(0.6)	3
Blood glucose increased	0			1	(0.6)	2	1	(0.6)	2
Blood lactate dehydrogenase increased	0			1	(0.6)	1	1	(0.6)	1
Blood triglycerides increased	0			1	(0.6)	1	1	(0.6)	1
Blood urea increased	0			1	(0.6)	1	1	(0.6)	1
C-reactive protein increased	0			1	(0.6)	1	1	(0.6)	1
Drug specific antibody present	0			1	(0.6)	1	1	(0.6)	1
Gamma-glutamyltransferase increased	0			1	(0.6)	1	1	(0.6)	1
Vascular disorders	1	(7.1)	1	6	(3.8)	6	7	(4.0)	7
Hypertension	0			5	(3.1)	5	5	(2.9)	5
Capillary fragility	0			1	(0.6)	1	1	(0.6)	1
Haematoma	1	(7.1)	1	0			1	(0.6)	1
Blood and lymphatic system disorders	0			6	(3.8)	7	6	(3.4)	7
Anaemia	0			2	(1.3)	2	2	(1.1)	2
Leukocytosis	0			2	(1.3)	2	2	(1.1)	2
Eosinophilia	0			1	(0.6)	1	1	(0.6)	1
Iron deficiency anaemia	0			1	(0.6)	1	1	(0.6)	1
Thrombocytopenia	0			1	(0.6)	1	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.17 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age (Safety Population)

System Organ Class Preferred Term	12 to <18 Years (N=14) n	(%)	E	>=18 to <=65 Years (N=160) n	(%)	E	Total (N=174) n	(%)	E
Immune system disorders	1	(7.1)	1	2	(1.3)	3	3	(1.7)	4
Hypersensitivity	1	(7.1)	1	1	(0.6)	2	2	(1.1)	3
Seasonal allergy	0			1	(0.6)	1	1	(0.6)	1
Renal and urinary disorders	1	(7.1)	1	2	(1.3)	2	3	(1.7)	3
Haematuria	0			1	(0.6)	1	1	(0.6)	1
Pollakiuria	1	(7.1)	1	0			1	(0.6)	1
Renal colic	0			1	(0.6)	1	1	(0.6)	1
Eye disorders	0			2	(1.3)	2	2	(1.1)	2
Conjunctivitis	0			2	(1.3)	2	2	(1.1)	2
Metabolism and nutrition disorders	0			2	(1.3)	2	2	(1.1)	2
Hyperuricaemia	0			1	(0.6)	1	1	(0.6)	1
Iron deficiency	0			1	(0.6)	1	1	(0.6)	1
Surgical and medical procedures	0			1	(0.6)	2	1	(0.6)	2
Tooth extraction	0			1	(0.6)	2	1	(0.6)	2
Cardiac disorders	0			1	(0.6)	1	1	(0.6)	1
Arrhythmia	0			1	(0.6)	1	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.17 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age (Safety Population)

System Organ Class Preferred Term	12 to <18 Years (N=14) n	(%)	E	>=18 to <=65 Years (N=160) n	(%)	E	Total (N=174) n	(%)	E
Ear and labyrinth disorders	1	(7.1)	1	0			1	(0.6)	1
Ear pain	1	(7.1)	1	0			1	(0.6)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0			1	(0.6)	1	1	(0.6)	1
Gastrointestinal tract adenoma	0			1	(0.6)	1	1	(0.6)	1
Psychiatric disorders	1	(7.1)	1	0			1	(0.6)	1
Suicidal ideation	1	(7.1)	1	0			1	(0.6)	1
Reproductive system and breast disorders	0			1	(0.6)	1	1	(0.6)	1
Penile discharge	0			1	(0.6)	1	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.18 Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age (Safety Population)

System Organ Class Preferred Term	12 to <18 Years (N=14) n	(%)	E	>=18 to <=65 Years (N=160) n	(%)	E	Total (N=174) n	(%)	E
Any Related Treatment-Emergent Adverse Events	1	(7.1)	2	12	(7.5)	17	13	(7.5)	19
General disorders and administration site conditions	0			4	(2.5)	5	4	(2.3)	5
Chills	0			1	(0.6)	2	1	(0.6)	2
Feeling hot	0			1	(0.6)	1	1	(0.6)	1
Injection site pain	0			1	(0.6)	1	1	(0.6)	1
Pyrexia	0			1	(0.6)	1	1	(0.6)	1
Nervous system disorders	0			3	(1.9)	3	3	(1.7)	3
Dizziness	0			2	(1.3)	2	2	(1.1)	2
Paraesthesia	0			1	(0.6)	1	1	(0.6)	1
Skin and subcutaneous tissue disorders	1	(7.1)	1	2	(1.3)	2	3	(1.7)	3
Erythema	0			1	(0.6)	1	1	(0.6)	1
Pruritus	1	(7.1)	1	0			1	(0.6)	1
Rash	0			1	(0.6)	1	1	(0.6)	1
Immune system disorders	1	(7.1)	1	1	(0.6)	2	2	(1.1)	3
Hypersensitivity	1	(7.1)	1	1	(0.6)	2	2	(1.1)	3

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.18 Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age (Safety Population)

System Organ Class Preferred Term	12 to <18 Years (N=14) n	(%)	E	>=18 to <=65 Years (N=160) n	(%)	E	Total (N=174) n	(%)	E
Musculoskeletal and connective tissue disorders	0			1	(0.6)	4	1	(0.6)	4
Arthralgia	0			1	(0.6)	3	1	(0.6)	3
Joint range of motion decreased	0			1	(0.6)	1	1	(0.6)	1
Investigations	0			1	(0.6)	1	1	(0.6)	1
Drug specific antibody present	0			1	(0.6)	1	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.3.1.2 Local Tolerability - Subject Assessment by Age
(Safety Population)

	Total (N=174)			
	n	(%)	E	(%)
Age Group: 12 to <18 Years				
>=1 Assessment	14	(82.4)	793	
Reaction				
None	14	(100.0)	791	(99.7)
Very Slight	1	(7.1)	1	(0.1)
Slight	0			
Moderate	1	(7.1)	1	(0.1)
Severe	0			
Age Group: >=18 to <=65 Years				
>=1 Assessment	158	(66.4)	12787	
Reaction				
None	158	(100.0)	12700	(99.3)
Very Slight	14	(8.9)	64	(0.5)
Slight	7	(4.4)	17	(0.1)
Moderate	3	(1.9)	6	(0.0)
Severe	0			

Source: Listing 16.2.7.5
Notes: [1] Where indicated, table presents number and percentage of subjects, and number and percentage of reactions

Table 14.3.3.2.2 Local Tolerability - Investigator Assessment by Age
(Safety Population)

	Total (N=174)			
	n	(%)	E	(%)
Age Group: 12 to <18 Years				
>=1 Assessment	13	(76.5)	36	
Erythema Assessment				
None	13	(100.0)	36	(100.0)
Very Slight (Barely Perceptible)	0		0	
Well-defined	0		0	
Moderate to Severe	0		0	
Severe (Beet Redness) to Slight Eschar Formation	0		0	
Maximum Size of the Edema or Induration at Smallest Diameter (mm)				
n	13			
Mean (SD)	0.0	(0.00)		
Median	0.0			
Min, Max	0	,0		
Maximum Size of the Edema or Induration at Largest Diameter (mm)				
n	13			
Mean (SD)	0.0	(0.00)		
Median	0.0			
Min, Max	0	,0		

Source: Listing 16.2.7.6
Notes: [1] Maximum size of edema/induration over all assessments is summarized.
[2] Where indicated, table presents number and percentage of reactions [(n(%)]
[3] Percentages are based on the total number of infusions for events and total number of reactions for patients

Table 14.3.3.2.2 Local Tolerability - Investigator Assessment by Age
(Safety Population)

	Total (N=174)			
	n	(%)	E	(%)
Age Group: 12 to <18 Years				
Itching Severity				
None	13	(100.0)	36	(100.0)
Very Slight	0		0	
Slight	0		0	
Moderate	0		0	
Severe	0		0	
Pain Severity				
None	13	(100.0)	36	(100.0)
Very Slight	0		0	
Slight	0		0	
Moderate	0		0	
Severe	0		0	
Heat Severity				
None	13	(100.0)	36	(100.0)
Very Slight	0		0	
Slight	0		0	
Moderate	0		0	
Severe	0		0	

Source: Listing 16.2.7.6
Notes: [1] Maximum size of edema/induration over all assessments is summarized.
[2] Where indicated, table presents number and percentage of reactions [(n(%)]
[3] Percentages are based on the total number of infusions for events and total number of reactions for patients

Table 14.3.3.2.2 Local Tolerability - Investigator Assessment by Age
(Safety Population)

	Total (N=174)			
	n	(%)	E	(%)
Age Group: >=18 to <=65 Years				
>=1 Assessment	140	(58.8)	517	
Erythema Assessment				
None	140	(100.0)	516	(99.8)
Very Slight (Barely Perceptible)	1	(0.7)	1	(0.2)
Well-defined	0		0	
Moderate to Severe	0		0	
Severe (Beet Redness) to Slight Eschar Formation	0		0	
Maximum Size of the Edema or Induration at Smallest Diameter (mm)				
n	140			
Mean (SD)	0.0	(0.00)		
Median	0.0			
Min, Max	0	,0		
Maximum Size of the Edema or Induration at Largest Diameter (mm)				
n	140			
Mean (SD)	0.0	(0.00)		
Median	0.0			
Min, Max	0	,0		

Source: Listing 16.2.7.6
Notes: [1] Maximum size of edema/induration over all assessments is summarized.
[2] Where indicated, table presents number and percentage of reactions [(n(%)]
[3] Percentages are based on the total number of infusions for events and total number of reactions for patients

Table 14.3.3.2.2 Local Tolerability - Investigator Assessment by Age
(Safety Population)

	Total (N=174)			
	n	(%)	E	(%)
Age Group: >=18 to <=65 Years				
Itching Severity				
None	140	(100.0)	517	(100.0)
Very Slight	0		0	
Slight	0		0	
Moderate	0		0	
Severe	0		0	
Pain Severity				
None	140	(100.0)	517	(100.0)
Very Slight	0		0	
Slight	0		0	
Moderate	0		0	
Severe	0		0	
Heat Severity				
None	140	(100.0)	517	(100.0)
Very Slight	0		0	
Slight	0		0	
Moderate	0		0	
Severe	0		0	

Source: Listing 16.2.7.6
Notes: [1] Maximum size of edema/induration over all assessments is summarized.
[2] Where indicated, table presents number and percentage of reactions [(n(%)]
[3] Percentages are based on the total number of infusions for events and total number of reactions for patients

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Hemoglobin (g/L)		
Screening		
n	172	
Mean (SD)	150.3 (11.97)	
Median	151.0	
Min, Max	100, 180	
Baseline		
n	173	
Mean (SD)	148.7 (12.49)	
Median	149.0	
Min, Max	96, 179	

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Hemoglobin (g/L)		
Month 1		
n	164	163
Mean (SD)	149.3 (11.76)	0.7 (8.79)
Median	149.0	1.0
Min, Max	104, 179	-26, 31
Month 2		
n	159	158
Mean (SD)	150.0 (12.94)	1.3 (10.64)
Median	152.0	1.0
Min, Max	92, 177	-58, 36
Month 3		
n	151	150
Mean (SD)	151.1 (11.62)	2.8 (9.63)
Median	151.0	3.0
Min, Max	102, 182	-21, 34

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Hemoglobin (g/L)		
Month 4		
n	133	132
Mean (SD)	151.4 (10.85)	2.7 (9.03)
Median	151.0	2.0
Min, Max	104, 180	-17, 41
Month 5		
n	106	105
Mean (SD)	149.8 (10.79)	1.5 (9.54)
Median	150.0	1.0
Min, Max	112, 176	-19, 48
Month 6		
n	86	86
Mean (SD)	151.0 (10.30)	2.7 (9.82)
Median	151.5	2.0
Min, Max	122, 177	-21, 49

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Hemoglobin (g/L)		
Month 9		
n	57	57
Mean (SD)	150.1 (9.58)	2.6 (9.67)
Median	150.0	2.0
Min, Max	119, 176	-14, 47
Month 12		
n	24	24
Mean (SD)	148.5 (11.68)	1.6 (14.04)
Median	149.5	4.5
Min, Max	107, 165	-41, 21
Month 15		
n	16	16
Mean (SD)	149.3 (9.10)	0.4 (7.83)
Median	149.5	0.5
Min, Max	135, 170	-13, 12

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Hemoglobin (g/L)		
Month 18		
n	12	12
Mean (SD)	151.3 (9.70)	3.9 (9.17)
Median	150.5	5.0
Min, Max	136, 168	-16, 21
Month 21		
n	8	8
Mean (SD)	151.8 (6.20)	8.1 (7.43)
Median	153.5	10.0
Min, Max	141, 158	-8, 17
EOS		
n	171	170
Mean (SD)	152.7 (11.98)	4.1 (11.51)
Median	151.0	4.0
Min, Max	106, 186	-26, 53

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Hematocrit (L/L)		
Screening		
n	172	
Mean (SD)	0.4 (0.03)	
Median	0.4	
Min, Max	0, 1	
Baseline		
n	173	
Mean (SD)	0.4 (0.04)	
Median	0.4	
Min, Max	0, 1	

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Hematocrit (L/L)		
Month 1		
n	164	163
Mean (SD)	0.4 (0.03)	0.0 (0.03)
Median	0.4	0.0
Min, Max	0, 1	-0, 0
Month 2		
n	159	158
Mean (SD)	0.4 (0.05)	0.0 (0.05)
Median	0.4	0.0
Min, Max	0, 1	-0, 0
Month 3		
n	151	150
Mean (SD)	0.4 (0.03)	0.0 (0.03)
Median	0.4	0.0
Min, Max	0, 1	-0, 0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Hematocrit (L/L)		
Month 4		
n	133	132
Mean (SD)	0.4 (0.03)	0.0 (0.03)
Median	0.4	0.0
Min, Max	0, 1	-0, 0
Month 5		
n	106	105
Mean (SD)	0.4 (0.03)	0.0 (0.03)
Median	0.4	0.0
Min, Max	0, 1	-0, 0
Month 6		
n	86	86
Mean (SD)	0.4 (0.03)	0.0 (0.03)
Median	0.4	0.0
Min, Max	0, 1	-0, 0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Hematocrit (L/L)		
Month 9		
n	57	57
Mean (SD)	0.4 (0.03)	0.0 (0.03)
Median	0.4	0.0
Min, Max	0, 0	-0, 0
Month 12		
n	24	24
Mean (SD)	0.4 (0.03)	0.0 (0.04)
Median	0.4	0.0
Min, Max	0, 0	-0, 0
Month 15		
n	16	16
Mean (SD)	0.4 (0.02)	-0.0 (0.03)
Median	0.4	-0.0
Min, Max	0, 0	-0, 0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Hematocrit (L/L)		
Month 18		
n	12	12
Mean (SD)	0.4 (0.02)	0.0 (0.02)
Median	0.4	0.0
Min, Max	0, 0	-0, 0
Month 21		
n	8	8
Mean (SD)	0.4 (0.02)	0.0 (0.03)
Median	0.4	0.0
Min, Max	0, 0	-0, 0
EOS		
n	171	170
Mean (SD)	0.4 (0.04)	0.0 (0.03)
Median	0.4	0.0
Min, Max	0, 1	-0, 0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Erythrocytes (10^12/L)		
Screening		
n	172	
Mean (SD)	5.1 (0.52)	
Median	5.1	
Min, Max	3, 7	
Baseline		
n	173	
Mean (SD)	5.1 (0.60)	
Median	5.0	
Min, Max	3, 8	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Erythrocytes (10^12/L)		
Month 1		
n	164	163
Mean (SD)	5.2 (0.63)	0.1 (0.49)
Median	5.1	0.1
Min, Max	3, 9	-1, 4
Month 2		
n	159	158
Mean (SD)	5.1 (0.56)	0.0 (0.48)
Median	5.1	0.1
Min, Max	3, 7	-4, 1
Month 3		
n	151	150
Mean (SD)	5.1 (0.51)	0.1 (0.46)
Median	5.1	0.1
Min, Max	4, 7	-4, 1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Erythrocytes (10^12/L)		
Month 4		
n	133	132
Mean (SD)	5.1 (0.49)	0.1 (0.46)
Median	5.1	0.1
Min, Max	4, 7	-4, 1
Month 5		
n	106	105
Mean (SD)	5.1 (0.54)	0.0 (0.51)
Median	5.1	0.0
Min, Max	3, 7	-4, 2
Month 6		
n	86	86
Mean (SD)	5.1 (0.50)	0.1 (0.32)
Median	5.0	0.1
Min, Max	3, 7	-1, 2

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Erythrocytes (10^12/L)		
Month 9		
n	57	57
Mean (SD)	5.1 (0.67)	0.1 (0.63)
Median	5.0	0.1
Min, Max	4, 9	-1, 4
Month 12		
n	24	24
Mean (SD)	5.0 (0.47)	0.0 (0.43)
Median	5.0	0.1
Min, Max	4, 6	-1, 1
Month 15		
n	16	16
Mean (SD)	5.0 (0.37)	-0.0 (0.32)
Median	5.0	-0.0
Min, Max	4, 6	-1, 1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Erythrocytes (10^12/L)		
Month 18		
n	12	12
Mean (SD)	5.0 (0.26)	0.1 (0.27)
Median	5.0	0.1
Min, Max	5, 6	-1, 1
Month 21		
n	8	8
Mean (SD)	5.1 (0.37)	0.3 (0.27)
Median	4.9	0.3
Min, Max	5, 6	-0, 1
EOS		
n	171	170
Mean (SD)	5.2 (0.57)	0.1 (0.49)
Median	5.1	0.1
Min, Max	3, 7	-4, 2

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Erythrocyte Mean Corpuscular Volume (fL)		
Screening		
n	170	
Mean (SD)	87.4 (6.31)	
Median	87.5	
Min, Max	64, 117	
Baseline		
n	172	
Mean (SD)	87.0 (7.90)	
Median	87.3	
Min, Max	32, 117	

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Erythrocyte Mean Corpuscular Volume (fL)		
Month 1		
n	164	163
Mean (SD)	86.6 (8.11)	-0.4 (2.44)
Median	87.1	-0.2
Min, Max	33, 115	-17, 8
Month 2		
n	159	157
Mean (SD)	86.8 (8.22)	-0.3 (6.87)
Median	87.2	-0.2
Min, Max	26, 117	-55, 54
Month 3		
n	151	149
Mean (SD)	87.0 (6.39)	-0.2 (5.06)
Median	87.0	-0.3
Min, Max	63, 116	-15, 51

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Erythrocyte Mean Corpuscular Volume (fL)		
Month 4		
n	133	131
Mean (SD)	86.9 (6.31)	-0.2 (5.04)
Median	86.9	-0.2
Min, Max	64, 115	-11, 51
Month 5		
n	106	104
Mean (SD)	86.7 (6.17)	-0.1 (5.62)
Median	87.0	-0.4
Min, Max	65, 117	-13, 51
Month 6		
n	86	86
Mean (SD)	87.4 (5.53)	0.1 (6.29)
Median	87.1	-0.1
Min, Max	75, 116	-13, 53

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Erythrocyte Mean Corpuscular Volume (fL)		
Month 9		
n	57	57
Mean (SD)	87.3 (4.47)	0.2 (3.04)
Median	87.0	0.5
Min, Max	79, 100	-14, 12
Month 12		
n	24	24
Mean (SD)	88.6 (5.03)	0.3 (3.17)
Median	88.0	1.0
Min, Max	80, 103	-13, 4
Month 15		
n	16	16
Mean (SD)	87.7 (5.18)	-0.2 (4.73)
Median	86.7	-0.5
Min, Max	80, 101	-13, 10

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Erythrocyte Mean Corpuscular Volume (fL)		
Month 18		
n	12	12
Mean (SD)	88.4 (4.48)	-0.8 (3.24)
Median	89.5	0.5
Min, Max	80, 95	-9, 2
Month 21		
n	8	8
Mean (SD)	88.6 (3.92)	-2.1 (4.61)
Median	90.4	-0.5
Min, Max	82, 92	-13, 1
EOS		
n	169	167
Mean (SD)	86.8 (6.56)	-0.5 (3.63)
Median	86.9	0.0
Min, Max	64, 121	-16, 11

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Leukocytes (10^9/L)		
Screening		
n	172	
Mean (SD)	6.4 (1.88)	
Median	6.2	
Min, Max	3, 13	
Baseline		
n	173	
Mean (SD)	6.4 (1.65)	
Median	6.2	
Min, Max	2, 12	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Leukocytes (10^9/L)		
Month 1		
n	163	162
Mean (SD)	6.7 (2.25)	0.3 (1.69)
Median	6.2	0.1
Min, Max	3, 15	-5, 8
Month 2		
n	159	158
Mean (SD)	6.5 (1.94)	0.0 (1.50)
Median	6.0	0.0
Min, Max	3, 14	-4, 5
Month 3		
n	151	150
Mean (SD)	6.4 (1.74)	-0.0 (1.34)
Median	6.2	0.1
Min, Max	3, 11	-4, 4

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Leukocytes (10^9/L)		
Month 4		
n	133	132
Mean (SD)	6.4 (1.89)	0.0 (1.72)
Median	6.4	-0.0
Min, Max	3, 15	-5, 9
Month 5		
n	106	105
Mean (SD)	6.4 (1.70)	-0.1 (1.59)
Median	6.3	-0.2
Min, Max	3, 11	-5, 6
Month 6		
n	86	86
Mean (SD)	6.7 (1.82)	0.2 (1.65)
Median	6.4	0.2
Min, Max	2, 12	-6, 6

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Leukocytes (10^9/L)		
Month 9		
n	56	56
Mean (SD)	6.3 (1.71)	0.0 (1.34)
Median	6.3	-0.0
Min, Max	2, 11	-4, 3
Month 12		
n	24	24
Mean (SD)	6.1 (1.69)	0.0 (1.57)
Median	5.9	-0.0
Min, Max	3, 10	-4, 2
Month 15		
n	16	16
Mean (SD)	6.2 (1.55)	0.1 (1.59)
Median	5.9	0.3
Min, Max	4, 10	-4, 3

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Leukocytes (10^9/L)		
Month 18		
n	12	12
Mean (SD)	7.2 (1.82)	0.8 (0.95)
Median	7.1	1.1
Min, Max	4, 10	-1, 2
Month 21		
n	8	8
Mean (SD)	5.5 (1.20)	-0.0 (1.08)
Median	5.5	0.0
Min, Max	4, 8	-2, 2
EOS		
n	171	170
Mean (SD)	6.7 (2.16)	0.2 (1.86)
Median	6.3	0.0
Min, Max	2, 17	-7, 8

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Neutrophils (10^9/L)		
Screening		
n	169	
Mean (SD)	3.7 (1.56)	
Median	3.5	
Min, Max	0, 11	
Baseline		
n	173	
Mean (SD)	3.7 (1.25)	
Median	3.6	
Min, Max	0, 8	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Neutrophils (10^9/L)		
Month 1		
n	160	159
Mean (SD)	4.0 (1.88)	0.3 (1.60)
Median	3.5	0.0
Min, Max	0, 12	-4, 7
Month 2		
n	159	158
Mean (SD)	3.8 (1.47)	0.1 (1.24)
Median	3.5	-0.0
Min, Max	1, 10	-3, 4
Month 3		
n	151	150
Mean (SD)	3.7 (1.38)	0.1 (1.24)
Median	3.4	0.1
Min, Max	1, 9	-4, 4

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Neutrophils (10^9/L)		
Month 4		
n	133	132
Mean (SD)	3.7 (1.49)	0.1 (1.49)
Median	3.5	0.0
Min, Max	1, 10	-3, 7
Month 5		
n	105	104
Mean (SD)	3.6 (1.31)	-0.0 (1.27)
Median	3.5	-0.1
Min, Max	1, 8	-3, 5
Month 6		
n	86	86
Mean (SD)	3.8 (1.31)	0.1 (1.34)
Median	3.6	0.1
Min, Max	1, 7	-4, 4

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Neutrophils (10^9/L)		
Month 9		
n	56	56
Mean (SD)	3.6 (1.27)	0.0 (1.18)
Median	3.6	-0.1
Min, Max	1, 7	-3, 3
Month 12		
n	24	24
Mean (SD)	3.3 (1.19)	-0.1 (1.31)
Median	3.3	-0.0
Min, Max	1, 7	-4, 3
Month 15		
n	16	16
Mean (SD)	3.7 (1.38)	0.2 (1.28)
Median	3.4	0.4
Min, Max	2, 8	-3, 3

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Neutrophils (10^9/L)		
Month 18		
n	12	12
Mean (SD)	3.8 (1.73)	0.3 (1.51)
Median	3.8	0.8
Min, Max	0, 7	-3, 2
Month 21		
n	8	8
Mean (SD)	3.0 (0.72)	-0.0 (0.97)
Median	3.0	-0.0
Min, Max	2, 4	-2, 1
EOS		
n	169	168
Mean (SD)	3.9 (1.65)	0.2 (1.47)
Median	3.6	0.1
Min, Max	1, 14	-4, 7

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Lymphocytes (10^9/L)		
Screening		
n	169	
Mean (SD)	1.9 (0.63)	
Median	1.9	
Min, Max	0, 4	
Baseline		
n	173	
Mean (SD)	2.0 (0.65)	
Median	1.9	
Min, Max	0, 4	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Lymphocytes (10^9/L)		
Month 1		
n	160	159
Mean (SD)	2.0 (0.65)	-0.0 (0.51)
Median	1.9	0.0
Min, Max	0, 5	-2, 1
Month 2		
n	158	157
Mean (SD)	2.0 (0.66)	-0.0 (0.61)
Median	1.9	-0.0
Min, Max	0, 5	-1, 2
Month 3		
n	151	150
Mean (SD)	1.9 (0.65)	-0.1 (0.45)
Median	1.9	-0.0
Min, Max	0, 5	-2, 1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Lymphocytes (10^9/L)		
Month 4		
n	133	132
Mean (SD)	2.0 (0.63)	-0.1 (0.52)
Median	1.9	-0.1
Min, Max	0, 5	-2, 2
Month 5		
n	105	104
Mean (SD)	2.0 (0.62)	-0.0 (0.48)
Median	1.9	-0.0
Min, Max	1, 5	-2, 2
Month 6		
n	86	86
Mean (SD)	2.1 (0.68)	0.0 (0.49)
Median	1.8	0.0
Min, Max	1, 4	-1, 1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Lymphocytes (10^9/L)		
Month 9		
n	56	56
Mean (SD)	1.9 (0.57)	-0.0 (0.41)
Median	1.9	-0.0
Min, Max	1, 3	-1, 1
Month 12		
n	24	24
Mean (SD)	1.9 (0.59)	0.1 (0.44)
Median	1.9	0.1
Min, Max	1, 3	-1, 1
Month 15		
n	16	16
Mean (SD)	1.8 (0.53)	-0.1 (0.45)
Median	1.6	0.0
Min, Max	1, 3	-1, 1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Lymphocytes (10^9/L)		
Month 18		
n	12	12
Mean (SD)	2.0 (1.10)	-0.0 (0.79)
Median	1.8	-0.0
Min, Max	0, 4	-2, 1
Month 21		
n	8	8
Mean (SD)	1.8 (0.50)	0.0 (0.14)
Median	1.9	0.1
Min, Max	1, 3	-0, 0
EOS		
n	169	168
Mean (SD)	2.0 (0.65)	0.0 (0.58)
Median	2.0	0.0
Min, Max	0, 4	-2, 2

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Monocytes (10^9/L)		
Screening		
n	169	
Mean (SD)	0.5 (0.21)	
Median	0.5	
Min, Max	0, 1	
Baseline		
n	173	
Mean (SD)	0.5 (0.21)	
Median	0.5	
Min, Max	0, 1	

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Monocytes (10^9/L)		
Month 1		
n	160	159
Mean (SD)	0.5 (0.21)	0.0 (0.20)
Median	0.5	0.0
Min, Max	0, 1	-0, 1
Month 2		
n	158	157
Mean (SD)	0.5 (0.22)	0.0 (0.19)
Median	0.5	0.0
Min, Max	0, 1	-1, 1
Month 3		
n	151	150
Mean (SD)	0.5 (0.21)	0.0 (0.21)
Median	0.5	0.0
Min, Max	0, 1	-1, 1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Monocytes (10^9/L)		
Month 4		
n	133	132
Mean (SD)	0.5 (0.22)	0.0 (0.21)
Median	0.5	0.0
Min, Max	0, 2	-1, 1
Month 5		
n	105	104
Mean (SD)	0.5 (0.21)	0.0 (0.20)
Median	0.5	0.0
Min, Max	0, 1	-0, 1
Month 6		
n	86	86
Mean (SD)	0.6 (0.22)	0.0 (0.20)
Median	0.5	0.0
Min, Max	0, 1	-1, 1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Monocytes (10^9/L)		
Month 9		
n	56	56
Mean (SD)	0.5 (0.16)	-0.0 (0.17)
Median	0.5	-0.0
Min, Max	0, 1	-1, 0
Month 12		
n	24	24
Mean (SD)	0.6 (0.20)	-0.0 (0.17)
Median	0.6	-0.0
Min, Max	0, 1	-0, 0
Month 15		
n	16	16
Mean (SD)	0.6 (0.21)	0.0 (0.25)
Median	0.6	-0.0
Min, Max	0, 1	-0, 1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Monocytes (10^9/L)		
Month 18		
n	12	12
Mean (SD)	0.7 (0.20)	0.1 (0.21)
Median	0.6	0.1
Min, Max	0, 1	-0, 0
Month 21		
n	8	8
Mean (SD)	0.5 (0.13)	-0.0 (0.19)
Median	0.5	-0.1
Min, Max	0, 1	-0, 0
EOS		
n	168	167
Mean (SD)	0.5 (0.23)	0.0 (0.23)
Median	0.5	0.0
Min, Max	0, 2	-1, 1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Eosinophils (10^9/L)		
Screening		
n	169	
Mean (SD)	0.2 (0.13)	
Median	0.1	
Min, Max	0, 1	
Baseline		
n	173	
Mean (SD)	0.2 (0.12)	
Median	0.1	
Min, Max	0, 1	

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Eosinophils (10^9/L)		
Month 1		
n	160	159
Mean (SD)	0.2 (0.13)	-0.0 (0.11)
Median	0.1	-0.0
Min, Max	0, 1	-0, 1
Month 2		
n	158	157
Mean (SD)	0.2 (0.11)	-0.0 (0.09)
Median	0.2	0.0
Min, Max	0, 1	-0, 0
Month 3		
n	151	150
Mean (SD)	0.2 (0.12)	-0.0 (0.10)
Median	0.1	0.0
Min, Max	0, 1	-0, 0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Eosinophils (10^9/L)		
Month 4		
n	133	132
Mean (SD)	0.2 (0.18)	-0.0 (0.16)
Median	0.1	-0.0
Min, Max	0, 2	-0, 1
Month 5		
n	105	104
Mean (SD)	0.2 (0.12)	0.0 (0.10)
Median	0.1	0.0
Min, Max	0, 1	-0, 0
Month 6		
n	86	86
Mean (SD)	0.2 (0.15)	0.0 (0.14)
Median	0.1	0.0
Min, Max	0, 1	-0, 1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Eosinophils (10^9/L)		
Month 9		
n	56	56
Mean (SD)	0.2 (0.11)	-0.0 (0.11)
Median	0.1	0.0
Min, Max	0, 0	-0, 0
Month 12		
n	24	24
Mean (SD)	0.2 (0.15)	0.0 (0.11)
Median	0.2	-0.0
Min, Max	0, 1	-0, 0
Month 15		
n	16	16
Mean (SD)	0.2 (0.10)	-0.0 (0.11)
Median	0.2	0.0
Min, Max	0, 0	-0, 0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Eosinophils (10^9/L)		
Month 18		
n	12	12
Mean (SD)	0.2 (0.14)	0.0 (0.15)
Median	0.1	0.0
Min, Max	0, 0	-0, 0
Month 21		
n	8	8
Mean (SD)	0.2 (0.10)	-0.0 (0.07)
Median	0.1	0.0
Min, Max	0, 0	-0, 0
EOS		
n	168	167
Mean (SD)	0.2 (0.15)	-0.0 (0.14)
Median	0.1	0.0
Min, Max	0, 1	-1, 1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Basophils (10^9/L)		
Screening		
n	169	
Mean (SD)	0.0 (0.05)	
Median	0.0	
Min, Max	0, 1	
Baseline		
n	173	
Mean (SD)	0.0 (0.03)	
Median	0.0	
Min, Max	0, 0	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Basophils (10^9/L)		
Month 1		
n	160	159
Mean (SD)	0.0 (0.06)	0.0 (0.06)
Median	0.0	0.0
Min, Max	0, 0	-0, 0
Month 2		
n	158	157
Mean (SD)	0.0 (0.07)	0.0 (0.07)
Median	0.0	0.0
Min, Max	0, 1	-0, 1
Month 3		
n	151	150
Mean (SD)	0.0 (0.03)	-0.0 (0.04)
Median	0.0	0.0
Min, Max	0, 0	-0, 0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Basophils (10^9/L)		
Month 4		
n	133	132
Mean (SD)	0.0 (0.04)	0.0 (0.04)
Median	0.0	0.0
Min, Max	0, 0	-0, 0
Month 5		
n	105	104
Mean (SD)	0.0 (0.03)	0.0 (0.03)
Median	0.0	0.0
Min, Max	0, 0	-0, 0
Month 6		
n	86	86
Mean (SD)	0.0 (0.03)	0.0 (0.03)
Median	0.0	0.0
Min, Max	0, 0	-0, 0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Basophils (10^9/L)		
Month 9		
n	56	56
Mean (SD)	0.0 (0.03)	0.0 (0.03)
Median	0.0	0.0
Min, Max	0, 0	-0, 0
Month 12		
n	24	24
Mean (SD)	0.0 (0.03)	0.0 (0.04)
Median	0.0	0.0
Min, Max	0, 0	-0, 0
Month 15		
n	16	16
Mean (SD)	0.0 (0.03)	0.0 (0.03)
Median	0.0	0.0
Min, Max	0, 0	-0, 0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Basophils (10^9/L)		
Month 18		
n	12	12
Mean (SD)	0.0 (0.04)	0.0 (0.04)
Median	0.0	0.0
Min, Max	0, 0	-0, 0
Month 21		
n	8	8
Mean (SD)	0.0 (0.01)	-0.0 (0.02)
Median	0.0	0.0
Min, Max	0, 0	-0, 0
EOS		
n	168	167
Mean (SD)	0.0 (0.03)	-0.0 (0.04)
Median	0.0	0.0
Min, Max	0, 0	-0, 0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Platelets (10^9/L)		
Screening		
n	172	
Mean (SD)	239.3 (55.92)	
Median	233.0	
Min, Max	101, 394	
Baseline		
n	173	
Mean (SD)	237.9 (54.91)	
Median	231.0	
Min, Max	116, 386	

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Platelets (10^9/L)		
Month 1		
n	164	163
Mean (SD)	237.4 (56.83)	0.6 (33.86)
Median	225.5	1.0
Min, Max	115, 407	-140, 118
Month 2		
n	159	158
Mean (SD)	242.4 (64.04)	5.5 (49.75)
Median	232.0	2.0
Min, Max	114, 636	-119, 418
Month 3		
n	151	150
Mean (SD)	236.6 (54.85)	1.6 (32.22)
Median	229.0	3.0
Min, Max	111, 386	-110, 133

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Platelets (10^9/L)		
Month 4		
n	133	132
Mean (SD)	237.0 (56.89)	1.8 (37.68)
Median	229.0	1.5
Min, Max	98, 393	-157, 173
Month 5		
n	106	105
Mean (SD)	236.8 (57.04)	1.6 (33.76)
Median	231.0	3.0
Min, Max	97, 417	-138, 101
Month 6		
n	86	86
Mean (SD)	238.3 (54.78)	4.9 (31.67)
Median	238.5	7.5
Min, Max	120, 382	-114, 90

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Platelets (10^9/L)		
Month 9		
n	57	57
Mean (SD)	235.3 (62.91)	2.1 (34.65)
Median	227.0	3.0
Min, Max	109, 480	-134, 128
Month 12		
n	24	24
Mean (SD)	223.5 (48.44)	-12.8 (37.92)
Median	229.5	-15.0
Min, Max	129, 306	-135, 51
Month 15		
n	16	16
Mean (SD)	220.1 (46.65)	-7.7 (18.96)
Median	224.0	-8.0
Min, Max	125, 316	-33, 28

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Platelets (10^9/L)		
Month 18		
n	12	12
Mean (SD)	216.1 (49.40)	-5.6 (24.06)
Median	209.5	-12.0
Min, Max	119, 315	-48, 33
Month 21		
n	8	8
Mean (SD)	191.3 (42.87)	-9.8 (15.10)
Median	193.0	-4.5
Min, Max	114, 241	-34, 7
EOS		
n	171	170
Mean (SD)	239.5 (60.34)	1.8 (41.49)
Median	226.0	1.0
Min, Max	94, 450	-132, 161

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Sodium (mmol/L)		
Screening		
n	169	
Mean (SD)	140.34 (2.556)	
Median	140.00	
Min, Max	130.0, 149.0	
Pre-Infusion		
n	172	
Mean (SD)	140.24 (3.105)	
Median	140.00	
Min, Max	125.0, 163.0	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Sodium (mmol/L)		
Month 1		
n	163	161
Mean (SD)	140.30 (3.349)	0.02 (4.169)
Median	140.00	0.00
Min, Max	128.0, 164.0	-24.8, 28.0
Month 2		
n	160	158
Mean (SD)	140.15 (3.426)	0.01 (3.328)
Median	140.00	0.00
Min, Max	111.0, 152.0	-30.0, 8.0
Month 3		
n	151	150
Mean (SD)	140.20 (3.232)	0.03 (2.722)
Median	140.10	0.00
Min, Max	118.4, 148.7	-11.0, 9.7

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Sodium (mmol/L)		
Month 4		
n	133	131
Mean (SD)	140.31 (3.402)	0.27 (3.222)
Median	140.00	0.00
Min, Max	126.0, 161.0	-10.0, 16.9
Month 5		
n	103	101
Mean (SD)	140.25 (2.316)	0.17 (2.453)
Median	140.00	0.00
Min, Max	136.0, 146.0	-6.0, 7.0
Month 6		
n	86	85
Mean (SD)	140.67 (2.027)	0.57 (2.198)
Median	141.00	0.00
Min, Max	136.0, 146.0	-4.0, 5.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Sodium (mmol/L)		
Month 9		
n	55	54
Mean (SD)	141.13 (1.981)	0.77 (2.197)
Median	141.00	1.00
Min, Max	136.0, 147.0	-4.0, 7.0
Month 12		
n	24	24
Mean (SD)	140.79 (2.519)	-0.04 (2.293)
Median	140.00	-0.50
Min, Max	138.0, 148.0	-4.0, 4.0
Month 15		
n	16	16
Mean (SD)	140.75 (2.082)	-0.25 (2.793)
Median	141.50	-1.00
Min, Max	137.0, 143.0	-5.0, 5.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Sodium (mmol/L)		
Month 18		
n	11	11
Mean (SD)	140.09 (1.221)	-1.09 (1.868)
Median	140.00	-2.00
Min, Max	138.0, 142.0	-4.0, 2.0
Month 21		
n	8	8
Mean (SD)	141.25 (1.982)	-0.88 (2.100)
Median	141.50	-1.00
Min, Max	138.0, 144.0	-4.0, 3.0
EOS		
n	168	166
Mean (SD)	140.16 (3.359)	-0.11 (4.183)
Median	140.00	0.00
Min, Max	120.0, 155.0	-24.1, 14.1

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Potassium (mmol/L)		
Screening		
n	169	
Mean (SD)	4.089 (0.4426)	
Median	4.100	
Min, Max	2.60, 5.70	
Pre-Infusion		
n	172	
Mean (SD)	4.068 (0.4344)	
Median	4.000	
Min, Max	3.00, 6.50	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Potassium (mmol/L)		
Month 1		
n	162	160
Mean (SD)	4.117 (0.4254)	0.058 (0.5034)
Median	4.100	0.100
Min, Max	2.60, 5.80	-2.40, 1.80
Month 2		
n	160	158
Mean (SD)	4.226 (0.6339)	0.179 (0.6358)
Median	4.200	0.200
Min, Max	2.20, 7.90	-1.70, 4.00
Month 3		
n	149	148
Mean (SD)	4.201 (0.4991)	0.154 (0.5079)
Median	4.100	0.125
Min, Max	3.20, 6.40	-1.20, 2.50

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Potassium (mmol/L)		
Month 4		
n	133	131
Mean (SD)	4.171 (0.3995)	0.145 (0.4413)
Median	4.190	0.100
Min, Max	3.20, 5.80	-1.00, 1.90
Month 5		
n	103	101
Mean (SD)	4.120 (0.3414)	0.116 (0.3602)
Median	4.200	0.140
Min, Max	3.38, 4.90	-1.10, 1.10
Month 6		
n	86	85
Mean (SD)	4.144 (0.3658)	0.185 (0.3513)
Median	4.100	0.200
Min, Max	3.30, 5.02	-0.70, 1.00

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Potassium (mmol/L)		
Month 9		
n	55	54
Mean (SD)	4.087 (0.3674)	0.139 (0.3439)
Median	4.000	0.100
Min, Max	3.40, 5.40	-0.50, 1.60
Month 12		
n	23	23
Mean (SD)	4.150 (0.3558)	0.117 (0.3835)
Median	4.100	0.100
Min, Max	3.50, 5.20	-0.60, 1.00
Month 15		
n	16	16
Mean (SD)	4.175 (0.3536)	0.121 (0.4254)
Median	4.050	0.100
Min, Max	3.60, 4.70	-0.70, 0.70

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Potassium (mmol/L)		
Month 18		
n	10	10
Mean (SD)	4.119 (0.4803)	0.083 (0.4499)
Median	3.950	0.000
Min, Max	3.40, 4.80	-0.50, 0.80
Month 21		
n	8	8
Mean (SD)	4.063 (0.2925)	0.063 (0.2774)
Median	4.050	0.100
Min, Max	3.70, 4.60	-0.50, 0.40
EOS		
n	167	165
Mean (SD)	4.093 (0.3774)	0.034 (0.4563)
Median	4.100	0.100
Min, Max	3.10, 5.00	-1.80, 1.30

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Chloride (mmol/L)		
Screening		
n	160	
Mean (SD)	103.45 (2.727)	
Median	103.00	
Min, Max	95.0, 110.0	
Pre-Infusion		
n	170	
Mean (SD)	103.54 (2.686)	
Median	104.00	
Min, Max	94.0, 114.0	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Chloride (mmol/L)		
Month 1		
n	158	158
Mean (SD)	103.37 (2.654)	-0.18 (2.578)
Median	103.00	0.00
Min, Max	96.0, 110.0	-8.4, 7.0
Month 2		
n	154	153
Mean (SD)	103.47 (2.827)	-0.06 (2.783)
Median	104.00	0.00
Min, Max	96.0, 110.0	-9.0, 8.0
Month 3		
n	148	146
Mean (SD)	103.28 (2.720)	-0.27 (2.828)
Median	103.00	0.00
Min, Max	96.0, 110.0	-16.0, 7.1

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Chloride (mmol/L)		
Month 4		
n	130	128
Mean (SD)	103.43 (2.526)	-0.24 (2.948)
Median	103.70	0.00
Min, Max	97.0, 109.0	-14.3, 6.0
Month 5		
n	97	95
Mean (SD)	103.95 (2.347)	0.02 (2.421)
Median	104.00	0.00
Min, Max	98.0, 109.0	-5.0, 6.0
Month 6		
n	83	81
Mean (SD)	104.00 (2.572)	0.02 (2.322)
Median	104.00	0.00
Min, Max	98.0, 110.0	-5.0, 6.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Chloride (mmol/L)		
Month 9		
n	54	54
Mean (SD)	104.13 (2.299)	0.04 (2.347)
Median	104.00	0.00
Min, Max	100.0, 111.0	-6.0, 6.0
Month 12		
n	24	24
Mean (SD)	103.83 (1.949)	-0.38 (2.356)
Median	104.00	0.00
Min, Max	101.0, 109.0	-7.0, 4.0
Month 15		
n	16	16
Mean (SD)	105.00 (2.608)	0.63 (3.074)
Median	104.50	1.00
Min, Max	100.0, 111.0	-5.0, 6.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Chloride (mmol/L)		
Month 18		
n	10	10
Mean (SD)	104.00 (1.700)	-0.50 (2.121)
Median	104.00	-0.50
Min, Max	101.0, 107.0	-4.0, 3.0
Month 21		
n	8	8
Mean (SD)	103.75 (1.488)	-1.25 (2.816)
Median	104.50	-1.00
Min, Max	102.0, 105.0	-6.0, 3.0
EOS		
n	161	160
Mean (SD)	102.91 (2.953)	-0.62 (2.784)
Median	103.00	0.00
Min, Max	90.0, 111.0	-11.0, 10.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Blood Urea Nitrogen (umol/L)		
Screening		
n	87	
Mean (SD)	4.6249 (1.62761)	
Median	4.6410	
Min, Max	1.703, 9.925	
Pre-Infusion		
n	88	
Mean (SD)	4.4546 (1.49094)	
Median	4.5732	
Min, Max	1.590, 8.008	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Blood Urea Nitrogen (umol/L)		
Month 1		
n	86	85
Mean (SD)	4.3069 (1.53193)	-0.1195 (1.18025)
Median	4.2840	0.0000
Min, Max	1.553, 8.568	-3.570, 3.142
Month 2		
n	80	80
Mean (SD)	4.2888 (1.59518)	-0.1101 (1.18533)
Median	4.2420	0.0000
Min, Max	1.239, 9.996	-3.213, 2.680
Month 3		
n	76	76
Mean (SD)	4.2212 (1.60146)	-0.1257 (1.19621)
Median	4.2840	0.0000
Min, Max	0.179, 8.925	-4.820, 2.499

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Blood Urea Nitrogen (umol/L)		
Month 4		
n	62	62
Mean (SD)	4.9174 (1.40215)	0.2395 (1.33409)
Median	4.6410	0.3213
Min, Max	1.785, 9.007	-2.356, 4.670
Month 5		
n	52	52
Mean (SD)	5.0972 (1.60064)	0.3118 (1.39679)
Median	4.6410	0.3570
Min, Max	1.999, 9.282	-3.570, 4.820
Month 6		
n	43	43
Mean (SD)	5.0918 (1.13839)	0.4104 (1.13604)
Median	5.0000	0.3570
Min, Max	2.856, 8.200	-1.785, 2.535

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Blood Urea Nitrogen (umol/L)		
Month 9		
n	29	29
Mean (SD)	4.8609 (1.63255)	0.1398 (1.70369)
Median	4.6410	0.0000
Min, Max	2.499, 11.674	-2.499, 7.211
Month 12		
n	10	10
Mean (SD)	5.4121 (1.49923)	0.4784 (1.30891)
Median	5.3550	0.2142
Min, Max	3.570, 8.211	-1.071, 3.177
Month 15		
n	8	8
Mean (SD)	4.8552 (1.77651)	-0.1294 (1.22097)
Median	4.2662	-0.3035
Min, Max	3.177, 8.211	-2.142, 2.142

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Blood Urea Nitrogen (umol/L)		
Month 18		
n	6	6
Mean (SD)	4.7184 (1.49334)	-0.0833 (0.67648)
Median	4.2662	-0.2142
Min, Max	2.856, 7.140	-1.071, 0.714
Month 21		
n	4	4
Mean (SD)	6.5153 (1.94174)	1.2495 (0.94453)
Median	6.7830	1.4280
Min, Max	3.927, 8.568	0.000, 2.142
EOS		
n	85	85
Mean (SD)	4.4854 (1.52278)	0.0396 (1.11745)
Median	4.2840	0.0000
Min, Max	1.607, 8.211	-3.570, 3.427

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Creatinine (umol/L)		
Screening		
n	172	
Mean (SD)	74.3852 (14.42669)	
Median	72.7440	
Min, Max	31.824, 121.108	
Pre-Infusion		
n	173	
Mean (SD)	74.7436 (15.06186)	
Median	73.8000	
Min, Max	37.000, 121.108	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Creatinine (umol/L)		
Month 1		
n	166	165
Mean (SD)	74.5627 (15.38556)	-0.0524 (12.11085)
Median	73.3720	0.8840
Min, Max	21.000, 132.600	-47.000, 50.800
Month 2		
n	157	156
Mean (SD)	73.6802 (14.81408)	-0.9498 (11.97421)
Median	73.0000	0.0000
Min, Max	34.476, 143.208	-46.000, 37.128
Month 3		
n	151	150
Mean (SD)	74.1965 (14.11840)	-0.9807 (12.27429)
Median	74.2560	0.0000
Min, Max	13.000, 119.340	-44.000, 47.800

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Creatinine (umol/L)		
Month 4		
n	133	132
Mean (SD)	75.1097 (16.19289)	1.1733 (10.90555)
Median	74.2560	0.0000
Min, Max	35.360, 149.396	-34.100, 43.000
Month 5		
n	105	104
Mean (SD)	74.2093 (13.87516)	1.2099 (8.15778)
Median	73.0000	1.7680
Min, Max	41.548, 118.456	-23.868, 23.000
Month 6		
n	86	86
Mean (SD)	73.4420 (13.27063)	1.4372 (8.43769)
Median	72.4880	1.7680
Min, Max	38.896, 115.804	-23.868, 18.200

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Creatinine (umol/L)		
Month 9		
n	57	57
Mean (SD)	73.7161 (13.21907)	2.2575 (8.50604)
Median	71.6040	3.5360
Min, Max	37.128, 113.152	-16.796, 17.680
Month 12		
n	24	24
Mean (SD)	74.9558 (12.28778)	2.9098 (7.42578)
Median	72.9300	2.6520
Min, Max	52.156, 101.660	-10.608, 20.332
Month 15		
n	16	16
Mean (SD)	74.9190 (12.19151)	4.0332 (9.03221)
Median	74.6980	3.9780
Min, Max	51.272, 93.704	-11.492, 20.332

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Creatinine (umol/L)		
Month 18		
n	11	11
Mean (SD)	76.1847 (10.51788)	4.5004 (9.90281)
Median	76.0240	6.1880
Min, Max	60.112, 93.704	-15.912, 20.332
Month 21		
n	8	8
Mean (SD)	79.5600 (13.99323)	4.4200 (8.33294)
Median	80.8860	2.2100
Min, Max	61.880, 97.240	-4.420, 21.216
EOS		
n	170	169
Mean (SD)	74.1476 (13.77221)	-0.7829 (12.31332)
Median	73.1860	0.0000
Min, Max	39.000, 118.000	-55.500, 47.400

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Gamma Glutamyl Transferase (U/L)		
Screening		
n	165	
Mean (SD)	42.51 (67.616)	
Median	25.00	
Min, Max	8.0, 598.0	
Pre-Infusion		
n	167	
Mean (SD)	43.41 (63.431)	
Median	25.00	
Min, Max	8.0, 454.0	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Gamma Glutamyl Transferase (U/L)		
Month 1		
n	162	160
Mean (SD)	43.42 (68.018)	0.66 (31.553)
Median	24.50	0.00
Min, Max	3.0, 609.0	-135.0, 307.0
Month 2		
n	152	149
Mean (SD)	41.15 (57.510)	1.04 (19.677)
Median	25.00	0.00
Min, Max	9.0, 425.0	-67.0, 153.0
Month 3		
n	148	145
Mean (SD)	41.95 (66.194)	0.05 (21.189)
Median	24.00	0.00
Min, Max	4.0, 508.0	-76.0, 155.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Gamma Glutamyl Transferase (U/L)		
Month 4		
n	131	126
Mean (SD)	44.60 (63.579)	0.09 (22.605)
Median	26.00	0.00
Min, Max	7.0, 411.0	-82.0, 133.0
Month 5		
n	104	101
Mean (SD)	43.59 (62.309)	1.11 (22.988)
Median	25.50	-1.00
Min, Max	7.0, 391.0	-63.0, 119.0
Month 6		
n	85	83
Mean (SD)	47.59 (65.113)	2.68 (29.503)
Median	25.00	0.00
Min, Max	8.0, 383.0	-141.0, 113.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Gamma Glutamyl Transferase (U/L)		
Month 9		
n	56	56
Mean (SD)	53.70 (79.779)	10.08 (40.821)
Median	22.50	0.00
Min, Max	8.0, 450.0	-44.0, 180.0
Month 12		
n	24	24
Mean (SD)	47.58 (70.130)	-1.71 (37.217)
Median	25.50	0.00
Min, Max	9.0, 292.0	-57.0, 156.0
Month 15		
n	16	16
Mean (SD)	51.19 (76.325)	-2.69 (11.068)
Median	29.50	-3.00
Min, Max	11.0, 328.0	-21.0, 26.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Gamma Glutamyl Transferase (U/L)		
Month 18		
n	10	10
Mean (SD)	65.70 (98.535)	2.70 (13.655)
Median	26.00	1.50
Min, Max	11.0, 334.0	-15.0, 32.0
Month 21		
n	8	8
Mean (SD)	25.38 (15.519)	-1.38 (8.450)
Median	21.00	-1.00
Min, Max	11.0, 59.0	-16.0, 11.0
EOS		
n	165	162
Mean (SD)	44.62 (71.561)	4.94 (37.783)
Median	25.00	0.00
Min, Max	8.0, 521.0	-70.0, 348.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Alkaline Phosphatase (U/L)		
Screening		
n	169	
Mean (SD)	116.38 (106.279)	
Median	84.00	
Min, Max	35.0, 989.0	
Pre-Infusion		
n	173	
Mean (SD)	112.93 (104.325)	
Median	85.00	
Min, Max	34.0, 1025.0	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Alkaline Phosphatase (U/L)		
Month 1		
n	166	165
Mean (SD)	115.81 (115.299)	2.56 (26.467)
Median	83.00	0.00
Min, Max	33.0, 1168.0	-116.0, 143.0
Month 2		
n	157	156
Mean (SD)	114.57 (123.840)	5.00 (36.809)
Median	84.00	0.00
Min, Max	38.0, 1344.0	-98.0, 319.0
Month 3		
n	151	150
Mean (SD)	116.07 (129.894)	6.09 (42.216)
Median	82.00	0.50
Min, Max	39.0, 1408.0	-118.0, 383.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Alkaline Phosphatase (U/L)		
Month 4		
n	132	131
Mean (SD)	117.25 (139.476)	7.80 (43.906)
Median	83.50	1.00
Min, Max	34.0, 1454.0	-92.0, 429.0
Month 5		
n	104	103
Mean (SD)	113.12 (144.624)	2.10 (37.519)
Median	80.00	0.00
Min, Max	38.0, 1365.0	-76.0, 340.0
Month 6		
n	85	85
Mean (SD)	121.02 (160.217)	5.00 (42.886)
Median	84.00	1.00
Min, Max	30.0, 1381.0	-59.0, 356.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Alkaline Phosphatase (U/L)		
Month 9		
n	57	57
Mean (SD)	123.97 (163.791)	-0.86 (28.208)
Median	77.00	-1.00
Min, Max	26.0, 1141.0	-111.0, 116.0
Month 12		
n	24	24
Mean (SD)	106.25 (96.719)	-6.50 (30.010)
Median	80.50	-3.00
Min, Max	35.0, 505.0	-136.0, 35.0
Month 15		
n	16	16
Mean (SD)	106.19 (99.915)	-12.25 (43.121)
Median	86.50	-2.00
Min, Max	49.0, 473.0	-168.0, 15.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Alkaline Phosphatase (U/L)		
Month 18		
n	11	11
Mean (SD)	85.64 (24.250)	2.09 (11.211)
Median	82.00	2.00
Min, Max	46.0, 126.0	-17.0, 20.0
Month 21		
n	8	8
Mean (SD)	77.63 (23.231)	-0.88 (16.907)
Median	84.50	2.00
Min, Max	48.0, 105.0	-38.0, 16.0
EOS		
n	165	164
Mean (SD)	115.72 (104.665)	1.76 (30.718)
Median	84.00	-1.00
Min, Max	33.0, 1055.0	-146.0, 147.3

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Alanine Aminotransferase (U/L)		
Screening		
n	172	
Mean (SD)	32.03 (23.688)	
Median	23.00	
Min, Max	6.0, 152.0	
Pre-Infusion		
n	173	
Mean (SD)	32.77 (27.169)	
Median	24.00	
Min, Max	7.0, 194.0	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Alanine Aminotransferase (U/L)		
Month 1		
n	166	165
Mean (SD)	34.75 (33.487)	1.72 (16.738)
Median	25.00	0.00
Min, Max	6.0, 304.0	-44.0, 110.0
Month 2		
n	158	157
Mean (SD)	36.44 (41.584)	3.38 (25.130)
Median	26.00	0.00
Min, Max	7.0, 438.0	-53.0, 244.0
Month 3		
n	150	149
Mean (SD)	33.11 (25.705)	1.51 (17.071)
Median	26.00	0.00
Min, Max	4.0, 166.0	-62.0, 110.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Alanine Aminotransferase (U/L)		
Month 4		
n	133	132
Mean (SD)	34.08 (24.568)	1.08 (13.917)
Median	27.00	1.00
Min, Max	7.0, 140.0	-44.7, 60.0
Month 5		
n	105	104
Mean (SD)	33.53 (24.166)	2.02 (14.928)
Median	26.00	1.00
Min, Max	6.0, 148.0	-46.0, 68.0
Month 6		
n	86	86
Mean (SD)	35.57 (28.537)	3.34 (15.800)
Median	25.00	1.00
Min, Max	6.0, 141.0	-27.0, 69.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Alanine Aminotransferase (U/L)		
Month 9		
n	57	57
Mean (SD)	39.46 (35.202)	7.17 (23.650)
Median	26.00	0.00
Min, Max	7.0, 175.0	-25.0, 100.0
Month 12		
n	24	24
Mean (SD)	40.17 (41.885)	4.42 (39.550)
Median	26.50	-1.50
Min, Max	11.0, 215.0	-40.0, 180.0
Month 15		
n	16	16
Mean (SD)	45.06 (33.646)	3.00 (13.726)
Median	34.00	0.50
Min, Max	15.0, 121.0	-15.0, 41.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Alanine Aminotransferase (U/L)		
Month 18		
n	11	11
Mean (SD)	52.64 (36.615)	2.36 (26.337)
Median	44.00	4.00
Min, Max	20.0, 140.0	-46.0, 60.0
Month 21		
n	8	8
Mean (SD)	42.88 (25.402)	2.38 (9.870)
Median	36.50	-0.50
Min, Max	20.0, 94.0	-9.0, 18.0
EOS		
n	169	168
Mean (SD)	35.25 (37.467)	2.40 (25.189)
Median	25.00	0.00
Min, Max	5.7, 327.0	-88.3, 199.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Aspartate Aminotransferase (U/L)		
Screening		
n	171	
Mean (SD)	26.98 (16.777)	
Median	23.00	
Min, Max	12.0, 177.0	
Pre-Infusion		
n	173	
Mean (SD)	27.68 (21.859)	
Median	23.00	
Min, Max	12.0, 199.0	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Aspartate Aminotransferase (U/L)		
Month 1		
n	165	164
Mean (SD)	29.08 (22.513)	1.20 (11.269)
Median	23.00	0.00
Min, Max	2.0, 198.0	-37.0, 68.4
Month 2		
n	158	157
Mean (SD)	29.20 (27.506)	1.61 (18.718)
Median	23.50	2.00
Min, Max	12.0, 323.0	-123.0, 155.0
Month 3		
n	150	149
Mean (SD)	26.96 (16.497)	0.46 (10.083)
Median	22.30	0.00
Min, Max	6.0, 145.0	-54.0, 36.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Aspartate Aminotransferase (U/L)		
Month 4		
n	133	132
Mean (SD)	26.14 (13.572)	-1.38 (11.495)
Median	22.00	0.00
Min, Max	11.0, 105.0	-94.0, 20.0
Month 5		
n	105	104
Mean (SD)	27.24 (12.632)	1.25 (10.267)
Median	24.00	1.00
Min, Max	9.0, 83.0	-44.0, 47.0
Month 6		
n	86	86
Mean (SD)	27.12 (12.968)	1.30 (9.265)
Median	23.00	1.00
Min, Max	11.0, 81.0	-46.0, 34.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Aspartate Aminotransferase (U/L)		
Month 9		
n	57	57
Mean (SD)	30.07 (25.302)	3.35 (22.547)
Median	22.00	1.00
Min, Max	7.0, 172.0	-29.0, 156.0
Month 12		
n	24	24
Mean (SD)	30.25 (22.838)	-1.75 (24.255)
Median	23.00	-1.50
Min, Max	14.0, 119.0	-62.0, 89.0
Month 15		
n	16	16
Mean (SD)	31.00 (19.110)	-5.19 (15.337)
Median	22.00	-2.50
Min, Max	12.0, 69.0	-58.0, 13.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Aspartate Aminotransferase (U/L)		
Month 18		
n	11	11
Mean (SD)	36.00 (24.751)	-7.09 (14.300)
Median	28.00	-1.00
Min, Max	8.0, 90.0	-37.0, 8.0
Month 21		
n	8	8
Mean (SD)	34.25 (21.009)	0.88 (5.793)
Median	26.50	0.50
Min, Max	17.0, 78.0	-8.0, 10.0
EOS		
n	168	167
Mean (SD)	28.03 (23.010)	0.69 (13.861)
Median	24.00	0.00
Min, Max	9.0, 248.0	-68.0, 80.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Albumin (g/dL)		
Screening		
n	169	
Mean (SD)	45.081 (3.7792)	
Median	45.100	
Min, Max	35.00, 56.00	
Pre-Infusion		
n	173	
Mean (SD)	44.596 (3.7633)	
Median	44.300	
Min, Max	34.79, 54.00	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Albumin (g/dL)		
Month 1		
n	160	160
Mean (SD)	44.472 (3.5648)	-0.144 (3.2182)
Median	45.000	0.000
Min, Max	28.30, 53.00	-11.10, 9.00
Month 2		
n	159	159
Mean (SD)	44.541 (3.8036)	-0.124 (3.4504)
Median	45.000	0.000
Min, Max	34.00, 55.00	-13.70, 11.00
Month 3		
n	150	150
Mean (SD)	45.095 (3.6561)	0.407 (3.2001)
Median	45.650	0.000
Min, Max	34.00, 53.00	-6.80, 11.00

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Albumin (g/dL)		
Month 4		
n	131	131
Mean (SD)	45.001 (3.6181)	0.287 (2.9951)
Median	45.000	0.000
Min, Max	35.00, 52.40	-7.00, 10.00
Month 5		
n	103	103
Mean (SD)	44.557 (3.6448)	0.000 (2.9264)
Median	45.000	0.000
Min, Max	35.00, 52.00	-7.00, 6.00
Month 6		
n	86	86
Mean (SD)	44.634 (3.6028)	0.080 (2.8700)
Median	45.000	0.300
Min, Max	36.00, 51.22	-7.10, 8.00

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Albumin (g/dL)		
Month 9		
n	57	57
Mean (SD)	44.696 (4.2390)	0.413 (3.8902)
Median	45.000	0.000
Min, Max	33.56, 54.30	-7.10, 18.50
Month 12		
n	24	24
Mean (SD)	45.492 (3.5238)	1.196 (4.0645)
Median	45.550	1.000
Min, Max	40.00, 57.00	-7.20, 8.20
Month 15		
n	16	16
Mean (SD)	45.394 (3.4992)	1.006 (1.8778)
Median	44.500	1.000
Min, Max	39.40, 52.00	-2.00, 4.00

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Albumin (g/dL)		
Month 18		
n	11	11
Mean (SD)	44.745 (4.2170)	1.364 (3.9055)
Median	43.000	0.000
Min, Max	40.00, 54.00	-2.30, 10.00
Month 21		
n	8	8
Mean (SD)	44.475 (3.1945)	0.512 (3.0451)
Median	44.400	1.000
Min, Max	40.00, 49.00	-4.90, 4.00
EOS		
n	165	165
Mean (SD)	45.472 (3.7303)	0.860 (3.8126)
Median	46.000	1.000
Min, Max	36.06, 59.00	-10.40, 15.00

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Bilirubin (umol/L)		
Screening		
n	171	
Mean (SD)	13.9900 (11.97324)	
Median	10.2624	
Min, Max	2.395, 104.000	
Pre-Infusion		
n	169	
Mean (SD)	12.9790 (11.54631)	
Median	10.0000	
Min, Max	3.000, 96.000	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Bilirubin (umol/L)		
Month 1		
n	164	159
Mean (SD)	12.8988 (9.93707)	-0.0334 (6.43029)
Median	10.2624	0.1000
Min, Max	1.710, 97.000	-32.840, 20.600
Month 2		
n	159	154
Mean (SD)	12.0589 (7.65624)	-0.3380 (5.59035)
Median	9.6000	0.0000
Min, Max	3.000, 46.181	-35.000, 19.841
Month 3		
n	150	146
Mean (SD)	12.3495 (7.27361)	0.0813 (5.89031)
Median	10.2624	0.0000
Min, Max	3.421, 41.050	-29.400, 19.300

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Bilirubin (umol/L)		
Month 4		
n	133	128
Mean (SD)	11.0221 (6.91645)	-0.2954 (5.79061)
Median	9.0000	0.0000
Min, Max	3.000, 45.900	-25.600, 31.700
Month 5		
n	105	100
Mean (SD)	11.4331 (5.96950)	0.1632 (5.06423)
Median	10.2624	0.0000
Min, Max	3.421, 38.142	-21.300, 14.400
Month 6		
n	86	82
Mean (SD)	10.7880 (6.01910)	-0.7287 (4.88626)
Median	8.7230	0.0000
Min, Max	3.000, 39.339	-22.800, 8.552

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Bilirubin (umol/L)		
Month 9		
n	56	53
Mean (SD)	11.3229 (5.93003)	-0.3413 (7.85013)
Median	9.8812	0.8552
Min, Max	3.800, 34.208	-41.221, 10.604
Month 12		
n	24	21
Mean (SD)	12.7639 (7.19285)	0.0977 (5.50142)
Median	11.9728	1.7104
Min, Max	3.421, 32.840	-14.709, 6.842
Month 15		
n	16	13
Mean (SD)	11.2031 (10.14985)	-0.2237 (4.00479)
Median	9.1506	0.0000
Min, Max	3.421, 47.891	-6.842, 5.815

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Bilirubin (umol/L)		
Month 18		
n	11	8
Mean (SD)	12.2527 (11.51730)	0.4704 (3.98904)
Median	8.5520	-0.5986
Min, Max	4.276, 45.326	-5.131, 7.013
Month 21		
n	8	6
Mean (SD)	11.5452 (2.89110)	2.1380 (2.72754)
Median	11.5452	1.6249
Min, Max	8.552, 16.249	-0.684, 6.842
EOS		
n	169	164
Mean (SD)	13.1706 (12.01843)	0.1500 (5.47814)
Median	10.4000	0.0000
Min, Max	2.000, 128.000	-22.000, 32.000

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Protein (g/L)		
Screening		
n	166	
Mean (SD)	76.452 (5.6793)	
Median	76.000	
Min, Max	53.00, 93.70	
Pre-Infusion		
n	166	
Mean (SD)	75.698 (6.7212)	
Median	75.620	
Min, Max	62.10, 122.00	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Protein (g/L)		
Month 1		
n	161	157
Mean (SD)	74.923 (5.8277)	-0.624 (7.2027)
Median	75.000	0.100
Min, Max	56.00, 90.00	-55.00, 14.00
Month 2		
n	157	152
Mean (SD)	74.765 (6.1432)	-0.686 (7.4017)
Median	75.300	0.000
Min, Max	52.00, 92.00	-55.00, 20.00
Month 3		
n	150	145
Mean (SD)	75.627 (6.3166)	0.195 (7.3364)
Median	75.250	1.000
Min, Max	43.60, 94.70	-43.00, 27.70

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Protein (g/L)		
Month 4		
n	132	126
Mean (SD)	74.737 (4.7048)	-0.288 (5.3533)
Median	74.100	0.000
Min, Max	65.40, 88.60	-15.00, 19.55
Month 5		
n	102	97
Mean (SD)	74.115 (4.6383)	-0.605 (4.7695)
Median	74.000	0.000
Min, Max	62.00, 86.00	-16.00, 9.00
Month 6		
n	86	80
Mean (SD)	74.547 (4.3806)	0.229 (4.7326)
Median	74.000	1.000
Min, Max	65.00, 88.10	-11.00, 11.20

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Protein (g/L)		
Month 9		
n	57	53
Mean (SD)	73.491 (4.2123)	-0.190 (4.7820)
Median	72.700	0.000
Min, Max	65.00, 83.00	-13.00, 9.30
Month 12		
n	24	21
Mean (SD)	74.188 (4.5746)	0.543 (4.1756)
Median	75.000	1.000
Min, Max	65.60, 83.00	-8.00, 8.00
Month 15		
n	16	13
Mean (SD)	74.375 (4.0483)	-0.392 (3.8967)
Median	76.000	0.000
Min, Max	67.00, 80.00	-7.00, 5.00

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Protein (g/L)		
Month 18		
n	11	8
Mean (SD)	74.918 (5.1755)	2.875 (6.3401)
Median	75.000	0.250
Min, Max	67.80, 87.00	-2.00, 17.00
Month 21		
n	8	6
Mean (SD)	73.750 (4.7434)	1.333 (3.8816)
Median	75.000	2.000
Min, Max	67.00, 80.00	-3.00, 7.00
EOS		
n	164	159
Mean (SD)	75.956 (5.3809)	0.394 (6.7250)
Median	75.000	1.000
Min, Max	66.00, 97.00	-43.00, 18.00

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Glucose (mmol/L)		
Screening		
n	165	
Mean (SD)	4.8908 (0.85793)	
Median	4.7730	
Min, Max	2.800, 8.492	
Pre-Infusion		
n	165	
Mean (SD)	5.0650 (3.00897)	
Median	4.7000	
Min, Max	3.219, 41.800	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Glucose (mmol/L)		
Month 1		
n	161	156
Mean (SD)	4.9029 (0.80120)	0.0532 (0.97779)
Median	4.8600	0.2000
Min, Max	2.700, 7.659	-6.327, 2.276
Month 2		
n	157	150
Mean (SD)	4.9539 (0.82659)	0.1213 (1.05725)
Median	4.8285	0.1110
Min, Max	2.331, 7.300	-5.994, 2.600
Month 3		
n	148	141
Mean (SD)	5.0330 (0.87578)	0.1973 (1.07781)
Median	4.9100	0.2000
Min, Max	2.997, 8.603	-4.940, 4.218

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Glucose (mmol/L)		
Month 4		
n	132	124
Mean (SD)	4.9229 (0.95735)	0.0493 (1.15271)
Median	4.8840	0.0000
Min, Max	2.720, 8.991	-5.384, 4.940
Month 5		
n	105	98
Mean (SD)	4.9826 (0.95314)	0.0858 (1.20134)
Median	4.8000	0.0728
Min, Max	2.498, 8.420	-6.161, 3.608
Month 6		
n	86	79
Mean (SD)	5.1140 (1.02512)	0.1797 (1.29611)
Median	5.0505	0.2220
Min, Max	2.900, 9.158	-5.828, 5.162

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Glucose (mmol/L)		
Month 9		
n	56	52
Mean (SD)	4.9171 (0.93560)	-0.0378 (1.42520)
Median	4.7993	0.1055
Min, Max	2.775, 8.381	-6.050, 2.831
Month 12		
n	23	20
Mean (SD)	4.9974 (1.23156)	0.2165 (0.98345)
Median	4.8840	-0.0833
Min, Max	2.831, 9.380	-1.720, 2.220
Month 15		
n	15	12
Mean (SD)	5.1356 (0.99919)	-0.0324 (0.79215)
Median	5.1060	0.2220
Min, Max	3.608, 7.770	-1.499, 1.110

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Glucose (mmol/L)		
Month 18		
n	11	8
Mean (SD)	5.2321 (1.02099)	0.0208 (0.87499)
Median	5.1060	0.1942
Min, Max	4.218, 7.937	-1.720, 1.221
Month 21		
n	8	6
Mean (SD)	5.5500 (0.48746)	0.2405 (1.24680)
Median	5.4668	0.5550
Min, Max	4.940, 6.494	-1.665, 1.443
EOS		
n	163	158
Mean (SD)	4.9292 (0.94121)	-0.1477 (2.74055)
Median	4.8400	0.0555
Min, Max	2.600, 10.000	-31.800, 3.330

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Calcium (mmol/L)		
Screening		
n	165	
Mean (SD)	2.3523 (0.19727)	
Median	2.3703	
Min, Max	0.930, 2.970	
Pre-Infusion		
n	171	
Mean (SD)	2.3176 (0.18671)	
Median	2.3300	
Min, Max	0.930, 2.900	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Calcium (mmol/L)		
Month 1		
n	161	160
Mean (SD)	2.3114 (0.19024)	-0.0032 (0.11905)
Median	2.3400	0.0000
Min, Max	0.930, 2.610	-0.590, 0.240
Month 2		
n	156	155
Mean (SD)	2.3240 (0.18525)	0.0058 (0.11778)
Median	2.3350	0.0000
Min, Max	0.990, 2.600	-0.500, 0.260
Month 3		
n	146	145
Mean (SD)	2.3108 (0.19237)	0.0017 (0.13681)
Median	2.3453	0.0000
Min, Max	1.030, 2.645	-0.700, 0.300

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Calcium (mmol/L)		
Month 4		
n	130	129
Mean (SD)	2.3319 (0.19328)	0.0164 (0.10418)
Median	2.3600	0.0250
Min, Max	1.030, 2.610	-0.299, 0.200
Month 5		
n	103	102
Mean (SD)	2.3327 (0.20720)	0.0195 (0.12137)
Median	2.3500	0.0225
Min, Max	1.160, 2.930	-0.249, 0.420
Month 6		
n	84	84
Mean (SD)	2.3252 (0.19986)	0.0175 (0.09661)
Median	2.3700	0.0275
Min, Max	1.190, 2.580	-0.250, 0.290

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Calcium (mmol/L)		
Month 9		
n	54	53
Mean (SD)	2.3028 (0.26995)	0.0008 (0.10489)
Median	2.3651	0.0250
Min, Max	0.980, 2.520	-0.274, 0.270
Month 12		
n	24	24
Mean (SD)	2.3625 (0.11463)	0.0087 (0.12168)
Median	2.3827	0.0550
Min, Max	2.096, 2.530	-0.274, 0.225
Month 15		
n	16	16
Mean (SD)	2.3530 (0.09544)	-0.0062 (0.11263)
Median	2.3601	0.0000
Min, Max	2.061, 2.480	-0.274, 0.175

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Calcium (mmol/L)		
Month 18		
n	11	11
Mean (SD)	2.3466 (0.05925)	0.0386 (0.10306)
Median	2.3500	0.0300
Min, Max	2.221, 2.443	-0.150, 0.217
Month 21		
n	8	8
Mean (SD)	2.3540 (0.11436)	0.0586 (0.08659)
Median	2.3703	0.0449
Min, Max	2.171, 2.495	-0.055, 0.225
EOS		
n	165	163
Mean (SD)	2.3347 (0.19551)	0.0196 (0.12330)
Median	2.3600	0.0250
Min, Max	0.980, 2.844	-0.590, 0.374

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Urea (mmol/L)		
Screening		
n	113	
Mean (SD)	4.9685 (1.65571)	
Median	4.8000	
Min, Max	1.860, 13.487	
Pre-Infusion		
n	113	
Mean (SD)	4.9742 (1.60469)	
Median	4.8285	
Min, Max	1.860, 12.488	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Urea (mmol/L)		
Month 1		
n	109	108
Mean (SD)	4.8423 (1.66054)	-0.0732 (1.15931)
Median	4.8000	-0.1665
Min, Max	1.800, 11.322	-3.200, 3.746
Month 2		
n	103	102
Mean (SD)	4.8236 (1.51672)	-0.1042 (1.19127)
Median	4.5000	-0.1832
Min, Max	2.700, 12.654	-3.330, 3.140
Month 3		
n	100	99
Mean (SD)	4.8251 (1.91683)	-0.1372 (1.27869)
Median	4.7000	-0.1000
Min, Max	2.200, 18.315	-3.663, 5.828

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Urea (mmol/L)		
Month 4		
n	84	83
Mean (SD)	5.1771 (2.18686)	0.2293 (1.55367)
Median	4.8000	0.0000
Min, Max	2.600, 18.981	-2.331, 6.494
Month 5		
n	59	58
Mean (SD)	5.1008 (1.94029)	0.1755 (1.34209)
Median	4.6620	0.0000
Min, Max	2.400, 12.700	-2.300, 6.500
Month 6		
n	48	48
Mean (SD)	5.3421 (2.00344)	0.3196 (1.20027)
Median	5.3307	0.3665
Min, Max	2.200, 14.486	-2.831, 3.000

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Urea (mmol/L)		
Month 9		
n	30	30
Mean (SD)	4.9383 (2.07212)	0.0855 (0.98846)
Median	4.6620	0.0000
Min, Max	2.700, 14.319	-1.499, 1.832
Month 12		
n	14	14
Mean (SD)	4.9831 (1.04789)	0.1308 (1.22383)
Median	4.9118	0.0000
Min, Max	3.330, 7.160	-1.499, 2.664
Month 15		
n	8	8
Mean (SD)	4.9950 (0.89884)	0.2289 (1.27717)
Median	4.9950	0.4163
Min, Max	3.830, 6.660	-1.832, 1.665

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Urea (mmol/L)		
Month 18		
n	5	5
Mean (SD)	5.6277 (1.38506)	0.8991 (1.39602)
Median	4.8285	0.4995
Min, Max	4.496, 7.826	-0.167, 3.330
Month 21		
n	4	4
Mean (SD)	4.8285 (0.69319)	0.2498 (0.51767)
Median	4.8285	0.2498
Min, Max	3.996, 5.661	-0.333, 0.833
EOS		
n	107	107
Mean (SD)	4.8581 (1.79370)	-0.1319 (1.31405)
Median	4.5000	-0.1000
Min, Max	1.998, 15.651	-4.300, 3.163

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Lactate Dehydrogenase (U/L)		
Screening		
n	147	
Mean (SD)	243.23 (104.289)	
Median	210.00	
Min, Max	88.0, 627.0	
Pre-Infusion		
n	160	
Mean (SD)	248.89 (104.646)	
Median	221.55	
Min, Max	88.0, 531.0	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Lactate Dehydrogenase (U/L)		
Month 1		
n	147	143
Mean (SD)	234.02 (98.751)	-20.29 (54.390)
Median	199.00	-16.00
Min, Max	36.0, 562.0	-211.0, 253.0
Month 2		
n	147	143
Mean (SD)	243.24 (116.196)	-8.19 (66.778)
Median	211.00	-8.90
Min, Max	91.0, 736.0	-222.0, 389.0
Month 3		
n	138	135
Mean (SD)	255.12 (220.838)	2.48 (202.748)
Median	204.50	-11.00
Min, Max	47.0, 2572.0	-230.0, 2263.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Lactate Dehydrogenase (U/L)		
Month 4		
n	125	119
Mean (SD)	233.57 (94.321)	-17.88 (56.859)
Median	196.00	-14.00
Min, Max	105.7, 495.0	-243.0, 110.4
Month 5		
n	101	96
Mean (SD)	242.68 (98.475)	-8.51 (68.407)
Median	214.00	-4.50
Min, Max	101.0, 548.0	-226.0, 352.0
Month 6		
n	84	81
Mean (SD)	239.34 (93.869)	-2.54 (63.127)
Median	204.50	2.00
Min, Max	87.0, 539.0	-223.0, 192.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Lactate Dehydrogenase (U/L)		
Month 9		
n	54	54
Mean (SD)	224.35 (99.935)	-14.81 (81.476)
Median	196.50	-6.50
Min, Max	88.0, 590.0	-251.0, 231.0
Month 12		
n	24	24
Mean (SD)	208.58 (84.242)	-34.83 (82.598)
Median	187.50	-11.00
Min, Max	104.0, 433.0	-294.0, 87.0
Month 15		
n	16	16
Mean (SD)	227.38 (123.160)	-32.06 (97.942)
Median	176.00	-6.50
Min, Max	102.0, 476.0	-275.0, 94.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	Total (N=174)	
	Absolute Value	Change from Baseline
Lactate Dehydrogenase (U/L)		
Month 18		
n	10	10
Mean (SD)	235.80 (141.118)	-21.80 (94.505)
Median	183.00	2.50
Min, Max	104.0, 499.0	-265.0, 75.0
Month 21		
n	8	8
Mean (SD)	249.00 (118.601)	-75.00 (107.053)
Median	189.50	-48.00
Min, Max	156.0, 459.0	-252.0, 44.0
EOS		
n	157	151
Mean (SD)	238.21 (100.685)	-12.32 (70.934)
Median	212.00	-4.00
Min, Max	78.8, 644.0	-295.0, 213.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Hemoglobin (g/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-5.6 (10.03)
Median	-4.0
Min, Max	-58, 21
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	9.0 (9.65)
Median	8.0
Min, Max	-21, 53
Change from Baseline to Final Value	
n	173
Mean (SD)	4.0 (11.49)
Median	4.0
Min, Max	-26, 53

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Hematocrit (L/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-0.0 (0.03)
Median	-0.0
Min, Max	-0, 0
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	0.0 (0.04)
Median	0.0
Min, Max	-0, 0
Change from Baseline to Final Value	
n	173
Mean (SD)	0.0 (0.03)
Median	0.0
Min, Max	-0, 0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Erythrocytes (10^12/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-0.2 (0.45)
Median	-0.2
Min, Max	-4, 1
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	0.3 (0.63)
Median	0.3
Min, Max	-4, 4
Change from Baseline to Final Value	
n	173
Mean (SD)	0.1 (0.49)
Median	0.1
Min, Max	-4, 2

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Erythrocyte Mean Corpuscular Volume (fL)	
Change from Baseline to Lowest Post-baseline Value	
n	172
Mean (SD)	-2.7 (5.09)
Median	-1.9
Min, Max	-55, 3
Change from Baseline to Highest Post-baseline Value	
n	172
Mean (SD)	2.0 (4.89)
Median	1.3
Min, Max	-9, 54
Change from Baseline to Final Value	
n	172
Mean (SD)	-0.2 (5.44)
Median	0.0
Min, Max	-16, 53

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	Total (N=174)
Leukocytes (10^9/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-1.0 (1.22)
Median	-0.9
Min, Max	-7, 3
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	1.7 (1.89)
Median	1.5
Min, Max	-3, 9
Change from Baseline to Final Value	
n	173
Mean (SD)	0.2 (1.86)
Median	0.0
Min, Max	-7, 8

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	Total (N=174)
Neutrophils (10^9/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-0.8 (1.04)
Median	-0.8
Min, Max	-4, 3
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	1.5 (1.71)
Median	1.2
Min, Max	-3, 7
Change from Baseline to Final Value	
n	173
Mean (SD)	0.2 (1.48)
Median	0.1
Min, Max	-4, 7

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Lymphocytes (10^9/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-0.4 (0.49)
Median	-0.4
Min, Max	-2, 1
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	0.4 (0.52)
Median	0.4
Min, Max	-1, 2
Change from Baseline to Final Value	
n	173
Mean (SD)	0.0 (0.58)
Median	0.0
Min, Max	-2, 2

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Monocytes (10^9/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-0.1 (0.19)
Median	-0.1
Min, Max	-1, 0
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	0.2 (0.21)
Median	0.2
Min, Max	-0, 1
Change from Baseline to Final Value	
n	173
Mean (SD)	0.0 (0.23)
Median	0.0
Min, Max	-1, 1

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Eosinophils (10^9/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-0.1 (0.11)
Median	-0.1
Min, Max	-1, 0
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	0.1 (0.16)
Median	0.1
Min, Max	-0, 1
Change from Baseline to Final Value	
n	173
Mean (SD)	-0.0 (0.14)
Median	0.0
Min, Max	-1, 1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Basophils (10^9/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-0.0 (0.03)
Median	-0.0
Min, Max	-0, 0
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	0.0 (0.09)
Median	0.0
Min, Max	-0, 1
Change from Baseline to Final Value	
n	173
Mean (SD)	-0.0 (0.04)
Median	0.0
Min, Max	-0, 0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	Total (N=174)
Platelets (10^9/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-22.9 (33.51)
Median	-19.0
Min, Max	-157, 75
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	32.7 (51.17)
Median	27.0
Min, Max	-75, 418
Change from Baseline to Final Value	
n	173
Mean (SD)	2.4 (41.82)
Median	1.0
Min, Max	-132, 161

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Sodium (mmol/L)	
Change from Baseline to Lowest Post-baseline Value	
n	172
Mean (SD)	-2.67 (4.219)
Median	-2.00
Min, Max	-30.00, 13.00
Change from Baseline to Highest Post-baseline Value	
n	172
Mean (SD)	2.91 (3.665)
Median	2.00
Min, Max	-5.70, 28.00
Change from Baseline to Final Value	
n	172
Mean (SD)	-0.06 (4.132)
Median	0.00
Min, Max	-24.10, 14.10

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Potassium (mmol/L)	
Change from Baseline to Lowest Post-baseline Value	
n	172
Mean (SD)	-0.254 (0.4371)
Median	-0.200
Min, Max	-2.400, 0.700
Change from Baseline to Highest Post-baseline Value	
n	172
Mean (SD)	0.503 (0.6200)
Median	0.400
Min, Max	-0.800, 4.000
Change from Baseline to Final Value	
n	172
Mean (SD)	0.035 (0.4547)
Median	0.100
Min, Max	-1.800, 1.300

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Chloride (mmol/L)	
Change from Baseline to Lowest Post-baseline Value	
n	170
Mean (SD)	-2.40 (2.640)
Median	-2.00
Min, Max	-16.00, 10.00
Change from Baseline to Highest Post-baseline Value	
n	170
Mean (SD)	2.02 (2.490)
Median	2.00
Min, Max	-8.40, 10.00
Change from Baseline to Final Value	
n	170
Mean (SD)	-0.64 (2.938)
Median	0.00
Min, Max	-14.30, 10.00

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Blood Urea Nitrogen (umol/L)	
Change from Baseline to Lowest Post-baseline Value	
n	88
Mean (SD)	-0.9918 (1.00569)
Median	-0.8962
Min, Max	-4.8195, 0.7854
Change from Baseline to Highest Post-baseline Value	
n	88
Mean (SD)	1.0815 (1.44445)
Median	0.9514
Min, Max	-2.1420, 7.2114
Change from Baseline to Final Value	
n	88
Mean (SD)	0.0426 (1.10822)
Median	0.0000
Min, Max	-3.5700, 3.4272

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Creatinine (umol/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-8.5999 (10.27276)
Median	-7.0000
Min, Max	-55.5000, 8.0000
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	8.3748 (11.26440)
Median	8.0000
Min, Max	-27.0000, 50.8000
Change from Baseline to Final Value	
n	173
Mean (SD)	-0.7992 (12.23242)
Median	0.0000
Min, Max	-55.5000, 47.4000

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Gamma Glutamyl Transferase (U/L)	
Change from Baseline to Lowest Post-baseline Value	
n	167
Mean (SD)	-8.64 (19.483)
Median	-4.00
Min, Max	-141.00, 71.00
Change from Baseline to Highest Post-baseline Value	
n	167
Mean (SD)	15.32 (44.968)
Median	5.00
Min, Max	-67.00, 348.00
Change from Baseline to Final Value	
n	167
Mean (SD)	4.09 (38.947)
Median	0.00
Min, Max	-141.00, 348.00

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	Total (N=174)
Alkaline Phosphatase (U/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-12.95 (22.643)
Median	-8.00
Min, Max	-168.00, 42.50
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	18.47 (43.205)
Median	9.00
Min, Max	-59.00, 429.00
Change from Baseline to Final Value	
n	173
Mean (SD)	1.57 (30.193)
Median	-1.00
Min, Max	-146.00, 147.30

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Alanine Aminotransferase (U/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-7.30 (14.610)
Median	-4.00
Min, Max	-88.30, 64.00
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	16.20 (29.817)
Median	10.00
Min, Max	-36.00, 244.00
Change from Baseline to Final Value	
n	173
Mean (SD)	2.36 (24.901)
Median	0.00
Min, Max	-88.30, 199.00

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Aspartate Aminotransferase (U/L)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-5.96 (13.565)
Median	-4.00
Min, Max	-123.00, 28.00
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	10.63 (21.175)
Median	6.00
Min, Max	-37.00, 156.00
Change from Baseline to Final Value	
n	173
Mean (SD)	0.38 (13.868)
Median	0.00
Min, Max	-68.00, 80.00

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	Total (N=174)
Albumin (g/dL)	
Change from Baseline to Lowest Post-baseline Value	
n	173
Mean (SD)	-2.513 (2.7633)
Median	-2.000
Min, Max	-13.700, 4.000
Change from Baseline to Highest Post-baseline Value	
n	173
Mean (SD)	2.963 (3.4846)
Median	3.000
Min, Max	-4.000, 18.500
Change from Baseline to Final Value	
n	173
Mean (SD)	0.797 (3.7656)
Median	1.000
Min, Max	-10.400, 15.000

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Bilirubin (umol/L)	
Change from Baseline to Lowest Post-baseline Value	
n	169
Mean (SD)	-3.9330 (6.98163)
Median	-2.3946
Min, Max	-50.0000, 9.0651
Change from Baseline to Highest Post-baseline Value	
n	169
Mean (SD)	4.0422 (6.01429)
Median	3.5918
Min, Max	-22.0000, 32.0000
Change from Baseline to Final Value	
n	169
Mean (SD)	0.1830 (5.40391)
Median	0.0000
Min, Max	-22.0000, 32.0000

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Protein (g/L)	
Change from Baseline to Lowest Post-baseline Value	
n	166
Mean (SD)	-4.714 (6.4016)
Median	-3.700
Min, Max	-55.000, 10.000
Change from Baseline to Highest Post-baseline Value	
n	166
Mean (SD)	4.334 (5.8457)
Median	4.050
Min, Max	-11.800, 27.700
Change from Baseline to Final Value	
n	166
Mean (SD)	0.285 (6.6424)
Median	1.000
Min, Max	-43.000, 18.000

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	Total (N=174)
Glucose (mmol/L)	
Change from Baseline to Lowest Post-baseline Value	
n	165
Mean (SD)	-0.8526 (2.59243)
Median	-0.5000
Min, Max	-31.8000, 1.5540
Change from Baseline to Highest Post-baseline Value	
n	165
Mean (SD)	0.7855 (2.79043)
Median	0.9000
Min, Max	-31.8000, 5.1615
Change from Baseline to Final Value	
n	165
Mean (SD)	-0.1508 (2.68224)
Median	0.0000
Min, Max	-31.8000, 3.3300

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Calcium (mmol/L)	
Change from Baseline to Lowest Post-baseline Value	
n	171
Mean (SD)	-0.0802 (0.10902)
Median	-0.0749
Min, Max	-0.7000, 0.1700
Change from Baseline to Highest Post-baseline Value	
n	171
Mean (SD)	0.0922 (0.11723)
Median	0.0998
Min, Max	-0.5000, 0.4200
Change from Baseline to Final Value	
n	171
Mean (SD)	0.0171 (0.12274)
Median	0.0250
Min, Max	-0.5900, 0.3743

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Urea (mmol/L)	
Change from Baseline to Lowest Post-baseline Value	
n	112
Mean (SD)	-1.0283 (0.97701)
Median	-0.9000
Min, Max	-4.3000, 1.3320
Change from Baseline to Highest Post-baseline Value	
n	112
Mean (SD)	1.0359 (1.56649)
Median	0.8663
Min, Max	-4.3000, 6.5000
Change from Baseline to Final Value	
n	112
Mean (SD)	-0.1272 (1.29242)
Median	-0.1000
Min, Max	-4.3000, 3.1635

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value
(Safety Population)

Parameter (Unit)	Total (N=174)
Lactate Dehydrogenase (U/L)	
Change from Baseline to Lowest Post-baseline Value	
n	160
Mean (SD)	-48.31 (59.720)
Median	-33.00
Min, Max	-295.00, 175.00
Change from Baseline to Highest Post-baseline Value	
n	160
Mean (SD)	52.08 (189.709)
Median	27.50
Min, Max	-166.00, 2263.00
Change from Baseline to Final Value	
n	160
Mean (SD)	-11.05 (77.409)
Median	-3.50
Min, Max	-295.00, 352.00

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.5 Hematology Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Hemoglobin (g/L)	
Month 1	0
Month 2	2 (1.1)
Month 3	0
Month 4	0
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0
Hematocrit (L/L)	
Month 1	0
Month 2	1 (0.6)
Month 3	0
Month 4	0
Month 5	0
Month 6	0

Source: Listing 16.2.8.1
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group

Table 14.3.4.5 Hematology Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Hematocrit (L/L)	
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	1 (0.6)
Erythrocytes (10^12/L)	
Month 1	0
Month 2	1 (0.6)
Month 3	0
Month 4	0
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0

Source: Listing 16.2.8.1
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group

Table 14.3.4.5 Hematology Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Erythrocyte Mean Corpuscular Volume (fL)	
Month 1	0
Month 2	0
Month 3	0
Month 4	0
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0
Leukocytes (10^9/L)	
Month 1	1 (0.6)
Month 2	2 (1.1)
Month 3	0
Month 4	0
Month 5	0
Month 6	0
Month 9	0
Month 12	0

Source: Listing 16.2.8.1
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group

Table 14.3.4.5 Hematology Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Leukocytes (10^9/L)	
Month 15	0
Month 18	0
Month 21	0
EOS	2 (1.1)
Neutrophils (10^9/L)	
Month 1	1 (0.6)
Month 2	0
Month 3	0
Month 4	1 (0.6)
Month 5	1 (0.6)
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	1 (0.6)
Lymphocytes (10^9/L)	
Month 1	1 (0.6)
Month 2	0

Source: Listing 16.2.8.1
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group

Table 14.3.4.5 Hematology Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Lymphocytes (10^9/L)	
Month 3	0
Month 4	0
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0
Monocytes (10^9/L)	
Month 1	1 (0.6)
Month 2	0
Month 3	0
Month 4	0
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0

Source: Listing 16.2.8.1
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group

Table 14.3.4.5 Hematology Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Monocytes (10^9/L)	
Month 21	0
EOS	0
Eosinophils (10^9/L)	
Month 1	0
Month 2	0
Month 3	0
Month 4	0
Month 5	0
Month 6	1 (0.6)
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0
Basophils (10^9/L)	
Month 1	0
Month 2	0
Month 3	0
Month 4	0

Source: Listing 16.2.8.1
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group

Table 14.3.4.5 Hematology Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Basophils (10^9/L)	
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0
Platelets (10^9/L)	
Month 1	0
Month 2	0
Month 3	0
Month 4	0
Month 5	1 (0.6)
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0

Source: Listing 16.2.8.1
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Sodium (mmol/L)	
Month 1	0
Month 2	0
Month 3	0
Month 4	0
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0
Potassium (mmol/L)	
Month 1	0
Month 2	0
Month 3	0
Month 4	0

Source: Listing 16.2.8.2
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group.

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Potassium (mmol/L)	
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0
Chloride (mmol/L)	
Month 1	0
Month 2	0
Month 3	0
Month 4	0
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0

Source: Listing 16.2.8.2
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group.

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) / Visit	Total (N=174) n	(%)
Blood Urea Nitrogen (umol/L)		
Month 1	0	
Month 2	0	
Month 3	0	
Month 4	0	
Month 5	0	
Month 6	0	
Month 9	0	
Month 12	0	
Month 15	0	
Month 18	0	
Month 21	0	
EOS	0	
Creatinine (umol/L)		
Month 1	0	
Month 2	1	(0.6)
Month 3	1	(0.6)
Month 4	1	(0.6)

Source: Listing 16.2.8.2
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group.

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Creatinine (umol/L)	
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0
Gamma Glutamyl Transferase (U/L)	
Month 1	0
Month 2	0
Month 3	0
Month 4	0
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0

Source: Listing 16.2.8.2
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group.

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) / Visit	Total (N=174) n	(%)
Alkaline Phosphatase (U/L)		
Month 1	0	
Month 2	0	
Month 3	0	
Month 4	0	
Month 5	0	
Month 6	0	
Month 9	0	
Month 12	0	
Month 15	0	
Month 18	0	
Month 21	0	
EOS	0	
Alanine Aminotransferase (U/L)		
Month 1	0	
Month 2	1	(0.6)
Month 3	0	
Month 4	1	(0.6)

Source: Listing 16.2.8.2
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group.

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Alanine Aminotransferase (U/L)	
Month 5	1 (0.6)
Month 6	1 (0.6)
Month 9	2 (1.1)
Month 12	1 (0.6)
Month 15	0
Month 18	0
Month 21	0
EOS	1 (0.6)
Aspartate Aminotransferase (U/L)	
Month 1	1 (0.6)
Month 2	1 (0.6)
Month 3	0
Month 4	1 (0.6)
Month 5	0
Month 6	0
Month 9	1 (0.6)
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0

Source: Listing 16.2.8.2
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group.

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Albumin (g/dL)	
Month 1	0
Month 2	0
Month 3	0
Month 4	0
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0
Bilirubin (umol/L)	
Month 1	1 (0.6)
Month 2	1 (0.6)
Month 3	1 (0.6)
Month 4	1 (0.6)

Source: Listing 16.2.8.2
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group.

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Bilirubin (umol/L)	
Month 5	1 (0.6)
Month 6	1 (0.6)
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0
Protein (g/L)	
Month 1	0
Month 2	1 (0.6)
Month 3	1 (0.6)
Month 4	1 (0.6)
Month 5	2 (1.1)
Month 6	0
Month 9	1 (0.6)
Month 12	0
Month 15	0
Month 18	1 (0.6)
Month 21	0
EOS	1 (0.6)

Source: Listing 16.2.8.2
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group.

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Glucose (mmol/L)	
Month 1	1 (0.6)
Month 2	0
Month 3	2 (1.1)
Month 4	1 (0.6)
Month 5	1 (0.6)
Month 6	1 (0.6)
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0
Calcium (mmol/L)	
Month 1	0
Month 2	0
Month 3	0
Month 4	0

Source: Listing 16.2.8.2
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group.

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Calcium (mmol/L)	
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0
Urea (mmol/L)	
Month 1	0
Month 2	0
Month 3	0
Month 4	0
Month 5	0
Month 6	0
Month 9	0
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0

Source: Listing 16.2.8.2
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group.

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	Total (N=174) n (%)
Lactate Dehydrogenase (U/L)	
Month 1	0
Month 2	0
Month 3	0
Month 4	0
Month 5	2 (1.1)
Month 6	0
Month 9	1 (0.6)
Month 12	0
Month 15	0
Month 18	0
Month 21	0
EOS	0

Source: Listing 16.2.8.2
Notes: [1] Treatment-emergent abnormal results are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by investigator
[2] Table presents number and proportion of subjects [n (%)]
[3] Percentages are based on the number of subjects in the respective group.

Table 14.3.5.2 Vital Signs Treatment-Emergent Potentially Clinically Significant Results
(Safety Population)

Parameter (Unit) Result Criterion	Total (N=174) n (%)
Diastolic Blood Pressure (mmHg)	
First Result Post-Baseline	
Low	1 (0.6)
High	1 (0.6)
Last Measured Result	
Low	0
High	0
Heart Rate (bpm)	
First Result Post-Baseline	
Low	0
High	0
Last Measured Result	
Low	0
High	0

Source: Listing 16.2.9.1
Notes: [1] Table presents number and percentage of subjects [(n (%)]
[2] Percentages are based on the number of subjects in the respective group.

Table 14.3.5.2 Vital Signs Treatment-Emergent Potentially Clinically Significant Results
(Safety Population)

Parameter (Unit) Result Criterion	Total (N=174) n (%)
Systolic Blood Pressure (mmHg)	
First Result Post-Baseline	
Low	0
High	0
Last Measured Result	
Low	0
High	0
Body Temperature (°C)	
First Result Post-Baseline	
Low	0
High	0
Last Measured Result	
Low	0
High	0

Source: Listing 16.2.9.1
Notes: [1] Table presents number and percentage of subjects [(n (%)]
[2] Percentages are based on the number of subjects in the respective group.

Table 14.1.5.1J Japanese Demographics
(Japanese Efficacy Population)

	On-Demand (N=1)	Prophylaxis (N=9)	Total (N=10)
Age (years)			
n	1	9	10
Mean (SD)	29.0 ( )	28.2 (12.33)	28.3 (11.62)
Median	29.0	34.0	31.5
Min, Max	29, 29	12, 46	12, 46
Age Group [n (%)]			
12 to <18 years	0	2 (22.2)	2 (20.0)
>=18 to <=65 years	1(100.0)	7 (77.8)	8 (80.0)
Race [n (%)]			
American Indian/Alaska Native	0	0	0
Asian	1 (100.0)	9 (100.0)	10 (100.0)
Black or African American	0	0	0
Native Hawaiian/Other Pacific Islander	0	0	0
White	0	0	0
Other	0	0	0
Ethnicity [n (%)]			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	1 (100.0)	9 (100.0)	10 (100.0)
Not Reported	0	0	0
Unknown	0	0	0
Country [n (%)]			
Japan	1 (100.0)	9 (100.0)	10 (100.0)

Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.

Table 14.1.5.1J Japanese Demographics
(Japanese Efficacy Population)

	On-Demand (N=1)	Prophylaxis (N=9)	Total (N=10)
Geographical Region [n (%)]			
Japan	1 (100.0)	9 (100.0)	10 (100.0)
Height (cm)			
n	1	9	10
Mean (SD)	160.0 ( )	166.6 (5.85)	165.9 (5.89)
Median	160.0	169.7	166.1
Min, Max	160, 160	159, 174	159, 174
Weight (kg)			
n	1	9	10
Mean (SD)	59.1 ( )	57.6 (11.47)	57.7 (10.83)
Median	59.1	59.5	59.3
Min, Max	59, 59	38, 74	38, 74
BMI (kg/m^2)			
n	1	9	10
Mean (SD)	23.1 ( )	20.6 (3.31)	20.9 (3.22)
Median	23.1	19.8	20.4
Min, Max	23, 23	15, 25	15, 25
BMI Category [n (%)]			
<30 kg/m2	1 (100.0)	9 (100.0)	10 (100.0)
>=30 kg/m2	0	0	0

Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.

Table 14.1.6.2J Japanese Medical/Surgical History
(Japanese Efficacy Population)

System Organ Class Preferred Term	Past History						Active History					
	On-Demand (N=1)		Prophylaxis (N=9)		Total (N=10)		On-Demand (N=1)		Prophylaxis (N=9)		Total (N=10)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any Medical/Surgical History	1	(100.0)	7	(77.8)	8	(80.0)	1	(100.0)	9	(100.0)	10	(100.0)
Musculoskeletal and connective tissue disorders	0		1	(11.1)	1	(10.0)	1	(100.0)	8	(88.9)	9	(90.0)
Haemophilic arthropathy	0		0		0		1	(100.0)	8	(88.9)	9	(90.0)
Muscle haemorrhage	0		1	(11.1)	1	(10.0)	0		0		0	
Surgical and medical procedures	1	(100.0)	5	(55.6)	6	(60.0)	0		1	(11.1)	1	(10.0)
Appendicectomy	0		2	(22.2)	2	(20.0)	0		0		0	
Synovectomy	0		2	(22.2)	2	(20.0)	0		0		0	
Tooth extraction	0		2	(22.2)	2	(20.0)	0		0		0	
Wisdom teeth removal	0		1	(11.1)	1	(10.0)	0		0		0	
Cataract operation	1	(100.0)	0		1	(10.0)	0		0		0	
Knee operation	1	(100.0)	0		1	(10.0)	0		0		0	
Cholecystectomy	0		1	(11.1)	1	(10.0)	0		0		0	
Hepatitis B immunisation	0		0		0		0		1	(11.1)	1	(10.0)
Lithotripsy	0		1	(11.1)	1	(10.0)	0		0		0	
Meniscus operation	0		1	(11.1)	1	(10.0)	0		0		0	
Mole excision	1	(100.0)	0		1	(10.0)	0		0		0	

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)].
[2] Medical/Surgical histories were coded using MedDRA Version 14.1.

Table 14.1.6.2J Japanese Medical/Surgical History
(Japanese Efficacy Population)

System Organ Class Preferred Term	Past History						Active History					
	On-Demand (N=1)		Prophylaxis (N=9)		Total (N=10)		On-Demand (N=1)		Prophylaxis (N=9)		Total (N=10)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Congenital, familial and genetic disorders	0		0		0		0		4	(44.4)	4	(40.0)
Factor VIII deficiency	0		0		0		0		4	(44.4)	4	(40.0)
Infections and infestations	0		1	(11.1)	1	(10.0)	0		3	(33.3)	3	(30.0)
Hepatitis C	0		1	(11.1)	1	(10.0)	0		2	(22.2)	2	(20.0)
HIV infection	0		0		0		0		2	(22.2)	2	(20.0)
Anal abscess	0		1	(11.1)	1	(10.0)	0		0		0	
Appendicitis	0		1	(11.1)	1	(10.0)	0		0		0	
Otitis externa	0		1	(11.1)	1	(10.0)	0		0		0	
Trichophytosis	0		1	(11.1)	1	(10.0)	0		0		0	
Respiratory, thoracic and mediastinal disorders	0		2	(22.2)	2	(20.0)	0		3	(33.3)	3	(30.0)
Rhinitis allergic	0		0		0		0		3	(33.3)	3	(30.0)
Asthma	0		1	(11.1)	1	(10.0)	0		0		0	
Pharyngeal haematoma	0		1	(11.1)	1	(10.0)	0		0		0	
Eye disorders	1	(100.0)	1	(11.1)	2	(20.0)	0		2	(22.2)	2	(20.0)
Conjunctivitis allergic	0		0		0		0		2	(22.2)	2	(20.0)
Cataract	1	(100.0)	0		1	(10.0)	0		0		0	
Retinopathy	0		1	(11.1)	1	(10.0)	0		0		0	

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)].
[2] Medical/Surgical histories were coded using MedDRA Version 14.1.

Table 14.1.6.2J Japanese Medical/Surgical History
(Japanese Efficacy Population)

System Organ Class Preferred Term	Past History						Active History					
	On-Demand (N=1)		Prophylaxis (N=9)		Total (N=10)		On-Demand (N=1)		Prophylaxis (N=9)		Total (N=10)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	0		0		0		0		3	(33.3)	3	(30.0)
Dental caries	0		0		0		0		2	(22.2)	2	(20.0)
Gingivitis	0		0		0		0		1	(11.1)	1	(10.0)
Nervous system disorders	0		1	(11.1)	1	(10.0)	0		2	(22.2)	2	(20.0)
Haemorrhage intracranial	0		1	(11.1)	1	(10.0)	0		0		0	
Headache	0		0		0		0		1	(11.1)	1	(10.0)
Syringomyelia	0		0		0		0		1	(11.1)	1	(10.0)
Immune system disorders	0		0		0		0		2	(22.2)	2	(20.0)
Seasonal allergy	0		0		0		0		2	(22.2)	2	(20.0)
Psychiatric disorders	0		0		0		0		2	(22.2)	2	(20.0)
Insomnia	0		0		0		0		1	(11.1)	1	(10.0)
Neurosis	0		0		0		0		1	(11.1)	1	(10.0)
Skin and subcutaneous tissue disorders	0		0		0		0		2	(22.2)	2	(20.0)
Dermatitis atopic	0		0		0		0		1	(11.1)	1	(10.0)
Leukoderma	0		0		0		0		1	(11.1)	1	(10.0)

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)].
[2] Medical/Surgical histories were coded using MedDRA Version 14.1.

Table 14.1.6.2J Japanese Medical/Surgical History
(Japanese Efficacy Population)

System Organ Class Preferred Term	Past History						Active History					
	On-Demand (N=1)		Prophylaxis (N=9)		Total (N=10)		On-Demand (N=1)		Prophylaxis (N=9)		Total (N=10)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hepatobiliary disorders	0		1	(11.1)	1	(10.0)	0		1	(11.1)	1	(10.0)
Cholelithiasis	0		1	(11.1)	1	(10.0)	0		0		0	
Hepatic function abnormal	0		0		0		0		1	(11.1)	1	(10.0)
Blood and lymphatic system disorders	0		1	(11.1)	1	(10.0)	0		0		0	
Anaemia haemolytic autoimmune	0		1	(11.1)	1	(10.0)	0		0		0	
Injury, poisoning and procedural complications	0		1	(11.1)	1	(10.0)	0		0		0	
Extradural haematoma	0		1	(11.1)	1	(10.0)	0		0		0	
Metabolism and nutrition disorders	0		0		0		0		1	(11.1)	1	(10.0)
Dyslipidaemia	0		0		0		0		1	(11.1)	1	(10.0)
Renal and urinary disorders	0		1	(11.1)	1	(10.0)	0		0		0	
Calculus urinary	0		1	(11.1)	1	(10.0)	0		0		0	
Reproductive system and breast disorders	0		0		0		0		1	(11.1)	1	(10.0)
Erectile dysfunction	0		0		0		0		1	(11.1)	1	(10.0)

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)].
[2] Medical/Surgical histories were coded using MedDRA Version 14.1.

Table 14.1.6.2J Japanese Medical/Surgical History
(Japanese Efficacy Population)

System Organ Class Preferred Term	Past History						Active History					
	On-Demand (N=1)		Prophylaxis (N=9)		Total (N=10)		On-Demand (N=1)		Prophylaxis (N=9)		Total (N=10)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Vascular disorders	0		0		0		0		1	(11.1)	1	(10.0)
Phlebitis superficial	0		0		0		0		1	(11.1)	1	(10.0)

Source: Listing 16.2.4.3
Notes: [1] Table presents number and percentage of subjects [n (%)].
[2] Medical/Surgical histories were coded using MedDRA Version 14.1.

Table 14.1.13J Japanese Preventive and Additional Doses
(Japanese Efficacy Population)

	On-demand (N=1)	Prophylaxis (N=9)	Total (N=10)
Preventative Doses			
Any Preventative Doses [n (%)]	1 (100.0)	3 (33.3)	4 (40.0)
Total Number of Preventative Doses			
n	1	3	4
Mean (SD)	16.0	2.3 (1.53)	5.8 (6.95)
Median	16.0	2.0	3.0
Min, Max	16, 16	1, 4	1, 16
Number of Preventative Doses	16	7	23
Additional Doses			
Any Additional Doses [n (%)]	0	0	0
Total Number of Additional Doses			
n	0	0	0
Mean (SD)	0	0	0
Median	0	0	0
Min, Max	0	0	0
Number of Additional Doses	0	0	0

Notes: [1] Where indicated, table presents number and percentage of subjects [n(%)].

Table 14.1.13J Japanese Preventive and Additional Doses
(Japanese Efficacy Population)

	On-demand (N=1)	Prophylaxis (N=9)	Total (N=10)
Preventative or Additional Doses			
Any Preventative or Additional Doses [n (%)]	1 (100.0)	3 (33.3)	4 (40.0)
Total Number of Preventative or Additional Doses			
n	1	3	4
Mean (SD)	16.0	2.3 (1.53)	5.8 (6.95)
Median	16.0	2.0	3.0
Min, Max	16, 16	1, 4	1, 16
Number of Preventative or Additional Doses	16	7	23

Source: Listing 16.2.5.4
Notes: [1] Where indicated, table presents number and percentage of subjects [n(%)].

Table 14.3.2.1J Summary of Adverse Events
(Japanese and Global Safety Population)

	Japanese (N=10)			Global (N=174)		
	n	(%)	E	n	(%)	E
Any Adverse Events	8	(80.0)	20	121	(69.5)	325
Any Treatment-Emergent Adverse Events	8	(80.0)	20	113	(64.9)	292
Any Treatment-Emergent Adverse Events Leading to Study Drug Withdrawal	0		0	0		0
Treatment-Emergent Adverse Event Severity						
Mild	8	(80.0)	18	94	(54.0)	225
Moderate	2	(20.0)	2	43	(24.7)	61
Severe	0		0	5	(2.9)	6
Any Treatment-Emergent Adverse Events Related to Study Drug	1	(10.0)	1	13	(7.5)	19
Treatment-Emergent Adverse Event Outcome						
Death Related to Adverse Event	0		0	0		0
Not Recovered/Not Resolved	3	(30.0)	3	22	(12.6)	25
Recovered/Resolved	8	(80.0)	17	104	(59.8)	256
Recovered/Resolved With Sequelae	0		0	1	(0.6)	1
Recovering/Resolving	0		0	9	(5.2)	10
Unknown	0		0	0		0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).

Table 14.3.2.1J Summary of Adverse Events
(Japanese and Global Safety Population)

	Japanese (N=10)			Global (N=174)		
	n	(%)	E	n	(%)	E
Any Serious Adverse Events	0		0	8	(4.6)	10
Any Treatment-Emergent Serious Adverse Events	0		0	7	(4.0)	9
Any Treatment-Emergent Serious Adverse Events Leading to Study Drug Withdrawal	0		0	0		0
Any Treatment-Emergent Serious Adverse Events Related to Study Drug	0		0	1	(0.6)	1
Treatment-Emergent Serious Adverse Event Severity						
Mild	0		0	1	(0.6)	2
Moderate	0		0	2	(1.1)	2
Severe	0		0	4	(2.3)	5
Treatment-Emergent Serious Adverse Event Outcome						
Death Related to Adverse Event	0		0	0		0
Not Recovered/Not Resolved	0		0	0		0
Recovered/Resolved	0		0	7	(4.0)	9
Recovered/Resolved With Sequelae	0		0	0		0
Recovering/Resolving	0		0	0		0
Unknown	0		0	0		0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).

Table 14.3.2.32J Summary of Treatment-Emergent Adverse Events Over Time
(Japanese and Global Safety Population)

Category / Population	All events N Sub.	All events n	All events (%)	All events E	Month 0-6 N Sub.	Month 0-6 n	Month 0-6 (%)	Month 0-6 E	Month 6-12 N Sub.	Month 6-12 n	Month 6-12 (%)	Month 6-12 E
Any adverse events												
Japanese	10	8	(80.0)	20	10	6	(60.0)	12	9	4	(44.4)	7
Global	174	113	(64.9)	292	174	101	(58.0)	231	101	24	(23.8)	39
Related adverse events												
Japanese	10	1	(10.0)	1	10	1	(10.0)	1	9	0		0
Global	174	13	(7.5)	19	174	12	(6.9)	17	101	2	(2.0)	2
Serious adverse events												
Japanese	10	0		0	10	0		0	9	0		0
Global	174	7	(4.0)	9	174	5	(2.9)	5	101	1	(1.0)	1
Discontinuation due to adverse events												
Japanese	10	0		0	10	0		0	9	0		0
Global	174	0		0	174	0		0	101	0		0

Notes: [1] N Sub. = Total number of subjects.
[2] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.

Table 14.3.2.32J Summary of Treatment-Emergent Adverse Events Over Time
(Japanese and Global Safety Population)

Category Population	Month 12-18 N Sub.	n	(%)	E	Month 18-24 N Sub.	n	(%)	E	Month 24-30 N Sub.	n	(%)	E
Any adverse events												
Japanese	3	1	(33.3)	1	0	0		0	0	0		0
Global	30	6	(20.0)	10	12	2	(16.7)	2	5	0		0
Related adverse events												
Japanese	3	0		0	0	0		0	0	0		0
Global	30	0		0	12	0		0	5	0		0
Serious adverse events												
Japanese	3	0		0	0	0		0	0	0		0
Global	30	2	(6.7)	3	12	0		0	5	0		0
Discontinuation due to adverse events												
Japanese	3	0		0	0	0		0	0	0		0
Global	30	0		0	12	0		0	5	0		0

Notes: [1] N Sub. = Total number of subjects.
[2] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Nasopharyngitis								
Japanese	10	4 (40.0)	10	2 (20.0)	9	2 (22.2)	3	0
Global	174	18 (10.3)	174	14 (8.0)	101	5 (5.0)	30	0
Arthralgia								
Japanese	10	0	10	0	9	0	3	0
Global	174	17 (9.8)	174	15 (8.6)	101	2 (2.0)	30	0
Headache								
Japanese	10	1 (10.0)	10	1 (10.0)	9	0	3	0
Global	174	12 (6.9)	174	10 (5.7)	101	2 (2.0)	30	0
Rash								
Japanese	10	1 (10.0)	10	1 (10.0)	9	0	3	0
Global	174	7 (4.0)	174	4 (2.3)	101	1 (1.0)	30	0
Toothache								
Japanese	10	0	10	0	9	0	3	0
Global	174	6 (3.4)	174	5 (2.9)	101	1 (1.0)	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Nasopharyngitis				
Japanese	0	0	0	0
Global	12	0	5	0
Arthralgia				
Japanese	0	0	0	0
Global	12	0	5	0
Headache				
Japanese	0	0	0	0
Global	12	0	5	0
Rash				
Japanese	0	0	0	0
Global	12	0	5	0
Toothache				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Upper respiratory tract infection								
Japanese	10	0	10	0	9	0	3	0
Global	174	6 (3.4)	174	6 (3.4)	101	0	30	0
Back pain								
Japanese	10	0	10	0	9	0	3	0
Global	174	5 (2.9)	174	5 (2.9)	101	1 (1.0)	30	0
Cough								
Japanese	10	0	10	0	9	0	3	0
Global	174	5 (2.9)	174	3 (1.7)	101	0	30	3 (10.0)
Hypertension								
Japanese	10	0	10	0	9	0	3	0
Global	174	5 (2.9)	174	5 (2.9)	101	0	30	0
Dizziness								
Japanese	10	1 (10.0)	10	1 (10.0)	9	0	3	0
Global	174	4 (2.3)	174	4 (2.3)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Upper respiratory tract infection				
Japanese	0	0	0	0
Global	12	0	5	0
Back pain				
Japanese	0	0	0	0
Global	12	0	5	0
Cough				
Japanese	0	0	0	0
Global	12	0	5	0
Hypertension				
Japanese	0	0	0	0
Global	12	0	5	0
Dizziness				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Pyrexia								
Japanese	10	0	10	0	9	0	3	0
Global	174	4 (2.3)	174	4 (2.3)	101	0	30	0
Influenza								
Japanese	10	2 (20.0)	10	2 (20.0)	9	0	3	0
Global	174	4 (2.3)	174	3 (1.7)	101	0	30	0
Haemophilic arthropathy								
Japanese	10	0	10	0	9	0	3	0
Global	174	3 (1.7)	174	3 (1.7)	101	1 (1.0)	30	0
Joint injury								
Japanese	10	0	10	0	9	0	3	0
Global	174	3 (1.7)	174	3 (1.7)	101	0	30	0
Viral infection								
Japanese	10	0	10	0	9	0	3	0
Global	174	3 (1.7)	174	3 (1.7)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Pyrexia				
Japanese	0	0	0	0
Global	12	0	5	0
Influenza				
Japanese	0	0	0	0
Global	12	0	5	0
Haemophilic arthropathy				
Japanese	0	0	0	0
Global	12	0	5	0
Joint injury				
Japanese	0	0	0	0
Global	12	0	5	0
Viral infection				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Dental caries								
Japanese	10	0	10	0	9	0	3	0
Global	174	3 (1.7)	174	1 (0.6)	101	2 (2.0)	30	0
Fall								
Japanese	10	0	10	0	9	0	3	0
Global	174	3 (1.7)	174	2 (1.1)	101	0	30	0
Oropharyngeal pain								
Japanese	10	0	10	0	9	0	3	0
Global	174	3 (1.7)	174	3 (1.7)	101	0	30	0
Sinusitis								
Japanese	10	1 (10.0)	10	1 (10.0)	9	0	3	0
Global	174	3 (1.7)	174	2 (1.1)	101	1 (1.0)	30	0
Abdominal pain								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	1 (0.6)	101	1 (1.0)	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Number (%) of subjects	Month 24-30 N Sub.	Number (%) of subjects
Dental caries				
Japanese	0	0	0	0
Global	12	0	5	0
Fall				
Japanese	0	0	0	0
Global	12	1 (8.3)	5	0
Oropharyngeal pain				
Japanese	0	0	0	0
Global	12	0	5	0
Sinusitis				
Japanese	0	0	0	0
Global	12	0	5	0
Abdominal pain				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Hypersensitivity								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Limb injury								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Pain in extremity								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Acne								
Japanese	10	1 (10.0)	10	0	9	1 (11.1)	3	0
Global	174	2 (1.1)	174	1 (0.6)	101	1 (1.0)	30	0
Anaemia								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	1 (0.6)	101	0	30	1 (3.3)

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Hypersensitivity				
Japanese	0	0	0	0
Global	12	0	5	0
Limb injury				
Japanese	0	0	0	0
Global	12	0	5	0
Pain in extremity				
Japanese	0	0	0	0
Global	12	0	5	0
Acne				
Japanese	0	0	0	0
Global	12	0	5	0
Anaemia				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Asthenia								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	1 (0.6)	101	1 (1.0)	30	0
Chest pain								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Conjunctivitis								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	1 (0.6)	101	1 (1.0)	30	0
Contusion								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Gastroenteritis								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	1 (0.6)	101	1 (1.0)	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Asthenia				
Japanese	0	0	0	0
Global	12	0	5	0
Chest pain				
Japanese	0	0	0	0
Global	12	0	5	0
Conjunctivitis				
Japanese	0	0	0	0
Global	12	0	5	0
Contusion				
Japanese	0	0	0	0
Global	12	0	5	0
Gastroenteritis				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Gastroenteritis viral								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Injection site pain								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Laceration								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Leukocytosis								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Ligament sprain								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	1 (0.6)	101	1 (1.0)	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Gastroenteritis viral				
Japanese	0	0	0	0
Global	12	0	5	0
Injection site pain				
Japanese	0	0	0	0
Global	12	0	5	0
Laceration				
Japanese	0	0	0	0
Global	12	0	5	0
Leukocytosis				
Japanese	0	0	0	0
Global	12	0	5	0
Ligament sprain				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Sub.	 Number (%) of subjects	Month 0-6 N Sub.	 Number (%) of subjects	Month 6-12 N Sub.	 Number (%) of subjects	Month 12-18 N Sub.	 Number (%) of subjects
Liver function test abnormal								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	1 (0.6)	101	1 (1.0)	30	0
Nasal congestion								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	1 (0.6)	101	0	30	1 (3.3)
Paraesthesia								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Pharyngitis								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Post-traumatic pain								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Number (%) of subjects	Month 24-30 N Sub.	Number (%) of subjects
Liver function test abnormal				
Japanese	0	0	0	0
Global	12	0	5	0
Nasal congestion				
Japanese	0	0	0	0
Global	12	0	5	0
Paraesthesia				
Japanese	0	0	0	0
Global	12	0	5	0
Pharyngitis				
Japanese	0	0	0	0
Global	12	0	5	0
Post-traumatic pain				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Rhinorrhoea								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Thermal burn								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Viral upper respiratory tract infection								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	1 (0.6)	101	1 (1.0)	30	0
Wound								
Japanese	10	0	10	0	9	0	3	0
Global	174	2 (1.1)	174	2 (1.1)	101	0	30	0
Blood uric acid increased								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Number (%) of subjects	Month 24-30 N Sub.	Number (%) of subjects
Rhinorrhoea				
Japanese	0	0	0	0
Global	12	0	5	0
Thermal burn				
Japanese	0	0	0	0
Global	12	0	5	0
Viral upper respiratory tract infection				
Japanese	0	0	0	0
Global	12	0	5	0
Wound				
Japanese	0	0	0	0
Global	12	0	5	0
Blood uric acid increased				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Sub.	 Number (%) of subjects	Month 0-6 N Sub.	 Number (%) of subjects	Month 6-12 N Sub.	 Number (%) of subjects	Month 12-18 N Sub.	 Number (%) of subjects
Somnolence								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Blood glucose increased								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Chills								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Tooth extraction								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Actinic keratosis								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Number (%) of subjects	Month 24-30 N Sub.	Number (%) of subjects
Somnolence				
Japanese	0	0	0	0
Global	12	0	5	0
Blood glucose increased				
Japanese	0	0	0	0
Global	12	0	5	0
Chills				
Japanese	0	0	0	0
Global	12	0	5	0
Tooth extraction				
Japanese	0	0	0	0
Global	12	0	5	0
Actinic keratosis				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Adverse drug reaction								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Ankle fracture								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	0	30	1 (3.3)
Arrhythmia								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Arthropod bite								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Blood lactate dehydrogenase increased								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Number (%) of subjects	Month 24-30 N Sub.	Number (%) of subjects
Adverse drug reaction				
Japanese	0	0	0	0
Global	12	0	5	0
Ankle fracture				
Japanese	0	0	0	0
Global	12	0	5	0
Arrhythmia				
Japanese	0	0	0	0
Global	12	0	5	0
Arthropod bite				
Japanese	0	0	0	0
Global	12	0	5	0
Blood lactate dehydrogenase increased				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Blood triglycerides increased								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Blood urea increased								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Bronchitis								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
C-reactive protein increased								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Capillary fragility								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Blood triglycerides increased				
Japanese	0	0	0	0
Global	12	0	5	0
Blood urea increased				
Japanese	0	0	0	0
Global	12	0	5	0
Bronchitis				
Japanese	0	0	0	0
Global	12	0	5	0
C-reactive protein increased				
Japanese	0	0	0	0
Global	12	0	5	0
Capillary fragility				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Chillblains								
Japanese	10	1 (10.0)	10	1 (10.0)	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Conjunctival abrasion								
Japanese	10	1 (10.0)	10	0	9	0	3	1 (33.3)
Global	174	1 (0.6)	174	0	101	0	30	1 (3.3)
Constipation								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0
Dermatitis								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	0	30	0
Dermatitis allergic								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Number (%) of subjects	Month 24-30 N Sub.	Number (%) of subjects
Chillblains				
Japanese	0	0	0	0
Global	12	0	5	0
Conjunctival abrasion				
Japanese	0	0	0	0
Global	12	0	5	0
Constipation				
Japanese	0	0	0	0
Global	12	0	5	0
Dermatitis				
Japanese	0	0	0	0
Global	12	1 (8.3)	5	0
Dermatitis allergic				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Sub.	 Number (%) of subjects	Month 0-6 N Sub.	 Number (%) of subjects	Month 6-12 N Sub.	 Number (%) of subjects	Month 12-18 N Sub.	 Number (%) of subjects
Dermatitis atopic								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	0	30	0
Dermatitis contact								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Diarrhoea								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0
Drug specific antibody present								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Dyshidrosis								
Japanese	10	1 (10.0)	10	0	9	1 (11.1)	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Number (%) of subjects	Month 24-30 N Sub.	Number (%) of subjects
Dermatitis atopic				
Japanese	0	0	0	0
Global	12	0	5	0
Dermatitis contact				
Japanese	0	0	0	0
Global	12	0	5	0
Diarrhoea				
Japanese	0	0	0	0
Global	12	0	5	0
Drug specific antibody present				
Japanese	0	0	0	0
Global	12	0	5	0
Dyshidrosis				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Ear infection								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Ear pain								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Ecchymosis								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Eosinophilia								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0
Erythema								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Ear infection				
Japanese	0	0	0	0
Global	12	0	5	0
Ear pain				
Japanese	0	0	0	0
Global	12	0	5	0
Ecchymosis				
Japanese	0	0	0	0
Global	12	0	5	0
Eosinophilia				
Japanese	0	0	0	0
Global	12	0	5	0
Erythema				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Feeling hot								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Fungal skin infection								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Furuncle								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	0	30	1 (3.3)
Gamma-glutamyltransferase increased								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Gastritis								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Feeling hot				
Japanese	0	0	0	0
Global	12	0	5	0
Fungal skin infection				
Japanese	0	0	0	0
Global	12	0	5	0
Furuncle				
Japanese	0	0	0	0
Global	12	0	5	0
Gamma-glutamyltransferase increased				
Japanese	0	0	0	0
Global	12	0	5	0
Gastritis				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Gastrointestinal tract adenoma								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Groin pain								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Haematochezia								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Haematoma								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Haematuria								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Gastrointestinal tract adenoma				
Japanese	0	0	0	0
Global	12	0	5	0
Groin pain				
Japanese	0	0	0	0
Global	12	0	5	0
Haematochezia				
Japanese	0	0	0	0
Global	12	0	5	0
Haematoma				
Japanese	0	0	0	0
Global	12	0	5	0
Haematuria				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Haemorrhoidal haemorrhage								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Hand fracture								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0
Heat rash								
Japanese	10	1 (10.0)	10	1 (10.0)	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Hyperuricaemia								
Japanese	10	1 (10.0)	10	1 (10.0)	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Hypoaesthesia								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
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Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Haemorrhoidal haemorrhage				
Japanese	0	0	0	0
Global	12	0	5	0
Hand fracture				
Japanese	0	0	0	0
Global	12	0	5	0
Heat rash				
Japanese	0	0	0	0
Global	12	0	5	0
Hyperuricaemia				
Japanese	0	0	0	0
Global	12	0	5	0
Hypoaesthesia				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
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Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Iron deficiency								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Iron deficiency anaemia								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Joint range of motion decreased								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Joint swelling								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Local swelling								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Iron deficiency				
Japanese	0	0	0	0
Global	12	0	5	0
Iron deficiency anaemia				
Japanese	0	0	0	0
Global	12	0	5	0
Joint range of motion decreased				
Japanese	0	0	0	0
Global	12	0	5	0
Joint swelling				
Japanese	0	0	0	0
Global	12	0	5	0
Local swelling				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Localised oedema								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Loose tooth								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0
Lower respiratory tract infection								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0
Lumbar spinal stenosis								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Malaise								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
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Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Number (%) of subjects	Month 24-30 N Sub.	Number (%) of subjects
Localised oedema				
Japanese	0	0	0	0
Global	12	0	5	0
Loose tooth				
Japanese	0	0	0	0
Global	12	0	5	0
Lower respiratory tract infection				
Japanese	0	0	0	0
Global	12	0	5	0
Lumbar spinal stenosis				
Japanese	0	0	0	0
Global	12	0	5	0
Malaise				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Migraine								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Muscle spasms								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Muscle strain								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Nasal mucosal disorder								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Neck pain								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
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Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Migraine				
Japanese	0	0	0	0
Global	12	0	5	0
Muscle spasms				
Japanese	0	0	0	0
Global	12	0	5	0
Muscle strain				
Japanese	0	0	0	0
Global	12	0	5	0
Nasal mucosal disorder				
Japanese	0	0	0	0
Global	12	0	5	0
Neck pain				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Oedema peripheral								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Oesophagitis								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Oral fungal infection								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Oral herpes								
Japanese	10	1 (10.0)	10	0	9	1 (11.1)	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0
Otitis media								
Japanese	10	1 (10.0)	10	1 (10.0)	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Number (%) of subjects	Month 24-30 N Sub.	Number (%) of subjects
Oedema peripheral				
Japanese	0	0	0	0
Global	12	0	5	0
Oesophagitis				
Japanese	0	0	0	0
Global	12	0	5	0
Oral fungal infection				
Japanese	0	0	0	0
Global	12	0	5	0
Oral herpes				
Japanese	0	0	0	0
Global	12	0	5	0
Otitis media				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Pain								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	0	30	1 (3.3)
Penile discharge								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Perirectal abscess								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Petechiae								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Pharyngeal erythema								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Number (%) of subjects	Month 24-30 N Sub.	Number (%) of subjects
Pain				
Japanese	0	0	0	0
Global	12	0	5	0
Penile discharge				
Japanese	0	0	0	0
Global	12	0	5	0
Perirectal abscess				
Japanese	0	0	0	0
Global	12	0	5	0
Petechiae				
Japanese	0	0	0	0
Global	12	0	5	0
Pharyngeal erythema				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Pollakiuria								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Pruritus								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Renal colic								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Respiratory tract infection								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Rhinitis								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Pollakiuria				
Japanese	0	0	0	0
Global	12	0	5	0
Pruritus				
Japanese	0	0	0	0
Global	12	0	5	0
Renal colic				
Japanese	0	0	0	0
Global	12	0	5	0
Respiratory tract infection				
Japanese	0	0	0	0
Global	12	0	5	0
Rhinitis				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Road traffic accident								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Seasonal allergy								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Sneezing								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Suicidal ideation								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Sunburn								
Japanese	10	1 (10.0)	10	0	9	1 (11.1)	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Road traffic accident				
Japanese	0	0	0	0
Global	12	0	5	0
Seasonal allergy				
Japanese	0	0	0	0
Global	12	0	5	0
Sneezing				
Japanese	0	0	0	0
Global	12	0	5	0
Suicidal ideation				
Japanese	0	0	0	0
Global	12	0	5	0
Sunburn				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Sub.	 Number (%) of subjects	Month 0-6 N Sub.	 Number (%) of subjects	Month 6-12 N Sub.	 Number (%) of subjects	Month 12-18 N Sub.	 Number (%) of subjects
Synovial cyst								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0
Tendon rupture								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Thrombocytopenia								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	0	30	1 (3.3)
Tongue injury								
Japanese	10	1 (10.0)	10	0	9	1 (11.1)	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0
Tonsillar haemorrhage								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Month 18-24 Number (%) of subjects	Month 24-30 N Sub.	Month 24-30 Number (%) of subjects
Synovial cyst				
Japanese	0	0	0	0
Global	12	0	5	0
Tendon rupture				
Japanese	0	0	0	0
Global	12	0	5	0
Thrombocytopenia				
Japanese	0	0	0	0
Global	12	0	5	0
Tongue injury				
Japanese	0	0	0	0
Global	12	0	5	0
Tonsillar haemorrhage				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Tonsillitis								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Tooth abscess								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Traumatic haematoma								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Umbilical hernia								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0
Urinary tract infection								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Number (%) of subjects	Month 24-30 N Sub.	Number (%) of subjects
Tonsillitis				
Japanese	0	0	0	0
Global	12	0	5	0
Tooth abscess				
Japanese	0	0	0	0
Global	12	0	5	0
Traumatic haematoma				
Japanese	0	0	0	0
Global	12	0	5	0
Umbilical hernia				
Japanese	0	0	0	0
Global	12	0	5	0
Urinary tract infection				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Sub.	All events Number (%) of subjects	Month 0-6 N Sub.	Month 0-6 Number (%) of subjects	Month 6-12 N Sub.	Month 6-12 Number (%) of subjects	Month 12-18 N Sub.	Month 12-18 Number (%) of subjects
Varices oesophageal								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	0	101	1 (1.0)	30	0
Wound haemorrhage								
Japanese	10	0	10	0	9	0	3	0
Global	174	1 (0.6)	174	1 (0.6)	101	0	30	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.33J Incidence of Treatment-Emergent Adverse Event by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Sub.	Number (%) of subjects	Month 24-30 N Sub.	Number (%) of subjects
Varices oesophageal				
Japanese	0	0	0	0
Global	12	0	5	0
Wound haemorrhage				
Japanese	0	0	0	0
Global	12	0	5	0

Notes: [1] N Sub. = Total number of subjects.
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse events with an incomplete start date are included in the 'All events' group only.
[4] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Inf.	All events Number (rate) of AEs	Month 0-6 N Inf.	Month 0-6 Number (rate) of AEs	Month 6-12 N Inf.	Month 6-12 Number (rate) of AEs	Month 12-18 N Inf.	Month 12-18 Number (rate) of AEs
Nasopharyngitis								
Japanese	838	4 (0.005)	465	2 (0.004)	337	2 (0.006)	36	0
Global	14592	22 (0.002)	9315	15 (0.002)	3668	5 (0.001)	1020	0
Arthralgia								
Japanese	838	0	465	0	337	0	36	0
Global	14592	19 (0.001)	9315	16 (0.002)	3668	2 (0.001)	1020	0
Headache								
Japanese	838	1 (0.001)	465	1 (0.002)	337	0	36	0
Global	14592	13 (0.001)	9315	11 (0.001)	3668	2 (0.001)	1020	0
Rash								
Japanese	838	1 (0.001)	465	1 (0.002)	337	0	36	0
Global	14592	8 (0.001)	9315	5 (0.001)	3668	1 (<0.001)	1020	0
Toothache								
Japanese	838	0	465	0	337	0	36	0
Global	14592	8 (0.001)	9315	7 (0.001)	3668	1 (<0.001)	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Nasopharyngitis				
Japanese	0	0	0	0
Global	573	0	16	0
Arthralgia				
Japanese	0	0	0	0
Global	573	0	16	0
Headache				
Japanese	0	0	0	0
Global	573	0	16	0
Rash				
Japanese	0	0	0	0
Global	573	0	16	0
Toothache				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Upper respiratory tract infection								
Japanese	838	0	465	0	337	0	36	0
Global	14592	6 (<0.001)	9315	6 (0.001)	3668	0	1020	0
Back pain								
Japanese	838	0	465	0	337	0	36	0
Global	14592	6 (<0.001)	9315	5 (0.001)	3668	1 (<0.001)	1020	0
Cough								
Japanese	838	0	465	0	337	0	36	0
Global	14592	6 (<0.001)	9315	3 (<0.001)	3668	0	1020	3 (0.003)
Hypertension								
Japanese	838	0	465	0	337	0	36	0
Global	14592	5 (<0.001)	9315	5 (0.001)	3668	0	1020	0
Dizziness								
Japanese	838	1 (0.001)	465	1 (0.002)	337	0	36	0
Global	14592	5 (<0.001)	9315	5 (0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Upper respiratory tract infection				
Japanese	0	0	0	0
Global	573	0	16	0
Back pain				
Japanese	0	0	0	0
Global	573	0	16	0
Cough				
Japanese	0	0	0	0
Global	573	0	16	0
Hypertension				
Japanese	0	0	0	0
Global	573	0	16	0
Dizziness				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Inf.	All events Number (rate) of AEs	Month 0-6 N Inf.	Month 0-6 Number (rate) of AEs	Month 6-12 N Inf.	Month 6-12 Number (rate) of AEs	Month 12-18 N Inf.	Month 12-18 Number (rate) of AEs
Pyrexia								
Japanese	838	0	465	0	337	0	36	0
Global	14592	5 (<0.001)	9315	5 (0.001)	3668	0	1020	0
Influenza								
Japanese	838	2 (0.002)	465	2 (0.004)	337	0	36	0
Global	14592	4 (<0.001)	9315	3 (<0.001)	3668	0	1020	0
Haemophilic arthropathy								
Japanese	838	0	465	0	337	0	36	0
Global	14592	11 (0.001)	9315	10 (0.001)	3668	1 (<0.001)	1020	0
Joint injury								
Japanese	838	0	465	0	337	0	36	0
Global	14592	4 (<0.001)	9315	4 (<0.001)	3668	0	1020	0
Viral infection								
Japanese	838	0	465	0	337	0	36	0
Global	14592	4 (<0.001)	9315	4 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Pyrexia				
Japanese	0	0	0	0
Global	573	0	16	0
Influenza				
Japanese	0	0	0	0
Global	573	0	16	0
Haemophilic arthropathy				
Japanese	0	0	0	0
Global	573	0	16	0
Joint injury				
Japanese	0	0	0	0
Global	573	0	16	0
Viral infection				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Inf.	All events Number (rate) of AEs	Month 0-6 N Inf.	Month 0-6 Number (rate) of AEs	Month 6-12 N Inf.	Month 6-12 Number (rate) of AEs	Month 12-18 N Inf.	Month 12-18 Number (rate) of AEs
Dental caries								
Japanese	838	0	465	0	337	0	36	0
Global	14592	3 (<0.001)	9315	1 (<0.001)	3668	2 (0.001)	1020	0
Fall								
Japanese	838	0	465	0	337	0	36	0
Global	14592	3 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Oropharyngeal pain								
Japanese	838	0	465	0	337	0	36	0
Global	14592	3 (<0.001)	9315	3 (<0.001)	3668	0	1020	0
Sinusitis								
Japanese	838	1 (0.001)	465	1 (0.002)	337	0	36	0
Global	14592	3 (<0.001)	9315	2 (<0.001)	3668	1 (<0.001)	1020	0
Abdominal pain								
Japanese	838	0	465	0	337	0	36	0
Global	14592	3 (<0.001)	9315	1 (<0.001)	3668	2 (0.001)	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Number (rate) of AEs	Month 24-30 N Inf.	Number (rate) of AEs
Dental caries				
Japanese	0	0	0	0
Global	573	0	16	0
Fall				
Japanese	0	0	0	0
Global	573	1 (0.002)	16	0
Oropharyngeal pain				
Japanese	0	0	0	0
Global	573	0	16	0
Sinusitis				
Japanese	0	0	0	0
Global	573	0	16	0
Abdominal pain				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Hypersensitivity								
Japanese	838	0	465	0	337	0	36	0
Global	14592	3 (<0.001)	9315	3 (<0.001)	3668	0	1020	0
Limb injury								
Japanese	838	0	465	0	337	0	36	0
Global	14592	3 (<0.001)	9315	3 (<0.001)	3668	0	1020	0
Pain in extremity								
Japanese	838	0	465	0	337	0	36	0
Global	14592	3 (<0.001)	9315	3 (<0.001)	3668	0	1020	0
Acne								
Japanese	838	1 (0.001)	465	0	337	1 (0.003)	36	0
Global	14592	2 (<0.001)	9315	1 (<0.001)	3668	1 (<0.001)	1020	0
Anaemia								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	1 (<0.001)	3668	0	1020	1 (0.001)

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Hypersensitivity				
Japanese	0	0	0	0
Global	573	0	16	0
Limb injury				
Japanese	0	0	0	0
Global	573	0	16	0
Pain in extremity				
Japanese	0	0	0	0
Global	573	0	16	0
Acne				
Japanese	0	0	0	0
Global	573	0	16	0
Anaemia				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Asthenia								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	1 (<0.001)	3668	1 (<0.001)	1020	0
Chest pain								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Conjunctivitis								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	1 (<0.001)	3668	1 (<0.001)	1020	0
Contusion								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Gastroenteritis								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	1 (<0.001)	3668	1 (<0.001)	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Asthenia				
Japanese	0	0	0	0
Global	573	0	16	0
Chest pain				
Japanese	0	0	0	0
Global	573	0	16	0
Conjunctivitis				
Japanese	0	0	0	0
Global	573	0	16	0
Contusion				
Japanese	0	0	0	0
Global	573	0	16	0
Gastroenteritis				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Gastroenteritis viral								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Injection site pain								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Laceration								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Leukocytosis								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Ligament sprain								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	1 (<0.001)	3668	1 (<0.001)	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Gastroenteritis viral				
Japanese	0	0	0	0
Global	573	0	16	0
Injection site pain				
Japanese	0	0	0	0
Global	573	0	16	0
Laceration				
Japanese	0	0	0	0
Global	573	0	16	0
Leukocytosis				
Japanese	0	0	0	0
Global	573	0	16	0
Ligament sprain				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Liver function test abnormal								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	1 (<0.001)	3668	1 (<0.001)	1020	0
Nasal congestion								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	1 (<0.001)	3668	0	1020	1 (0.001)
Paraesthesia								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Pharyngitis								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Post-traumatic pain								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Liver function test abnormal				
Japanese	0	0	0	0
Global	573	0	16	0
Nasal congestion				
Japanese	0	0	0	0
Global	573	0	16	0
Paraesthesia				
Japanese	0	0	0	0
Global	573	0	16	0
Pharyngitis				
Japanese	0	0	0	0
Global	573	0	16	0
Post-traumatic pain				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Rhinorrhoea								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Thermal burn								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Viral upper respiratory tract infection								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	1 (<0.001)	3668	1 (<0.001)	1020	0
Wound								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Blood uric acid increased								
Japanese	838	0	465	0	337	0	36	0
Global	14592	3 (<0.001)	9315	3 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Rhinorrhoea				
Japanese	0	0	0	0
Global	573	0	16	0
Thermal burn				
Japanese	0	0	0	0
Global	573	0	16	0
Viral upper respiratory tract infection				
Japanese	0	0	0	0
Global	573	0	16	0
Wound				
Japanese	0	0	0	0
Global	573	0	16	0
Blood uric acid increased				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Inf.	All events Number (rate) of AEs	Month 0-6 N Inf.	Month 0-6 Number (rate) of AEs	Month 6-12 N Inf.	Month 6-12 Number (rate) of AEs	Month 12-18 N Inf.	Month 12-18 Number (rate) of AEs
Somnolence								
Japanese	838	0	465	0	337	0	36	0
Global	14592	3 (<0.001)	9315	3 (<0.001)	3668	0	1020	0
Blood glucose increased								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Chills								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Tooth extraction								
Japanese	838	0	465	0	337	0	36	0
Global	14592	2 (<0.001)	9315	2 (<0.001)	3668	0	1020	0
Actinic keratosis								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Somnolence				
Japanese	0	0	0	0
Global	573	0	16	0
Blood glucose increased				
Japanese	0	0	0	0
Global	573	0	16	0
Chills				
Japanese	0	0	0	0
Global	573	0	16	0
Tooth extraction				
Japanese	0	0	0	0
Global	573	0	16	0
Actinic keratosis				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Adverse drug reaction								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Ankle fracture								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	0	1020	1 (0.001)
Arrhythmia								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Arthropod bite								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Blood lactate dehydrogenase increased								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Adverse drug reaction				
Japanese	0	0	0	0
Global	573	0	16	0
Ankle fracture				
Japanese	0	0	0	0
Global	573	0	16	0
Arrhythmia				
Japanese	0	0	0	0
Global	573	0	16	0
Arthropod bite				
Japanese	0	0	0	0
Global	573	0	16	0
Blood lactate dehydrogenase increased				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Blood triglycerides increased								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Blood urea increased								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Bronchitis								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
C-reactive protein increased								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Capillary fragility								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Blood triglycerides increased				
Japanese	0	0	0	0
Global	573	0	16	0
Blood urea increased				
Japanese	0	0	0	0
Global	573	0	16	0
Bronchitis				
Japanese	0	0	0	0
Global	573	0	16	0
C-reactive protein increased				
Japanese	0	0	0	0
Global	573	0	16	0
Capillary fragility				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Inf.	All events Number (rate) of AEs	Month 0-6 N Inf.	Month 0-6 Number (rate) of AEs	Month 6-12 N Inf.	Month 6-12 Number (rate) of AEs	Month 12-18 N Inf.	Month 12-18 Number (rate) of AEs
Chillblains								
Japanese	838	1 (0.001)	465	1 (0.002)	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Conjunctival abrasion								
Japanese	838	1 (0.001)	465	0	337	0	36	1 (0.028)
Global	14592	1 (<0.001)	9315	0	3668	0	1020	1 (0.001)
Constipation								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0
Dermatitis								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	0	1020	0
Dermatitis allergic								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Number (rate) of AEs	Month 24-30 N Inf.	Number (rate) of AEs
Chillblains				
Japanese	0	0	0	0
Global	573	0	16	0
Conjunctival abrasion				
Japanese	0	0	0	0
Global	573	0	16	0
Constipation				
Japanese	0	0	0	0
Global	573	0	16	0
Dermatitis				
Japanese	0	0	0	0
Global	573	1 (0.002)	16	0
Dermatitis allergic				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Inf.	All events Number (rate) of AEs	Month 0-6 N Inf.	Month 0-6 Number (rate) of AEs	Month 6-12 N Inf.	Month 6-12 Number (rate) of AEs	Month 12-18 N Inf.	Month 12-18 Number (rate) of AEs
Dermatitis atopic								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	0	1020	0
Dermatitis contact								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Diarrhoea								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0
Drug specific antibody present								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Dyshidrosis								
Japanese	838	1 (0.001)	465	0	337	1 (0.003)	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Dermatitis atopic				
Japanese	0	0	0	0
Global	573	0	16	0
Dermatitis contact				
Japanese	0	0	0	0
Global	573	0	16	0
Diarrhoea				
Japanese	0	0	0	0
Global	573	0	16	0
Drug specific antibody present				
Japanese	0	0	0	0
Global	573	0	16	0
Dyshidrosis				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
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[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Ear infection								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Ear pain								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Ecchymosis								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Eosinophilia								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0
Erythema								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
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Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Ear infection				
Japanese	0	0	0	0
Global	573	0	16	0
Ear pain				
Japanese	0	0	0	0
Global	573	0	16	0
Ecchymosis				
Japanese	0	0	0	0
Global	573	0	16	0
Eosinophilia				
Japanese	0	0	0	0
Global	573	0	16	0
Erythema				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Inf.	All events Number (rate) of AEs	Month 0-6 N Inf.	Month 0-6 Number (rate) of AEs	Month 6-12 N Inf.	Month 6-12 Number (rate) of AEs	Month 12-18 N Inf.	Month 12-18 Number (rate) of AEs
Feeling hot								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Fungal skin infection								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Furuncle								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	0	1020	1 (0.001)
Gamma-glutamyltransferase increased								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Gastritis								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time (Japanese and Global Safety Population)

Preferred Term / Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Feeling hot				
Japanese	0	0	0	0
Global	573	0	16	0
Fungal skin infection				
Japanese	0	0	0	0
Global	573	0	16	0
Furuncle				
Japanese	0	0	0	0
Global	573	0	16	0
Gamma-glutamyltransferase increased				
Japanese	0	0	0	0
Global	573	0	16	0
Gastritis				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Gastrointestinal tract adenoma								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Groin pain								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Haematochezia								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Haematoma								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Haematuria								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Gastrointestinal tract adenoma				
Japanese	0	0	0	0
Global	573	0	16	0
Groin pain				
Japanese	0	0	0	0
Global	573	0	16	0
Haematochezia				
Japanese	0	0	0	0
Global	573	0	16	0
Haematoma				
Japanese	0	0	0	0
Global	573	0	16	0
Haematuria				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	Number (rate) of AEs	Month 0-6 N Inf.	Number (rate) of AEs	Month 6-12 N Inf.	Number (rate) of AEs	Month 12-18 N Inf.	Number (rate) of AEs
Haemorrhoidal haemorrhage								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Hand fracture								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0
Heat rash								
Japanese	838	1 (0.001)	465	1 (0.002)	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Hyperuricaemia								
Japanese	838	1 (0.001)	465	1 (0.002)	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Hypoaesthesia								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Haemorrhoidal haemorrhage				
Japanese	0	0	0	0
Global	573	0	16	0
Hand fracture				
Japanese	0	0	0	0
Global	573	0	16	0
Heat rash				
Japanese	0	0	0	0
Global	573	0	16	0
Hyperuricaemia				
Japanese	0	0	0	0
Global	573	0	16	0
Hypoaesthesia				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Inf.	All events Number (rate) of AEs	Month 0-6 N Inf.	Month 0-6 Number (rate) of AEs	Month 6-12 N Inf.	Month 6-12 Number (rate) of AEs	Month 12-18 N Inf.	Month 12-18 Number (rate) of AEs
Iron deficiency								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Iron deficiency anaemia								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Joint range of motion decreased								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Joint swelling								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Local swelling								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Iron deficiency				
Japanese	0	0	0	0
Global	573	0	16	0
Iron deficiency anaemia				
Japanese	0	0	0	0
Global	573	0	16	0
Joint range of motion decreased				
Japanese	0	0	0	0
Global	573	0	16	0
Joint swelling				
Japanese	0	0	0	0
Global	573	0	16	0
Local swelling				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term / Population	All events N Inf.	All events Number (rate) of AEs	Month 0-6 N Inf.	Month 0-6 Number (rate) of AEs	Month 6-12 N Inf.	Month 6-12 Number (rate) of AEs	Month 12-18 N Inf.	Month 12-18 Number (rate) of AEs
Localised oedema								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Loose tooth								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0
Lower respiratory tract infection								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0
Lumbar spinal stenosis								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Malaise								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
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(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Localised oedema				
Japanese	0	0	0	0
Global	573	0	16	0
Loose tooth				
Japanese	0	0	0	0
Global	573	0	16	0
Lower respiratory tract infection				
Japanese	0	0	0	0
Global	573	0	16	0
Lumbar spinal stenosis				
Japanese	0	0	0	0
Global	573	0	16	0
Malaise				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Migraine								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Muscle spasms								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Muscle strain								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Nasal mucosal disorder								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Neck pain								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
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Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Migraine				
Japanese	0	0	0	0
Global	573	0	16	0
Muscle spasms				
Japanese	0	0	0	0
Global	573	0	16	0
Muscle strain				
Japanese	0	0	0	0
Global	573	0	16	0
Nasal mucosal disorder				
Japanese	0	0	0	0
Global	573	0	16	0
Neck pain				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
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Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Oedema peripheral								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Oesophagitis								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Oral fungal infection								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Oral herpes								
Japanese	838	1 (0.001)	465	0	337	1 (0.003)	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0
Otitis media								
Japanese	838	1 (0.001)	465	1 (0.002)	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Oedema peripheral				
Japanese	0	0	0	0
Global	573	0	16	0
Oesophagitis				
Japanese	0	0	0	0
Global	573	0	16	0
Oral fungal infection				
Japanese	0	0	0	0
Global	573	0	16	0
Oral herpes				
Japanese	0	0	0	0
Global	573	0	16	0
Otitis media				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
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Preferred Term / Population	All events N Inf.	All events Number (rate) of AEs	Month 0-6 N Inf.	Month 0-6 Number (rate) of AEs	Month 6-12 N Inf.	Month 6-12 Number (rate) of AEs	Month 12-18 N Inf.	Month 12-18 Number (rate) of AEs
Pain								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	0	1020	1 (0.001)
Penile discharge								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Perirectal abscess								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Petechiae								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Pharyngeal erythema								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
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Pain				
Japanese	0	0	0	0
Global	573	0	16	0
Penile discharge				
Japanese	0	0	0	0
Global	573	0	16	0
Perirectal abscess				
Japanese	0	0	0	0
Global	573	0	16	0
Petechiae				
Japanese	0	0	0	0
Global	573	0	16	0
Pharyngeal erythema				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
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Pollakiuria								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Pruritus								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Renal colic								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Respiratory tract infection								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Rhinitis								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
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Pollakiuria				
Japanese	0	0	0	0
Global	573	0	16	0
Pruritus				
Japanese	0	0	0	0
Global	573	0	16	0
Renal colic				
Japanese	0	0	0	0
Global	573	0	16	0
Respiratory tract infection				
Japanese	0	0	0	0
Global	573	0	16	0
Rhinitis				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Road traffic accident								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Seasonal allergy								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Sneezing								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Suicidal ideation								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Sunburn								
Japanese	838	1 (0.001)	465	0	337	1 (0.003)	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
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Road traffic accident				
Japanese	0	0	0	0
Global	573	0	16	0
Seasonal allergy				
Japanese	0	0	0	0
Global	573	0	16	0
Sneezing				
Japanese	0	0	0	0
Global	573	0	16	0
Suicidal ideation				
Japanese	0	0	0	0
Global	573	0	16	0
Sunburn				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Synovial cyst								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0
Tendon rupture								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Thrombocytopenia								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	0	1020	1 (0.001)
Tongue injury								
Japanese	838	1 (0.001)	465	0	337	1 (0.003)	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0
Tonsillar haemorrhage								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Synovial cyst				
Japanese	0	0	0	0
Global	573	0	16	0
Tendon rupture				
Japanese	0	0	0	0
Global	573	0	16	0
Thrombocytopenia				
Japanese	0	0	0	0
Global	573	0	16	0
Tongue injury				
Japanese	0	0	0	0
Global	573	0	16	0
Tonsillar haemorrhage				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Tonsillitis								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Tooth abscess								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Traumatic haematoma								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Umbilical hernia								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0
Urinary tract infection								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Tonsillitis				
Japanese	0	0	0	0
Global	573	0	16	0
Tooth abscess				
Japanese	0	0	0	0
Global	573	0	16	0
Traumatic haematoma				
Japanese	0	0	0	0
Global	573	0	16	0
Umbilical hernia				
Japanese	0	0	0	0
Global	573	0	16	0
Urinary tract infection				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
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Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	All events N Inf.	 Number (rate) of AEs	Month 0-6 N Inf.	 Number (rate) of AEs	Month 6-12 N Inf.	 Number (rate) of AEs	Month 12-18 N Inf.	 Number (rate) of AEs
Varices oesophageal								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	0	3668	1 (<0.001)	1020	0
Wound haemorrhage								
Japanese	838	0	465	0	337	0	36	0
Global	14592	1 (<0.001)	9315	1 (<0.001)	3668	0	1020	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.3.2.34J Rate of Treatment-Emergent Adverse Events by Preferred Term Over Time
(Japanese and Global Safety Population)

Preferred Term Population	Month 18-24 N Inf.	Month 18-24 Number (rate) of AEs	Month 24-30 N Inf.	Month 24-30 Number (rate) of AEs
Varices oesophageal				
Japanese	0	0	0	0
Global	573	0	16	0
Wound haemorrhage				
Japanese	0	0	0	0
Global	573	0	16	0

Notes: [1] N Inf. = Number of infusions.
[2] Rate of AEs = Number of AEs/Number of infusions.
[3] Events with onset date during the surgical period are excluded from this summary.
[4] Adverse events with an incomplete start date are included in the 'All events' group only.
[5] Adverse events were coded using MedDRA Version 14.1.

Table 14.1.5.1.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History						Active History					
	<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)		<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any Medical/Surgical History	23	(65.7)	35	(71.4)	58	(69.0)	9	(25.7)	24	(49.0)	33	(39.3)
Surgical and medical procedures	14	(40.0)	22	(44.9)	36	(42.9)	1	(2.9)	3	(6.1)	4	(4.8)
Circumcision	6	(17.1)	10	(20.4)	16	(19.0)	0		0		0	
Central venous catheterisation	6	(17.1)	4	(8.2)	10	(11.9)	1	(2.9)	2	(4.1)	3	(3.6)
Arteriovenous shunt operation	0		2	(4.1)	2	(2.4)	0		0		0	
Dental care	1	(2.9)	1	(2.0)	2	(2.4)	0		0		0	
Catheterisation venous	0		1	(2.0)	1	(1.2)	0		0		0	
Toe amputation	0		1	(2.0)	1	(1.2)	0		0		0	
Abscess drainage	1	(2.9)	0		1	(1.2)	0		0		0	
Catheter placement	0		1	(2.0)	1	(1.2)	0		0		0	
Central venous catheter removal	0		1	(2.0)	1	(1.2)	0		0		0	
Fasciectomy	1	(2.9)	0		1	(1.2)	0		0		0	
Fracture treatment	0		1	(2.0)	1	(1.2)	0		0		0	
Haematoma evacuation	0		1	(2.0)	1	(1.2)	0		0		0	
Inguinal hernia repair	1	(2.9)	0		1	(1.2)	0		0		0	
Orchidopexy	0		1	(2.0)	1	(1.2)	0		0		0	
Suture insertion	1	(2.9)	0		1	(1.2)	0		0		0	

Source: Listing 16.2.4.3
Notes: [1] Past histories are those that are not indicated as ongoing at Screening.
[2] Active histories are those that are indicated as ongoing at Screening.
[3] Tables present number and percentage of subjects [n (%)].
[4] The occurrence of spontaneous and traumatic hematomas in this population of subjects with severe hemophilia (study inclusion criteria) was coded as hemophilia – bleeding disorder.

Table 14.1.5.1.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History						Active History					
	<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)		<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Surgical and medical procedures (continued)	0		0		0		0		0		0	
Synovectomy	0		1	(2.0)	1	(1.2)	0		0		0	
Synoviorthesis	0		0		0		0		1	(2.0)	1	(1.2)
Tongue tie operation	0		1	(2.0)	1	(1.2)	0		0		0	
Tonsillectomy	0		1	(2.0)	1	(1.2)	0		0		0	
Tooth extraction	0		1	(2.0)	1	(1.2)	0		0		0	
Musculoskeletal and connective tissue disorders	3	(8.6)	10	(20.4)	13	(15.5)	3	(8.6)	16	(32.7)	19	(22.6)
Haemarthrosis	3	(8.6)	6	(12.2)	9	(10.7)	0		2	(4.1)	2	(2.4)
Haemophilic arthropathy	0		1	(2.0)	1	(1.2)	1	(2.9)	9	(18.4)	10	(11.9)
Arthralgia	0		2	(4.1)	2	(2.4)	0		0		0	
Joint contracture	0		0		0		0		2	(4.1)	2	(2.4)
Joint swelling	0		1	(2.0)	1	(1.2)	0		1	(2.0)	1	(1.2)
Muscle atrophy	0		1	(2.0)	1	(1.2)	0		1	(2.0)	1	(1.2)
Rickets	0		0		0		2	(5.7)	0		2	(2.4)
Synovitis	0		0		0		0		2	(4.1)	2	(2.4)
Synovial cyst	0		0		0		0		1	(2.0)	1	(1.2)
Flank pain	0		1	(2.0)	1	(1.2)	0		0		0	
Joint range of motion decreased	0		1	(2.0)	1	(1.2)	0		0		0	

Source: Listing 16.2.4.3
Notes: [1] Past histories are those that are not indicated as ongoing at Screening.
[2] Active histories are those that are indicated as ongoing at Screening.
[3] Tables present number and percentage of subjects [n (%)].
[4] The occurrence of spontaneous and traumatic hematomas in this population of subjects with severe hemophilia (study inclusion criteria) was coded as hemophilia - bleeding disorder.

Table 14.1.5.1.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History						Active History					
	<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)		<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Congenital, familial and genetic disorders	8	(22.9)	9	(18.4)	17	(20.2)	0		3	(6.1)	3	(3.6)
Haemophilia	7	(20.0)	7	(14.3)	14	(16.7)	0		2	(4.1)	2	(2.4)
Ankyloglossia congenital	0		1	(2.0)	1	(1.2)	0		0		0	
Congenital hearing disorder	0		0		0		0		1	(2.0)	1	(1.2)
Cryptorchism	1	(2.9)	0		1	(1.2)	0		0		0	
Hydrocele	0		1	(2.0)	1	(1.2)	0		0		0	
Infections and infestations	7	(20.0)	9	(18.4)	16	(19.0)	0		1	(2.0)	1	(1.2)
Gastroenteritis	3	(8.6)	1	(2.0)	4	(4.8)	0		0		0	
Nasopharyngitis	2	(5.7)	1	(2.0)	3	(3.6)	0		0		0	
Lower respiratory tract infection	0		2	(4.1)	2	(2.4)	0		0		0	
Varicella	1	(2.9)	1	(2.0)	2	(2.4)	0		0		0	
Upper respiratory tract infection	0		1	(2.0)	1	(1.2)	0		0		0	
Acute tonsillitis	1	(2.9)	0		1	(1.2)	0		0		0	
Bronchopneumonia	1	(2.9)	0		1	(1.2)	0		0		0	
Dacryocystitis	1	(2.9)	0		1	(1.2)	0		0		0	
Gingivitis	1	(2.9)	0		1	(1.2)	0		0		0	
Herpes simplex	1	(2.9)	0		1	(1.2)	0		0		0	

Source: Listing 16.2.4.3
Notes: [1] Past histories are those that are not indicated as ongoing at Screening.
[2] Active histories are those that are indicated as ongoing at Screening.
[3] Tables present number and percentage of subjects [n (%)].
[4] The occurrence of spontaneous and traumatic hematomas in this population of subjects with severe hemophilia (study inclusion criteria) was coded as hemophilia - bleeding disorder.

Table 14.1.5.1.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History						Active History					
	<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)		<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations (continued)	0		0		0		0		0		0	
Otitis media	0		1	(2.0)	1	(1.2)	0		0		0	
Paronychia	0		1	(2.0)	1	(1.2)	0		0		0	
Periodontitis	0		0		0		0		1	(2.0)	1	(1.2)
Pharyngitis	1	(2.9)	0		1	(1.2)	0		0		0	
Pharyngotonsillitis	0		1	(2.0)	1	(1.2)	0		0		0	
Pneumonia	0		1	(2.0)	1	(1.2)	0		0		0	
Sinusitis	1	(2.9)	0		1	(1.2)	0		0		0	
Viral rhinitis	0		1	(2.0)	1	(1.2)	0		0		0	
Injury, poisoning and procedural complications	4	(11.4)	8	(16.3)	12	(14.3)	0		1	(2.0)	1	(1.2)
Laceration	1	(2.9)	2	(4.1)	3	(3.6)	0		0		0	
Head injury	2	(5.7)	0		2	(2.4)	0		0		0	
Ligament sprain	0		2	(4.1)	2	(2.4)	0		0		0	
Animal bite	1	(2.9)	1	(2.0)	2	(2.4)	0		0		0	
Contusion	0		1	(2.0)	1	(1.2)	0		1	(2.0)	1	(1.2)
Fall	1	(2.9)	0		1	(1.2)	0		0		0	
Femur fracture	0		1	(2.0)	1	(1.2)	0		0		0	
Forearm fracture	0		1	(2.0)	1	(1.2)	0		0		0	
Road traffic accident	0		1	(2.0)	1	(1.2)	0		0		0	

Source: Listing 16.2.4.3
Notes: [1] Past histories are those that are not indicated as ongoing at Screening.
[2] Active histories are those that are indicated as ongoing at Screening.
[3] Tables present number and percentage of subjects [n (%)].
[4] The occurrence of spontaneous and traumatic hematomas in this population of subjects with severe hemophilia (study inclusion criteria) was coded as hemophilia - bleeding disorder.

Table 14.1.5.1.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History						Active History					
	<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)		<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications (continued)	0		0		0		0		0		0	
Tongue injury	1	(2.9)	0		1	(1.2)	0		0		0	
Traumatic haemorrhage	0		1	(2.0)	1	(1.2)	0		0		0	
Respiratory, thoracic and mediastinal disorders	2	(5.7)	1	(2.0)	3	(3.6)	2	(5.7)	4	(8.2)	6	(7.1)
Asthma	0		1	(2.0)	1	(1.2)	2	(5.7)	1	(2.0)	3	(3.6)
Rhinitis allergic	0		1	(2.0)	1	(1.2)	1	(2.9)	2	(4.1)	3	(3.6)
Cough	1	(2.9)	0		1	(1.2)	0		0		0	
Epistaxis	0		0		0		0		1	(2.0)	1	(1.2)
Neonatal respiratory distress syndrome	1	(2.9)	0		1	(1.2)	0		0		0	
Nervous system disorders	3	(8.6)	4	(8.2)	7	(8.3)	1	(2.9)	1	(2.0)	2	(2.4)
Headache	0		3	(6.1)	3	(3.6)	0		0		0	
Convulsion	0		1	(2.0)	1	(1.2)	0		0		0	
Brain injury	1	(2.9)	0		1	(1.2)	0		0		0	
Dystonia	1	(2.9)	0		1	(1.2)	0		0		0	
Febrile convulsion	1	(2.9)	0		1	(1.2)	0		0		0	

Source: Listing 16.2.4.3
Notes: [1] Past histories are those that are not indicated as ongoing at Screening.
[2] Active histories are those that are indicated as ongoing at Screening.
[3] Tables present number and percentage of subjects [n (%)].
[4] The occurrence of spontaneous and traumatic hematomas in this population of subjects with severe hemophilia (study inclusion criteria) was coded as hemophilia - bleeding disorder.

Table 14.1.5.1.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History						Active History					
	<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)		<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders (continued)	0		0		0		0		0		0	
Hypoxic-ischaemic encephalopathy	1	(2.9)	0		1	(1.2)	0		0		0	
Posterior reversible encephalopathy syndrome	0		0		0		0		1	(2.0)	1	(1.2)
Pyramidal tract syndrome	0		0		0		1	(2.9)	0		1	(1.2)
Blood and lymphatic system disorders	1	(2.9)	5	(10.2)	6	(7.1)	0		1	(2.0)	1	(1.2)
Deficiency anaemia	1	(2.9)	2	(4.1)	3	(3.6)	0		0		0	
Anaemia	0		3	(6.1)	3	(3.6)	0		0		0	
Haemorrhagic anaemia	0		1	(2.0)	1	(1.2)	0		0		0	
Iron deficiency anaemia	0		0		0		0		1	(2.0)	1	(1.2)
Gastrointestinal disorders	0		3	(6.1)	3	(3.6)	2	(5.7)	2	(4.1)	4	(4.8)
Dental caries	0		0		0		1	(2.9)	1	(2.0)	2	(2.4)
Abdominal pain	0		0		0		0		1	(2.0)	1	(1.2)
Constipation	0		1	(2.0)	1	(1.2)	0		0		0	
Gastritis	0		1	(2.0)	1	(1.2)	0		0		0	
Inguinal hernia	0		1	(2.0)	1	(1.2)	0		0		0	
Umbilical hernia	0		0		0		1	(2.9)	0		1	(1.2)

Source: Listing 16.2.4.3
Notes: [1] Past histories are those that are not indicated as ongoing at Screening.
[2] Active histories are those that are indicated as ongoing at Screening.
[3] Tables present number and percentage of subjects [n (%)].
[4] The occurrence of spontaneous and traumatic hematomas in this population of subjects with severe hemophilia (study inclusion criteria) was coded as hemophilia - bleeding disorder.

Table 14.1.5.1.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History						Active History					
	<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)		<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Immune system disorders	0		0		0		0		3	(6.1)	3	(3.6)
Multiple allergies	0		0		0		0		2	(4.1)	2	(2.4)
Food allergy	0		0		0		0		1	(2.0)	1	(1.2)
Metabolism and nutrition disorders	1	(2.9)	0		1	(1.2)	0		2	(4.1)	2	(2.4)
Iron deficiency	1	(2.9)	0		1	(1.2)	0		1	(2.0)	1	(1.2)
Overweight	0		0		0		0		1	(2.0)	1	(1.2)
Skin and subcutaneous tissue disorders	0		2	(4.1)	2	(2.4)	1	(2.9)	0		1	(1.2)
Dry skin	0		0		0		1	(2.9)	0		1	(1.2)
Eczema	0		1	(2.0)	1	(1.2)	0		0		0	
Henoch-Schonlein purpura	0		1	(2.0)	1	(1.2)	0		0		0	
Psychiatric disorders	0		1	(2.0)	1	(1.2)	1	(2.9)	0		1	(1.2)
Anxiety	0		1	(2.0)	1	(1.2)	0		0		0	
Attention deficit/hyperactivity disorder	0		0		0		1	(2.9)	0		1	(1.2)
Expressive language disorder	0		0		0		1	(2.9)	0		1	(1.2)

Source: Listing 16.2.4.3
Notes: [1] Past histories are those that are not indicated as ongoing at Screening.
[2] Active histories are those that are indicated as ongoing at Screening.
[3] Tables present number and percentage of subjects [n (%)].
[4] The occurrence of spontaneous and traumatic hematomas in this population of subjects with severe hemophilia (study inclusion criteria) was coded as hemophilia – bleeding disorder.

Table 14.1.5.1.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History						Active History					
	<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)		<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Eye disorders	0		2	(4.1)	2	(2.4)	0		0		0	
Conjunctivitis	0		2	(4.1)	2	(2.4)	0		0		0	
Investigations	0		0		0		0		2	(4.1)	2	(2.4)
Blood cholesterol increased	0		0		0		0		1	(2.0)	1	(1.2)
Weight increased	0		0		0		0		1	(2.0)	1	(1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(2.9)	0		1	(1.2)	1	(2.9)	0		1	(1.2)
Haemangioma	1	(2.9)	0		1	(1.2)	0		0		0	
Lymphangioma	0		0		0		1	(2.9)	0		1	(1.2)
Pregnancy, puerperium and perinatal conditions	1	(2.9)	0		1	(1.2)	0		0		0	
Jaundice neonatal	1	(2.9)	0		1	(1.2)	0		0		0	
Premature baby	1	(2.9)	0		1	(1.2)	0		0		0	
Cardiac disorders	0		0		0		1	(2.9)	0		1	(1.2)
Metabolic cardiomyopathy	0		0		0		1	(2.9)	0		1	(1.2)

Source: Listing 16.2.4.3
Notes: [1] Past histories are those that are not indicated as ongoing at Screening.
[2] Active histories are those that are indicated as ongoing at Screening.
[3] Tables present number and percentage of subjects [n (%)].
[4] The occurrence of spontaneous and traumatic hematomas in this population of subjects with severe hemophilia (study inclusion criteria) was coded as hemophilia – bleeding disorder.

Table 14.1.5.1.1 Medical/Surgical History
(Safety Population)

System Organ Class Preferred Term	Past History						Active History					
	<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)		<6 years (N=35)		>=6 to <12 yrs (N=49)		Total (N=84)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hepatobiliary disorders	0		1	(2.0)	1	(1.2)	0		0		0	
Biliary dyskinesia	0		1	(2.0)	1	(1.2)	0		0		0	
Renal and urinary disorders	0		1	(2.0)	1	(1.2)	0		0		0	
Haematuria	0		1	(2.0)	1	(1.2)	0		0		0	

Source: Listing 16.2.4.3
Notes: [1] Past histories are those that are not indicated as ongoing at Screening.
[2] Active histories are those that are indicated as ongoing at Screening.
[3] Tables present number and percentage of subjects [n (%)].
[4] The occurrence of spontaneous and traumatic hematomas in this population of subjects with severe hemophilia (study inclusion criteria) was coded as hemophilia - bleeding disorder.

Table 14.1.5.2 Medical/Surgical History Related to Viral Diseases
(Safety Population)

	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)

There were no Medical/Surgical histories related to Viral Diseases

Source: Listing 16.2.4.3, 16.2.4.4
Notes: [1] Tables present number and percentage of subjects [n (%)].

Table 14.1.8.5.1 Extent of Exposure to CSL627
(Safety Population)

	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Exposure Days (EDs)			
n	35	49	84
Mean (SD)	56.7 (18.90)	66.4 (27.64)	62.4 (24.73)
Median	52.0	59.0	58.5
Min, Max	4, 98	9, 142	4, 142
<50 EDs [n (%)]	8 (22.9)	11 (22.4)	19 (22.6)
>=50 EDs [n (%)]	27 (77.1)	38 (77.6)	65 (77.4)
>=100 EDs [n (%)]	0	8 (16.3)	8 (9.5)

CSL Behring GmbH: CSL627_3002/CIL-MJ/FINAL/EXT01P.SAS
Produced: [redacted] 20[redacted], 10:00
Source: Listing 16.2.5.1, 16.2.5.2, 16.2.5.5
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.
[2] In one subject, the reporting of bleeding events and factor administration by the caregiver was deemed unreliable and not included. Only factor administration by a health care professional or those witnessed by a health care professional were included in the analysis.

Table 14.1.8.5.1 Extent of Exposure to CSL627
(Safety Population)

	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Number of Infusions			
n	35	49	84
Mean (SD)	56.9 (19.20)	67.8 (28.93)	63.3 (25.77)
Median	52.0	60.0	59.0
Min, Max	4, 100	9, 145	4, 145
Total Number of Infusions	1991	3322	5313
Dose Per Infusion Administered (IU/kg)			
n	1991	3322	5313
Mean (SD)	38.3 (11.21)	35.0 (12.11)	36.3 (11.89)
Median	37.7	30.8	33.0
Min, Max	16, 76	11, 93	11, 93
Total IU Administered			
n	35	49	84
Mean (SD)	2263.5 (1011.13)	2471.8 (1371.59)	2385.0 (1231.84)
Median	2079.1	2124.2	2079.2
Min, Max	176, 5918	222, 7831	176, 7831

Source: Listing 16.2.5.1, 16.2.5.2, 16.2.5.5
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.
[2] In one subject, the reporting of bleeding events and factor administration by the caregiver was deemed unreliable and not included. Only factor administration by a health care professional or those witnessed by a health care professional were included in the analysis.

Table 14.1.8.7.1 Preventive and Additional Doses
(Efficacy Population)

	On-demand (N=3)	Prophylaxis (N=80)	Total (N=83)
Preventative Doses			
Number of Subjects with Preventative Doses [n (%)]	2 (66.7)	17 (21.3)	19 (22.9)
Number of Preventative Doses			
n	2	17	19
Mean (SD)	9.5 (0.71)	3.4 (3.45)	4.1 (3.78)
Median	9.5	2.0	2.0
Min, Max	9, 10	1, 12	1, 12
Total Number of Preventative Doses	19	58	77
Additional Doses			
Number of Subjects with Additional Doses [n (%)]	0	21 (26.3)	21 (25.3)
Number of Additional Doses			
n	0	21	21
Mean (SD)		8.2 (16.83)	8.2 (16.83)
Median		4.0	4.0
Min, Max		1, 79	1, 79
Total Number of Additional Doses		173	173

Source: Listing 16.2.5.2, 16.2.5.4
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.
[2] All additional doses that have been associated with a bleed after adjudication are included.

Table 14.1.8.7.1 Preventive and Additional Doses
(Efficacy Population)

	On-demand (N=3)	Prophylaxis (N=80)	Total (N=83)
Additional Doses			
Bleeds Requiring Additional Doses [2]			
Number of Subjects [n (%)]	0	12 (15.0)	12 (14.5)
Number of Bleeds	0	17	17
Number of Additional Doses per Subject			
n	0	12	12
Mean (SD)		4.2 (3.69)	4.2 (3.69)
Median		3.0	3.0
Min, Max		1, 13	1, 13
Total Number of Additional Doses		50	50
Number of Additional Doses per Bleed			
n	0	17	17
Mean (SD)		2.9 (2.97)	2.9 (2.97)
Median		2.0	2.0
Min, Max		1, 13	1, 13
Total Number of Additional Doses		50	50

Source: Listing 16.2.5.2, 16.2.5.4
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.
[2] All additional doses that have been associated with a bleed after adjudication are included.

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Any Concomitant Medication	28 (80.0)	38 (77.6)	66 (78.6)
ANILIDES	13 (37.1)	23 (46.9)	36 (42.9)
PARACETAMOL	13 (37.1)	23 (46.9)	36 (42.9)
CHLORPHENAMINE W/PARACETAMOL/PHENYLEPHRINE/	0	1 (2.0)	1 (1.2)
SINGLET /00554101/	1 (2.9)	0	1 (1.2)
SYMPATHOMIMETICS	2 (5.7)	7 (14.3)	9 (10.7)
BENYLIN DUAL ACTION DRY	0	2 (4.1)	2 (2.4)
PSEUDOEPHEDRINE	1 (2.9)	1 (2.0)	2 (2.4)
CONTAC /00014501/	0	1 (2.0)	1 (1.2)
DEMAZIN /00179501/	0	1 (2.0)	1 (1.2)
PHENYLEPHRINE	1 (2.9)	0	1 (1.2)
PHENYLEPHRINE HYDROCHLORIDE	1 (2.9)	0	1 (1.2)
PHENYLPROPANOLAMINE HYDROCHLORIDE	0	1 (2.0)	1 (1.2)
RESPAIRE-SR-120	0	1 (2.0)	1 (1.2)
COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE	4 (11.4)	3 (6.1)	7 (8.3)
AMOXI-CLAVULANICO	1 (2.9)	2 (4.1)	3 (3.6)
SPEKTRAMOX	2 (5.7)	1 (2.0)	3 (3.6)
AUGMENTIN /00756801/	1 (2.9)	0	1 (1.2)

Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
IRON BIVALENT, ORAL PREPARATIONS	2 (5.7)	5 (10.2)	7 (8.3)
FERROUS SULFATE	0	3 (6.1)	3 (3.6)
FERROUS FUMARATE	0	2 (4.1)	2 (2.4)
FERROUS SULFATE W/VITAMINS NOS	2 (5.7)	0	2 (2.4)
PENICILLINS WITH EXTENDED SPECTRUM	4 (11.4)	3 (6.1)	7 (8.3)
AMOXICILLIN	2 (5.7)	3 (6.1)	5 (6.0)
AMOXICILLIN TRIHYDRATE	2 (5.7)	0	2 (2.4)
MUCOLYTICS	3 (8.6)	3 (6.1)	6 (7.1)
ACETYLCYSTEINE	0	1 (2.0)	1 (1.2)
AMBROXOL	1 (2.9)	0	1 (1.2)
AMBROXOL HYDROCHLORIDE	0	1 (2.0)	1 (1.2)
BROMHEXINE HYDROCHLORIDE	0	1 (2.0)	1 (1.2)
CARBOCISTEINE	1 (2.9)	0	1 (1.2)
L-CARBOCYSTEINE	1 (2.9)	0	1 (1.2)
PROPIONIC ACID DERIVATIVES	1 (2.9)	5 (10.2)	6 (7.1)
IBUPROFEN	1 (2.9)	5 (10.2)	6 (7.1)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	2 (5.7)	4 (8.2)	6 (7.1)
HEDERA HELIX LEAF	0	2 (4.1)	2 (2.4)
BRONCHIPRET /01257501/	0	1 (2.0)	1 (1.2)
CETRARIA ISLANDICA EXTRACT	0	1 (2.0)	1 (1.2)
EUPHRASIA OFFICINALIS	1 (2.9)	0	1 (1.2)
HEDERA HELIX	1 (2.9)	0	1 (1.2)
HERBAL PREPARATION	1 (2.9)	0	1 (1.2)
IRON TRIVALENT, ORAL PREPARATIONS	1 (2.9)	4 (8.2)	5 (6.0)
FERLIN /01415501/	0	2 (4.1)	2 (2.4)
FERRIC HYDROXIDE POLYMALTOSE COMPLEX	0	2 (4.1)	2 (2.4)
SODIUM FEREDETATE	1 (2.9)	0	1 (1.2)
AMINO ACIDS	2 (5.7)	2 (4.1)	4 (4.8)
TRANEXAMIC ACID	2 (5.7)	2 (4.1)	4 (4.8)
FIRST-GENERATION CEPHALOSPORINS	2 (5.7)	2 (4.1)	4 (4.8)
CEFADROXIL	1 (2.9)	0	1 (1.2)
CEFALEXIN	1 (2.9)	0	1 (1.2)
CEFAZOLIN	0	1 (2.0)	1 (1.2)
CEFAZOLIN SODIUM	0	1 (2.0)	1 (1.2)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
MACROLIDES	2 (5.7)	2 (4.1)	4 (4.8)
CLARITHROMYCIN	1 (2.9)	2 (4.1)	3 (3.6)
AZITHROMYCIN	1 (2.9)	0	1 (1.2)
SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	2 (5.7)	2 (4.1)	4 (4.8)
SALBUTAMOL	2 (5.7)	2 (4.1)	4 (4.8)
SALBUTAMOL SULFATE	1 (2.9)	0	1 (1.2)
THIRD-GENERATION CEPHALOSPORINS	3 (8.6)	1 (2.0)	4 (4.8)
CEFDINIR	0	1 (2.0)	1 (1.2)
CEFPODOXIME	1 (2.9)	0	1 (1.2)
CEFTRIAXONE	1 (2.9)	0	1 (1.2)
CEFTRIAXONE SODIUM	1 (2.9)	0	1 (1.2)
BETA-LACTAMASE RESISTANT PENICILLINS	1 (2.9)	2 (4.1)	3 (3.6)
CLOXACILLIN	1 (2.9)	1 (2.0)	2 (2.4)
DICLOXACILLIN	0	1 (2.0)	1 (1.2)
GLUCOCORTICOIDS	0	3 (6.1)	3 (3.6)
DEXAMETHASONE	0	1 (2.0)	1 (1.2)
MOMETASONE	0	1 (2.0)	1 (1.2)
PREDNISONE	0	1 (2.0)	1 (1.2)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
OTHER COLD PREPARATIONS	2 (5.7)	1 (2.0)	3 (3.6)
ACONITUM NAPELLUS W/CAPSICUM ANNUUM/ECHINACEA	0	1 (2.0)	1 (1.2)
ARNICA MONTANA W/ATROPA BELLADONNA/COCHINEAL/	1 (2.9)	0	1 (1.2)
SINUPRET /00578801/	1 (2.9)	0	1 (1.2)
OTHER NASAL PREPARATIONS	2 (5.7)	1 (2.0)	3 (3.6)
SODIUM CHLORIDE	2 (5.7)	0	2 (2.4)
SEA WATER	0	1 (2.0)	1 (1.2)
OTHER THERAPEUTIC PRODUCTS	2 (5.7)	1 (2.0)	3 (3.6)
GRIPP-HEEL	0	1 (2.0)	1 (1.2)
HOMEOPATHIC PREPARATION	1 (2.9)	0	1 (1.2)
LACTOBACILLUS RHAMNOSUS	1 (2.9)	0	1 (1.2)
PIPERAZINE DERIVATIVES	1 (2.9)	2 (4.1)	3 (3.6)
CETIRIZINE	1 (2.9)	1 (2.0)	2 (2.4)
CETIRIZINE HYDROCHLORIDE	0	1 (2.0)	1 (1.2)
PYRAZOLONES	1 (2.9)	2 (4.1)	3 (3.6)
METAMIZOLE SODIUM	1 (2.9)	2 (4.1)	3 (3.6)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	1 (2.9)	2 (4.1)	3 (3.6)
ELECTROLYTES NOS W/GLUCOSE	1 (2.9)	0	1 (1.2)
OSMOTAN	0	1 (2.0)	1 (1.2)
RINGER-LACTATE	0	1 (2.0)	1 (1.2)
SYMPATHOMIMETICS, COMBINATIONS EXCL. CORTICOSTEROI	1 (2.9)	2 (4.1)	3 (3.6)
NASIC	0	2 (4.1)	2 (2.4)
TRIOFAN	1 (2.9)	0	1 (1.2)
SYMPATHOMIMETICS, PLAIN	0	3 (6.1)	3 (3.6)
XYLOMETAZOLINE HYDROCHLORIDE	0	3 (6.1)	3 (3.6)
VITAMIN D AND ANALOGUES	2 (5.7)	1 (2.0)	3 (3.6)
COLECALCIFEROL	2 (5.7)	0	2 (2.4)
VITAMIN D NOS	0	1 (2.0)	1 (1.2)
ANESTHETICS FOR TOPICAL USE	1 (2.9)	1 (2.0)	2 (2.4)
TETRACAINE	1 (2.9)	1 (2.0)	2 (2.4)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
ANTIBIOTICS	1 (2.9)	1 (2.0)	2 (2.4)
NEOMYCIN SULFATE	0	1 (2.0)	1 (1.2)
NETILMICIN SULFATE	1 (2.9)	0	1 (1.2)
ASCORBIC ACID (VITAMIN C), PLAIN	1 (2.9)	1 (2.0)	2 (2.4)
ASCORBIC ACID	1 (2.9)	1 (2.0)	2 (2.4)
BLOOD COAGULATION FACTORS	1 (2.9)	1 (2.0)	2 (2.4)
FACTOR VIII, RECOMBINANT	1 (2.9)	1 (2.0)	2 (2.4)
CORTICOSTEROIDS	1 (2.9)	1 (2.0)	2 (2.4)
MOMETASONE FUROATE	1 (2.9)	1 (2.0)	2 (2.4)
CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION	0	2 (4.1)	2 (2.4)
PANOTILE /00474401/	0	1 (2.0)	1 (1.2)
TERRA CORTRIL /03127501/	0	1 (2.0)	1 (1.2)
ENZYME PREPARATIONS	1 (2.9)	1 (2.0)	2 (2.4)
ALPHA-AMYLASE SWINE PANCREAS	1 (2.9)	1 (2.0)	2 (2.4)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
FOLIC ACID AND DERIVATIVES	0	2 (4.1)	2 (2.4)
FOLIC ACID	0	2 (4.1)	2 (2.4)
LEUKOTRIENE RECEPTOR ANTAGONISTS	1 (2.9)	1 (2.0)	2 (2.4)
MONTELUKAST	1 (2.9)	1 (2.0)	2 (2.4)
OPIUM ALKALOIDS AND DERIVATIVES	0	2 (4.1)	2 (2.4)
ACTIFED COMPOUND LINCTUS /00676001/	0	1 (2.0)	1 (1.2)
TOSCAL GRADUMET	0	1 (2.0)	1 (1.2)
OTHER AMINOGLYCOSIDES	1 (2.9)	1 (2.0)	2 (2.4)
AMIKACIN	1 (2.9)	0	1 (1.2)
GENTAMICIN	0	1 (2.0)	1 (1.2)
OTHER ANTIBIOTICS FOR TOPICAL USE	1 (2.9)	1 (2.0)	2 (2.4)
FUSIDIC ACID	1 (2.9)	0	1 (1.2)
MUPIROCIN	0	1 (2.0)	1 (1.2)
OTHER ANTIHISTAMINES FOR SYSTEMIC USE	1 (2.9)	1 (2.0)	2 (2.4)
DESLORATADINE	0	1 (2.0)	1 (1.2)
LORATADINE	1 (2.9)	0	1 (1.2)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
OTHER CICATRIZANTS	2 (5.7)	0	2 (2.4)
DEXPANTHENOL	1 (2.9)	0	1 (1.2)
OCRILATE	1 (2.9)	0	1 (1.2)
OTHER COUGH SUPPRESSANTS	0	2 (4.1)	2 (2.4)
CLOBUTINOL HYDROCHLORIDE	0	1 (2.0)	1 (1.2)
OTHER COUGH SUPPRESSANTS	0	1 (2.0)	1 (1.2)
PERTUSSIS VACCINES	2 (5.7)	0	2 (2.4)
VACCIN IPAD D.T.C.	2 (5.7)	0	2 (2.4)
SUBSTITUTED ALKYLAMINES	1 (2.9)	1 (2.0)	2 (2.4)
BROMPHENIRAMINE	1 (2.9)	0	1 (1.2)
DEXCHLORPHENIRAMINE MALEATE	0	1 (2.0)	1 (1.2)
ADRENERGIC AND DOPAMINERGIC AGENTS	1 (2.9)	0	1 (1.2)
DOPAMINE	1 (2.9)	0	1 (1.2)
NOREPINEPHRINE	1 (2.9)	0	1 (1.2)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
ANALGESICS AND ANESTHETICS	1 (2.9)	0	1 (1.2)
OTIPAX /01006301/	1 (2.9)	0	1 (1.2)
ANTIALLERGIC AGENTS, EXCL. CORTICOSTEROIDS	0	1 (2.0)	1 (1.2)
CROMOGLICIC ACID	0	1 (2.0)	1 (1.2)
ANTIDIARRHEAL MICROORGANISMS	0	1 (2.0)	1 (1.2)
ANTIDIARRHEAL MICROORGANISMS	0	1 (2.0)	1 (1.2)
ANTIDOTES	1 (2.9)	0	1 (1.2)
METHYLTHIONINIUM CHLORIDE	1 (2.9)	0	1 (1.2)
ANTISEPTICS	0	1 (2.0)	1 (1.2)
BENZYDAMINE HYDROCHLORIDE	0	1 (2.0)	1 (1.2)
STREPSILS /00200801/	0	1 (2.0)	1 (1.2)
ASCORBIC ACID (VITAMIN C), COMBINATIONS	0	1 (2.0)	1 (1.2)
VITAMIN C WITH ZINC	0	1 (2.0)	1 (1.2)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
BARBITURATES AND DERIVATIVES	0	1 (2.0)	1 (1.2)
PHENOBARBITAL	0	1 (2.0)	1 (1.2)
BELLADONNA ALKALOIDS, SEMISYNTHETIC, QUATERNARY AM	0	1 (2.0)	1 (1.2)
HYOSCINE BUTYLBROMIDE	0	1 (2.0)	1 (1.2)
BENZIMIDAZOLE DERIVATIVES	0	1 (2.0)	1 (1.2)
ALBENDAZOLE	0	1 (2.0)	1 (1.2)
BENZODIAZEPINE DERIVATIVES	0	1 (2.0)	1 (1.2)
MIDAZOLAM	0	1 (2.0)	1 (1.2)
CARBAPENEMS	1 (2.9)	0	1 (1.2)
MEROPENEM	1 (2.9)	0	1 (1.2)
COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INC	1 (2.9)	0	1 (1.2)
BACTRIM	1 (2.9)	0	1 (1.2)
CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	1 (2.9)	0	1 (1.2)
DESONIDE	1 (2.9)	0	1 (1.2)

Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
CORTICOSTEROIDS, POTENT, OTHER COMBINATIONS	0	1 (2.0)	1 (1.2)
TRAVOCORT	0	1 (2.0)	1 (1.2)
COUGH AND COLD PREPARATIONS	0	1 (2.0)	1 (1.2)
COUGH AND COLD PREPARATIONS	0	1 (2.0)	1 (1.2)
COXIBS	0	1 (2.0)	1 (1.2)
CELECOXIB	0	1 (2.0)	1 (1.2)
EMOLLIENTS AND PROTECTIVES	1 (2.9)	0	1 (1.2)
EMOLLIENTS AND PROTECTIVES	1 (2.9)	0	1 (1.2)
FATTY ACID DERIVATIVES	0	1 (2.0)	1 (1.2)
VALPROIC ACID	0	1 (2.0)	1 (1.2)
HEMOPHILUS INFLUENZAE B VACCINES	0	1 (2.0)	1 (1.2)
HAEMOPHILUS INFLUENZA TYPE B VACCINE	0	1 (2.0)	1 (1.2)
HEPARIN GROUP	1 (2.9)	0	1 (1.2)
HEPARIN	1 (2.9)	0	1 (1.2)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
HEPATITIS VACCINES	1 (2.9)	0	1 (1.2)
HEPATITIS B VACCINE	1 (2.9)	0	1 (1.2)
MULTIVITAMINS WITH MINERALS	1 (2.9)	0	1 (1.2)
MULTI-SANOSTOL /02376701/	1 (2.9)	0	1 (1.2)
MULTIVITAMINS, OTHER COMBINATIONS	1 (2.9)	0	1 (1.2)
MULTIVITAMINS	1 (2.9)	0	1 (1.2)
NATURAL OPIUM ALKALOIDS	0	1 (2.0)	1 (1.2)
MORPHINE	0	1 (2.0)	1 (1.2)
OPIOID ANESTHETICS	0	1 (2.0)	1 (1.2)
FENTANYL	0	1 (2.0)	1 (1.2)
OTHER AGENTS FOR LOCAL ORAL TREATMENT	1 (2.9)	0	1 (1.2)
TRANEXAMIC ACID	1 (2.9)	0	1 (1.2)
OTHER ANTIBACTERIALS	1 (2.9)	0	1 (1.2)
FUSAFUNGINE	1 (2.9)	0	1 (1.2)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
OTHER ANTIEMETICS	1 (2.9)	0	1 (1.2)
TRIMETHOBENZAMIDE	1 (2.9)	0	1 (1.2)
OTHER ANTIEPILEPTICS	0	1 (2.0)	1 (1.2)
LEVETIRACETAM	0	1 (2.0)	1 (1.2)
OTHER BLOOD PRODUCTS	0	1 (2.0)	1 (1.2)
RED BLOOD CELLS	0	1 (2.0)	1 (1.2)
OTHER GENERAL ANESTHETICS	0	1 (2.0)	1 (1.2)
PROPOFOL	0	1 (2.0)	1 (1.2)
OTHER HYPNOTICS AND SEDATIVES	0	1 (2.0)	1 (1.2)
DIPHENHYDRAMINE	0	1 (2.0)	1 (1.2)
OTHER NON-THERAPEUTIC AUXILIARY PRODUCTS	0	1 (2.0)	1 (1.2)
ENBUCRILATE	0	1 (2.0)	1 (1.2)
OTHER OPHTHALMOLOGICALS	1 (2.9)	0	1 (1.2)
DEXPANTHENOL	1 (2.9)	0	1 (1.2)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
PNEUMOCOCCAL VACCINES	0	1 (2.0)	1 (1.2)
PNEUMOCOCCAL VACCINE	0	1 (2.0)	1 (1.2)
POLIOMYELITIS VACCINES	1 (2.9)	0	1 (1.2)
POLIO VACCINE	1 (2.9)	0	1 (1.2)
PROTON PUMP INHIBITORS	0	1 (2.0)	1 (1.2)
ESOMEPRAZOLE	0	1 (2.0)	1 (1.2)
RESPIRATORY SYSTEM	0	1 (2.0)	1 (1.2)
HERBAL RESPIRATORY PREPARATION	0	1 (2.0)	1 (1.2)
SEROTONIN (5HT3) ANTAGONISTS	0	1 (2.0)	1 (1.2)
GRANISETRON	0	1 (2.0)	1 (1.2)
TETANUS VACCINES	1 (2.9)	0	1 (1.2)
TETANUS VACCINE	1 (2.9)	0	1 (1.2)
THYROID HORMONES	1 (2.9)	0	1 (1.2)
LEVOTHYROXINE SODIUM	1 (2.9)	0	1 (1.2)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.1.9.1 Concomitant Medications
(Safety Population)

ATC Class Preferred Drug Name	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
VITAMIN B-COMPLEX WITH MINERALS	0	1 (2.0)	1 (1.2)
VITAMIN B COMPLEX WITH IRON	0	1 (2.0)	1 (1.2)
WART AND ANTI-CORN PREPARATIONS	1 (2.9)	0	1 (1.2)
WART AND ANTI-CORN PREPARATIONS	1 (2.9)	0	1 (1.2)
ZINC	1 (2.9)	0	1 (1.2)
ZINC SULFATE HEPTAHYDRATE	1 (2.9)	0	1 (1.2)

Source: Listing 16.2.4.9
Notes: [1] Concomitant medications are all medications taken during the study, including those started before but ongoing at first dose.
[2] Table presents number and percentage of subjects [(n(%)].

Table 14.3.1.1 Summary of Adverse Events
(Safety Population)

	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Any Adverse Events	28	(80.0)	85	36	(73.5)	108	64	(76.2)	193
Any Treatment Emergent Adverse Events	28	(80.0)	79	36	(73.5)	104	64	(76.2)	183
Any Treatment Emergent Adverse Events Leading to Withdrawal	0			1	(2.0)	1	1	(1.2)	1
Any Treatment Emergent Adverse Events of Potential Special Interest	6	(17.1)	9	8	(16.3)	11	14	(16.7)	20
Treatment Emergent Adverse Event Severity									
Mild	22	(62.9)	57	30	(61.2)	80	52	(61.9)	137
Moderate	11	(31.4)	19	14	(28.6)	23	25	(29.8)	42
Severe	3	(8.6)	3	1	(2.0)	1	4	(4.8)	4
Any Treatment Emergent Adverse Events Related to Study Drug	0			1	(2.0)	1	1	(1.2)	1

Source: Listing 16.2.7.1, 16.2.7.5
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)

Table 14.3.1.1 Summary of Adverse Events
(Safety Population)

	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Treatment Emergent Adverse Event Outcome									
Death Related to Adverse Event	0			0			0		
Not Recovered/Not Resolved	3	(8.6)	3	3	(6.1)	6	6	(7.1)	9
Recovered/Resolved	26	(74.3)	74	35	(71.4)	94	61	(72.6)	168
Recovered/Resolved With Sequelae	0			0			0		
Recovering/Resolving	1	(2.9)	1	3	(6.1)	3	4	(4.8)	4
Unknown	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Any Serious Adverse Events	4	(11.4)	6	5	(10.2)	6	9	(10.7)	12
Any Treatment Emergent Serious Adverse Events	4	(11.4)	6	5	(10.2)	5	9	(10.7)	11
Any Treatment Emergent SAEs Leading to Withdrawal	0			0			0		
Treatment Emergent Serious Adverse Event Severity									
Mild	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Moderate	1	(2.9)	3	3	(6.1)	3	4	(4.8)	6
Severe	2	(5.7)	2	1	(2.0)	1	3	(3.6)	3
Any Treatment Emergent Serious Adverse Events Related to Study Drug	0			0			0		

Source: Listing 16.2.7.1, 16.2.7.5
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)

Table 14.3.1.1 Summary of Adverse Events
(Safety Population)

	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Treatment Emergent Serious Adverse Event Outcome									
Death Related to Adverse Event	0			0			0		
Not Recovered/Not Resolved	0			0			0		
Recovered/Resolved	4	(11.4)	6	5	(10.2)	5	9	(10.7)	11
Recovered/Resolved With Sequelae	0			0			0		
Recovering/Resolving	0			0			0		
Unknown	0			0			0		

Source: Listing 16.2.7.1, 16.2.7.5
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)

Table 14.3.1.4.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Any Treatment Emergent Adverse Events	28	(80.0)	79	36	(73.5)	104	64	(76.2)	183
Infections and infestations	18	(51.4)	29	20	(40.8)	31	38	(45.2)	60
Nasopharyngitis	6	(17.1)	7	8	(16.3)	8	14	(16.7)	15
Upper respiratory tract infection	2	(5.7)	3	2	(4.1)	2	4	(4.8)	5
Rhinitis	0		0	4	(8.2)	4	4	(4.8)	4
Ear infection	1	(2.9)	1	2	(4.1)	2	3	(3.6)	3
Lower respiratory tract infection	1	(2.9)	2	1	(2.0)	1	2	(2.4)	3
Device related infection	2	(5.7)	2	0		0	2	(2.4)	2
Gastroenteritis	2	(5.7)	2	0		0	2	(2.4)	2
Pharyngitis	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Skin infection	0		0	2	(4.1)	2	2	(2.4)	2
Viral infection	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Acute tonsillitis	1	(2.9)	1	0		0	1	(1.2)	1
Bacteraemia	0		0	1	(2.0)	1	1	(1.2)	1
Bronchitis	1	(2.9)	1	0		0	1	(1.2)	1
Croup infectious	1	(2.9)	1	0		0	1	(1.2)	1
Gastroenteritis viral	0		0	1	(2.0)	1	1	(1.2)	1
Hordeolum	0		0	1	(2.0)	1	1	(1.2)	1
Infection parasitic	0		0	1	(2.0)	1	1	(1.2)	1
Laryngitis	1	(2.9)	1	0		0	1	(1.2)	1
Otitis externa	1	(2.9)	1	0		0	1	(1.2)	1
Otitis media	0		0	1	(2.0)	1	1	(1.2)	1
Otitis media acute	0		0	1	(2.0)	1	1	(1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.4.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Infections and infestations (continued)									
Paronychia	0		0	1	(2.0)	1	1	(1.2)	1
Parotitis	0		0	1	(2.0)	1	1	(1.2)	1
Pneumonia	1	(2.9)	1	0		0	1	(1.2)	1
Respiratory tract infection	0		0	1	(2.0)	1	1	(1.2)	1
Tonsillitis	1	(2.9)	1	0		0	1	(1.2)	1
Tracheobronchitis	1	(2.9)	1	0		0	1	(1.2)	1
Urinary tract infection	0		0	1	(2.0)	1	1	(1.2)	1
Viral myositis	1	(2.9)	1	0		0	1	(1.2)	1
Viral upper respiratory tract infection	1	(2.9)	1	0		0	1	(1.2)	1
Injury, poisoning and procedural complications	10	(28.6)	15	10	(20.4)	17	20	(23.8)	32
Head injury	3	(8.6)	3	2	(4.1)	3	5	(6.0)	6
Fall	3	(8.6)	3	1	(2.0)	1	4	(4.8)	4
Contusion	0		0	3	(6.1)	6	3	(3.6)	6
Laceration	1	(2.9)	1	2	(4.1)	3	3	(3.6)	4
Ligament sprain	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Limb injury	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Excoriation	1	(2.9)	1	0		0	1	(1.2)	1
Hand fracture	0		0	1	(2.0)	1	1	(1.2)	1
Joint injury	1	(2.9)	1	0		0	1	(1.2)	1
Lip injury	1	(2.9)	1	0		0	1	(1.2)	1
Splenic rupture	0		0	1	(2.0)	1	1	(1.2)	1
Tongue injury	1	(2.9)	1	0		0	1	(1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.4.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	<6 years (N=35) n (%)	E	>=6 to <12 years (N=49) n (%)	E	Total (N=84) n (%)	E
Injury, poisoning and procedural complications (continued)						
Upper limb fracture	1 (2.9)	1	0	0	1 (1.2)	1
Wound	1 (2.9)	1	0	0	1 (1.2)	1
Musculoskeletal and connective tissue disorders	4 (11.4)	4	11 (22.4)	14	15 (17.9)	18
Arthralgia	3 (8.6)	3	5 (10.2)	5	8 (9.5)	8
Pain in extremity	0	0	4 (8.2)	4	4 (4.8)	4
Musculoskeletal pain	0	0	2 (4.1)	2	2 (2.4)	2
Back pain	0	0	1 (2.0)	1	1 (1.2)	1
Flank pain	0	0	1 (2.0)	1	1 (1.2)	1
Synovial cyst	0	0	1 (2.0)	1	1 (1.2)	1
Synovial disorder	1 (2.9)	1	0	0	1 (1.2)	1
Respiratory, thoracic and mediastinal disorders	3 (8.6)	8	9 (18.4)	11	12 (14.3)	19
Cough	2 (5.7)	3	5 (10.2)	7	7 (8.3)	10
Oropharyngeal pain	1 (2.9)	1	2 (4.1)	2	3 (3.6)	3
Rhinitis allergic	1 (2.9)	1	2 (4.1)	2	3 (3.6)	3
Asthma	1 (2.9)	2	0	0	1 (1.2)	2
Tonsillar disorder	1 (2.9)	1	0	0	1 (1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.4.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	<6 years (N=35) n (%)	E	>=6 to <12 years (N=49) n (%)	E	Total (N=84) n (%)	E
Nervous system disorders	1 (2.9)	1	7 (14.3)	13	8 (9.5)	14
Headache	1 (2.9)	1	6 (12.2)	8	7 (8.3)	9
Convulsion	0	0	1 (2.0)	2	1 (1.2)	2
Dizziness	0	0	1 (2.0)	1	1 (1.2)	1
Paraesthesia	0	0	1 (2.0)	1	1 (1.2)	1
Post-traumatic headache	0	0	1 (2.0)	1	1 (1.2)	1
General disorders and administration site conditions	5 (14.3)	5	3 (6.1)	3	8 (9.5)	8
Pyrexia	4 (11.4)	4	1 (2.0)	1	5 (6.0)	5
Device occlusion	0	0	1 (2.0)	1	1 (1.2)	1
Pain	0	0	1 (2.0)	1	1 (1.2)	1
Systemic inflammatory response syndrome	1 (2.9)	1	0	0	1 (1.2)	1
Gastrointestinal disorders	3 (8.6)	3	4 (8.2)	5	7 (8.3)	8
Dental caries	1 (2.9)	1	1 (2.0)	1	2 (2.4)	2
Vomiting	1 (2.9)	1	1 (2.0)	1	2 (2.4)	2
Abdominal pain	0	0	1 (2.0)	1	1 (1.2)	1
Dyspepsia	1 (2.9)	1	0	0	1 (1.2)	1
Nausea	0	0	1 (2.0)	1	1 (1.2)	1
Tooth loss	0	0	1 (2.0)	1	1 (1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.4.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Blood and lymphatic system disorders	2	(5.7)	4	4	(8.2)	4	6	(7.1)	8
Anaemia	1	(2.9)	3	2	(4.1)	2	3	(3.6)	5
Iron deficiency anaemia	0		0	2	(4.1)	2	2	(2.4)	2
Hypochromic anaemia	1	(2.9)	1	0		0	1	(1.2)	1
Skin and subcutaneous tissue disorders	3	(8.6)	3	1	(2.0)	1	4	(4.8)	4
Dry skin	1	(2.9)	1	0		0	1	(1.2)	1
Ecchymosis	0		0	1	(2.0)	1	1	(1.2)	1
Eczema	1	(2.9)	1	0		0	1	(1.2)	1
Rash erythematous	1	(2.9)	1	0		0	1	(1.2)	1
Ear and labyrinth disorders	2	(5.7)	2	1	(2.0)	1	3	(3.6)	3
Ear pain	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Cerumen impaction	1	(2.9)	1	0		0	1	(1.2)	1
Eye disorders	2	(5.7)	2	1	(2.0)	1	3	(3.6)	3
Blepharitis	1	(2.9)	1	0		0	1	(1.2)	1
Conjunctivitis	1	(2.9)	1	0		0	1	(1.2)	1
Diplopia	0		0	1	(2.0)	1	1	(1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.4.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Investigations	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Cardiac murmur	1	(2.9)	1	0		0	1	(1.2)	1
Haemoglobin decreased	0		0	1	(2.0)	1	1	(1.2)	1
Cardiac disorders	0		0	1	(2.0)	1	1	(1.2)	1
Sinus arrhythmia	0		0	1	(2.0)	1	1	(1.2)	1
Immune system disorders	0		0	1	(2.0)	1	1	(1.2)	1
Hypersensitivity	0		0	1	(2.0)	1	1	(1.2)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(2.9)	1	0		0	1	(1.2)	1
Skin papilloma	1	(2.9)	1	0		0	1	(1.2)	1
Reproductive system and breast disorders	1	(2.9)	1	0		0	1	(1.2)	1
Balanitis	1	(2.9)	1	0		0	1	(1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.5 Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	<6 years (N=35) n (%)	E	>=6 to <12 years (N=49) n (%)	E	Total (N=84) n (%)	E
Any Related Treatment Emergent Adverse Events	0	0	1 (2.0)	1	1 (1.2)	1
Immune system disorders	0	0	1 (2.0)	1	1 (1.2)	1
Hypersensitivity	0	0	1 (2.0)	1	1 (1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Any Adverse Events			
Overall	28 (80.0)	36 (73.5)	64 (76.2)
Mild	15 (42.9)	21 (42.9)	36 (42.9)
Moderate	10 (28.6)	14 (28.6)	24 (28.6)
Severe	3 (8.6)	1 (2.0)	4 (4.8)
Infections And Infestations			
Overall	20 (57.1)	23 (46.9)	43 (51.2)
Mild	13 (37.1)	17 (34.7)	30 (35.7)
Moderate	6 (17.1)	6 (12.2)	12 (14.3)
Severe	1 (2.9)	0	1 (1.2)
Nasopharyngitis			
Overall	6 (17.1)	8 (16.3)	14 (16.7)
Mild	5 (14.3)	7 (14.3)	12 (14.3)
Moderate	1 (2.9)	1 (2.0)	2 (2.4)
Severe	0	0	0
Rhinitis			
Overall	0	4 (8.2)	4 (4.8)
Mild	0	3 (6.1)	3 (3.6)
Moderate	0	1 (2.0)	1 (1.2)
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Infections and infestations (continued)			
Upper Respiratory Tract Infection			
Overall	2 (5.7)	2 (4.1)	4 (4.8)
Mild	1 (2.9)	2 (4.1)	3 (3.6)
Moderate	1 (2.9)	0	1 (1.2)
Severe	0	0	0
Ear Infection			
Overall	1 (2.9)	2 (4.1)	3 (3.6)
Mild	1 (2.9)	1 (2.0)	2 (2.4)
Moderate	0	1 (2.0)	1 (1.2)
Severe	0	0	0
Device Related Infection			
Overall	2 (5.7)	0	2 (2.4)
Mild	1 (2.9)	0	1 (1.2)
Moderate	1 (2.9)	0	1 (1.2)
Severe	0	0	0
Gastroenteritis			
Overall	2 (5.7)	0	2 (2.4)
Mild	1 (2.9)	0	1 (1.2)
Moderate	1 (2.9)	0	1 (1.2)
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Infections and infestations (continued)			
Lower Respiratory Tract Infection			
Overall	1 (2.9)	1 (2.0)	2 (2.4)
Mild	1 (2.9)	1 (2.0)	2 (2.4)
Moderate	0	0	0
Severe	0	0	0
Pharyngitis			
Overall	1 (2.9)	1 (2.0)	2 (2.4)
Mild	1 (2.9)	1 (2.0)	2 (2.4)
Moderate	0	0	0
Severe	0	0	0
Skin Infection			
Overall	0	2 (4.1)	2 (2.4)
Mild	0	2 (4.1)	2 (2.4)
Moderate	0	0	0
Severe	0	0	0
Viral Infection			
Overall	1 (2.9)	1 (2.0)	2 (2.4)
Mild	0	1 (2.0)	1 (1.2)
Moderate	1 (2.9)	0	1 (1.2)
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Infections and infestations (continued)			
Acute Tonsillitis			
Overall	1 (2.9)	0	1 (1.2)
Mild	0	0	0
Moderate	1 (2.9)	0	1 (1.2)
Severe	0	0	0
Bacteraemia			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	0	0
Moderate	0	1 (2.0)	1 (1.2)
Severe	0	0	0
Bronchitis			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Croup Infectious			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Infections and infestations (continued)			
Gastroenteritis Viral			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Hordeolum			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Infection Parasitic			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Laryngitis			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Infections and infestations (continued)			
Otitis Externa			
Overall	1 (2.9)	0	1 (1.2)
Mild	0	0	0
Moderate	1 (2.9)	0	1 (1.2)
Severe	0	0	0
Otitis Media			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Otitis Media Acute			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Paronychia			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	0	0
Moderate	0	1 (2.0)	1 (1.2)
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Infections and infestations (continued)			
Parotitis			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	0	0
Moderate	0	1 (2.0)	1 (1.2)
Severe	0	0	0
Pneumonia			
Overall	1 (2.9)	0	1 (1.2)
Mild	0	0	0
Moderate	0	0	0
Severe	1 (2.9)	0	1 (1.2)
Respiratory Tract Infection			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Tonsillitis			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Infections and infestations (continued)			
Tracheobronchitis			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Urinary Tract Infection			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Viral Myositis			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Viral Upper Respiratory Tract Infection			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Injury, Poisoning And Procedural Complications			
Overall	10 (28.6)	11 (22.4)	21 (25.0)
Mild	8 (22.9)	5 (10.2)	13 (15.5)
Moderate	2 (5.7)	5 (10.2)	7 (8.3)
Severe	0	1 (2.0)	1 (1.2)
Head Injury			
Overall	3 (8.6)	2 (4.1)	5 (6.0)
Mild	3 (8.6)	1 (2.0)	4 (4.8)
Moderate	0	1 (2.0)	1 (1.2)
Severe	0	0	0
Fall			
Overall	3 (8.6)	1 (2.0)	4 (4.8)
Mild	1 (2.9)	1 (2.0)	2 (2.4)
Moderate	2 (5.7)	0	2 (2.4)
Severe	0	0	0
Contusion			
Overall	0	3 (6.1)	3 (3.6)
Mild	0	2 (4.1)	2 (2.4)
Moderate	0	1 (2.0)	1 (1.2)
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Injury, poisoning and procedural complications (continued)			
Laceration			
Overall	1 (2.9)	2 (4.1)	3 (3.6)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	2 (4.1)	2 (2.4)
Severe	0	0	0
Ligament Sprain			
Overall	1 (2.9)	1 (2.0)	2 (2.4)
Mild	1 (2.9)	1 (2.0)	2 (2.4)
Moderate	0	0	0
Severe	0	0	0
Limb Injury			
Overall	1 (2.9)	1 (2.0)	2 (2.4)
Mild	1 (2.9)	1 (2.0)	2 (2.4)
Moderate	0	0	0
Severe	0	0	0
Excoriation			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Injury, poisoning and procedural complications (continued)			
Hand Fracture			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	0	0
Moderate	0	1 (2.0)	1 (1.2)
Severe	0	0	0
Joint Injury			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Lip Injury			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Splenic Rupture			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	0	0
Moderate	0	0	0
Severe	0	1 (2.0)	1 (1.2)

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Injury, poisoning and procedural complications (continued)			
Tongue Injury			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Upper Limb Fracture			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Wound			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Musculoskeletal And Connective Tissue Disorders			
Overall	4 (11.4)	12 (24.5)	16 (19.0)
Mild	3 (8.6)	8 (16.3)	11 (13.1)
Moderate	1 (2.9)	4 (8.2)	5 (6.0)
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Musculoskeletal and connective tissue disorders (continued)			
Arthralgia			
Overall	3 (8.6)	5 (10.2)	8 (9.5)
Mild	2 (5.7)	2 (4.1)	4 (4.8)
Moderate	1 (2.9)	3 (6.1)	4 (4.8)
Severe	0	0	0
Pain In Extremity			
Overall	0	4 (8.2)	4 (4.8)
Mild	0	3 (6.1)	3 (3.6)
Moderate	0	1 (2.0)	1 (1.2)
Severe	0	0	0
Musculoskeletal Pain			
Overall	0	2 (4.1)	2 (2.4)
Mild	0	2 (4.1)	2 (2.4)
Moderate	0	0	0
Severe	0	0	0
Back Pain			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Musculoskeletal and connective tissue disorders (continued)			
Flank Pain			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Synovial Cyst			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Synovial Disorder			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Respiratory, Thoracic And Mediastinal Disorders			
Overall	4 (11.4)	9 (18.4)	13 (15.5)
Mild	2 (5.7)	7 (14.3)	9 (10.7)
Moderate	2 (5.7)	2 (4.1)	4 (4.8)
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Respiratory, thoracic and mediastinal disorders (continued)			
Cough			
Overall	2 (5.7)	5 (10.2)	7 (8.3)
Mild	1 (2.9)	5 (10.2)	6 (7.1)
Moderate	1 (2.9)	0	1 (1.2)
Severe	0	0	0
Oropharyngeal Pain			
Overall	1 (2.9)	2 (4.1)	3 (3.6)
Mild	1 (2.9)	1 (2.0)	2 (2.4)
Moderate	0	1 (2.0)	1 (1.2)
Severe	0	0	0
Rhinitis Allergic			
Overall	1 (2.9)	2 (4.1)	3 (3.6)
Mild	0	1 (2.0)	1 (1.2)
Moderate	1 (2.9)	1 (2.0)	2 (2.4)
Severe	0	0	0
Asthma			
Overall	1 (2.9)	0	1 (1.2)
Mild	0	0	0
Moderate	1 (2.9)	0	1 (1.2)
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Respiratory, thoracic and mediastinal disorders (continued)			
Tonsillar Disorder			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
General Disorders And Administration Site Conditions			
Overall	5 (14.3)	3 (6.1)	8 (9.5)
Mild	3 (8.6)	3 (6.1)	6 (7.1)
Moderate	1 (2.9)	0	1 (1.2)
Severe	1 (2.9)	0	1 (1.2)
Pyrexia			
Overall	4 (11.4)	1 (2.0)	5 (6.0)
Mild	3 (8.6)	1 (2.0)	4 (4.8)
Moderate	1 (2.9)	0	1 (1.2)
Severe	0	0	0
Device Occlusion			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
General disorders and administration site conditions (continued)			
Pain			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Systemic Inflammatory Response Syndrome			
Overall	1 (2.9)	0	1 (1.2)
Mild	0	0	0
Moderate	0	0	0
Severe	1 (2.9)	0	1 (1.2)
Nervous System Disorders			
Overall	1 (2.9)	7 (14.3)	8 (9.5)
Mild	1 (2.9)	6 (12.2)	7 (8.3)
Moderate	0	1 (2.0)	1 (1.2)
Severe	0	0	0
Headache			
Overall	1 (2.9)	6 (12.2)	7 (8.3)
Mild	1 (2.9)	5 (10.2)	6 (7.1)
Moderate	0	1 (2.0)	1 (1.2)
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Nervous system disorders (continued)			
Convulsion			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Dizziness			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Paraesthesia			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Post-Traumatic Headache			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	0	0
Moderate	0	1 (2.0)	1 (1.2)
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Gastrointestinal Disorders			
Overall	3 (8.6)	4 (8.2)	7 (8.3)
Mild	2 (5.7)	4 (8.2)	6 (7.1)
Moderate	0	0	0
Severe	1 (2.9)	0	1 (1.2)
Dental Caries			
Overall	1 (2.9)	1 (2.0)	2 (2.4)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	1 (2.9)	0	1 (1.2)
Vomiting			
Overall	1 (2.9)	1 (2.0)	2 (2.4)
Mild	1 (2.9)	1 (2.0)	2 (2.4)
Moderate	0	0	0
Severe	0	0	0
Abdominal Pain			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Gastrointestinal disorders (continued)			
Dyspepsia			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Nausea			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Tooth Loss			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Blood And Lymphatic System Disorders			
Overall	2 (5.7)	4 (8.2)	6 (7.1)
Mild	1 (2.9)	3 (6.1)	4 (4.8)
Moderate	1 (2.9)	1 (2.0)	2 (2.4)
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Blood and lymphatic system disorders (continued)			
Anaemia			
Overall	1 (2.9)	2 (4.1)	3 (3.6)
Mild	0	1 (2.0)	1 (1.2)
Moderate	1 (2.9)	1 (2.0)	2 (2.4)
Severe	0	0	0
Iron Deficiency Anaemia			
Overall	0	2 (4.1)	2 (2.4)
Mild	0	2 (4.1)	2 (2.4)
Moderate	0	0	0
Severe	0	0	0
Hypochromic Anaemia			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Skin And Subcutaneous Tissue Disorders			
Overall	3 (8.6)	1 (2.0)	4 (4.8)
Mild	3 (8.6)	1 (2.0)	4 (4.8)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Skin and subcutaneous tissue disorders (continued)			
Dry Skin			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Ecchymosis			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Eczema			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Rash Erythematous			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Ear And Labyrinth Disorders			
Overall	2 (5.7)	1 (2.0)	3 (3.6)
Mild	2 (5.7)	1 (2.0)	3 (3.6)
Moderate	0	0	0
Severe	0	0	0
Ear Pain			
Overall	1 (2.9)	1 (2.0)	2 (2.4)
Mild	1 (2.9)	1 (2.0)	2 (2.4)
Moderate	0	0	0
Severe	0	0	0
Cerumen Impaction			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Eye Disorders			
Overall	2 (5.7)	1 (2.0)	3 (3.6)
Mild	2 (5.7)	1 (2.0)	3 (3.6)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Eye disorders (continued)			
Blepharitis			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Conjunctivitis			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Diplopia			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Investigations			
Overall	1 (2.9)	1 (2.0)	2 (2.4)
Mild	0	1 (2.0)	1 (1.2)
Moderate	1 (2.9)	0	1 (1.2)
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Investigations (continued)			
Cardiac Murmur			
Overall	1 (2.9)	0	1 (1.2)
Mild	0	0	0
Moderate	1 (2.9)	0	1 (1.2)
Severe	0	0	0
Haemoglobin Decreased			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Cardiac Disorders			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Sinus Arrhythmia			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Immune System Disorders			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Hypersensitivity			
Overall	0	1 (2.0)	1 (1.2)
Mild	0	1 (2.0)	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	1 (2.9)	0	1 (1.2)
Overall			
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Skin Papilloma			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.10 Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

System Organ Class Preferred Term Severity	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Reproductive System And Breast Disorders			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0
Balanitis			
Overall	1 (2.9)	0	1 (1.2)
Mild	1 (2.9)	0	1 (1.2)
Moderate	0	0	0
Severe	0	0	0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event, by maximum severity.
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.15 Treatment Emergent Adverse Events in Decreasing Frequency of Preferred Term (Safety Population)

Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Any Treatment Emergent Adverse Events	28	(80.0)	79	36	(73.5)	104	64	(76.2)	183
Nasopharyngitis	6	(17.1)	7	8	(16.3)	8	14	(16.7)	15
Arthralgia	3	(8.6)	3	5	(10.2)	5	8	(9.5)	8
Cough	2	(5.7)	3	5	(10.2)	7	7	(8.3)	10
Headache	1	(2.9)	1	6	(12.2)	8	7	(8.3)	9
Head injury	3	(8.6)	3	2	(4.1)	3	5	(6.0)	6
Pyrexia	4	(11.4)	4	1	(2.0)	1	5	(6.0)	5
Upper respiratory tract infection	2	(5.7)	3	2	(4.1)	2	4	(4.8)	5
Fall	3	(8.6)	3	1	(2.0)	1	4	(4.8)	4
Pain in extremity	0		0	4	(8.2)	4	4	(4.8)	4
Rhinitis	0		0	4	(8.2)	4	4	(4.8)	4
Contusion	0		0	3	(6.1)	6	3	(3.6)	6
Anaemia	1	(2.9)	3	2	(4.1)	2	3	(3.6)	5
Laceration	1	(2.9)	1	2	(4.1)	3	3	(3.6)	4
Ear infection	1	(2.9)	1	2	(4.1)	2	3	(3.6)	3
Oropharyngeal pain	1	(2.9)	1	2	(4.1)	2	3	(3.6)	3
Rhinitis allergic	1	(2.9)	1	2	(4.1)	2	3	(3.6)	3
Lower respiratory tract infection	1	(2.9)	2	1	(2.0)	1	2	(2.4)	3
Dental caries	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Device related infection	2	(5.7)	2	0		0	2	(2.4)	2

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[3] Adverse Events were coded using MedDRA Version 16.1

Table 14.3.1.15 Treatment Emergent Adverse Events in Decreasing Frequency of Preferred Term (Safety Population)

Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Ear pain	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Gastroenteritis	2	(5.7)	2	0		0	2	(2.4)	2
Iron deficiency anaemia	0		0	2	(4.1)	2	2	(2.4)	2
Ligament sprain	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Limb injury	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Musculoskeletal pain	0		0	2	(4.1)	2	2	(2.4)	2
Pharyngitis	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Skin infection	0		0	2	(4.1)	2	2	(2.4)	2
Viral infection	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Vomiting	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Asthma	1	(2.9)	2	0		0	1	(1.2)	2
Convulsion	0		0	1	(2.0)	2	1	(1.2)	2
Abdominal pain	0		0	1	(2.0)	1	1	(1.2)	1
Acute tonsillitis	1	(2.9)	1	0		0	1	(1.2)	1
Back pain	0		0	1	(2.0)	1	1	(1.2)	1
Bacteraemia	0		0	1	(2.0)	1	1	(1.2)	1
Balanitis	1	(2.9)	1	0		0	1	(1.2)	1
Blepharitis	1	(2.9)	1	0		0	1	(1.2)	1
Bronchitis	1	(2.9)	1	0		0	1	(1.2)	1
Cardiac murmur	1	(2.9)	1	0		0	1	(1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[3] Adverse Events were coded using MedDRA Version 16.1

Table 14.3.1.15 Treatment Emergent Adverse Events in Decreasing Frequency of Preferred Term (Safety Population)

Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Cerumen impaction	1	(2.9)	1	0		0	1	(1.2)	1
Conjunctivitis	1	(2.9)	1	0		0	1	(1.2)	1
Croup infectious	1	(2.9)	1	0		0	1	(1.2)	1
Device occlusion	0		0	1	(2.0)	1	1	(1.2)	1
Diplopia	0		0	1	(2.0)	1	1	(1.2)	1
Dizziness	0		0	1	(2.0)	1	1	(1.2)	1
Dry skin	1	(2.9)	1	0		0	1	(1.2)	1
Dyspepsia	1	(2.9)	1	0		0	1	(1.2)	1
Ecchymosis	0		0	1	(2.0)	1	1	(1.2)	1
Eczema	1	(2.9)	1	0		0	1	(1.2)	1
Excoriation	1	(2.9)	1	0		0	1	(1.2)	1
Flank pain	0		0	1	(2.0)	1	1	(1.2)	1
Gastroenteritis viral	0		0	1	(2.0)	1	1	(1.2)	1
Haemoglobin decreased	0		0	1	(2.0)	1	1	(1.2)	1
Hand fracture	0		0	1	(2.0)	1	1	(1.2)	1
Hordeolum	0		0	1	(2.0)	1	1	(1.2)	1
Hypersensitivity	0		0	1	(2.0)	1	1	(1.2)	1
Hypochromic anaemia	1	(2.9)	1	0		0	1	(1.2)	1
Infection parasitic	0		0	1	(2.0)	1	1	(1.2)	1
Joint injury	1	(2.9)	1	0		0	1	(1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[3] Adverse Events were coded using MedDRA Version 16.1

Table 14.3.1.15 Treatment Emergent Adverse Events in Decreasing Frequency of Preferred Term (Safety Population)

Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Laryngitis	1	(2.9)	1	0		0	1	(1.2)	1
Lip injury	1	(2.9)	1	0		0	1	(1.2)	1
Nausea	0		0	1	(2.0)	1	1	(1.2)	1
Otitis externa	1	(2.9)	1	0		0	1	(1.2)	1
Otitis media	0		0	1	(2.0)	1	1	(1.2)	1
Otitis media acute	0		0	1	(2.0)	1	1	(1.2)	1
Pain	0		0	1	(2.0)	1	1	(1.2)	1
Paraesthesia	0		0	1	(2.0)	1	1	(1.2)	1
Paronychia	0		0	1	(2.0)	1	1	(1.2)	1
Parotitis	0		0	1	(2.0)	1	1	(1.2)	1
Pneumonia	1	(2.9)	1	0		0	1	(1.2)	1
Post-traumatic headache	0		0	1	(2.0)	1	1	(1.2)	1
Rash erythematous	1	(2.9)	1	0		0	1	(1.2)	1
Respiratory tract infection	0		0	1	(2.0)	1	1	(1.2)	1
Sinus arrhythmia	0		0	1	(2.0)	1	1	(1.2)	1
Skin papilloma	1	(2.9)	1	0		0	1	(1.2)	1
Splenic rupture	0		0	1	(2.0)	1	1	(1.2)	1
Synovial cyst	0		0	1	(2.0)	1	1	(1.2)	1
Synovial disorder	1	(2.9)	1	0		0	1	(1.2)	1
Systemic inflammatory response syndrome	1	(2.9)	1	0		0	1	(1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[3] Adverse Events were coded using MedDRA Version 16.1

Table 14.3.1.15 Treatment Emergent Adverse Events in Decreasing Frequency of Preferred Term (Safety Population)

Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Tongue injury	1	(2.9)	1	0		0	1	(1.2)	1
Tonsillar disorder	1	(2.9)	1	0		0	1	(1.2)	1
Tonsillitis	1	(2.9)	1	0		0	1	(1.2)	1
Tooth loss	0		0	1	(2.0)	1	1	(1.2)	1
Tracheobronchitis	1	(2.9)	1	0		0	1	(1.2)	1
Upper limb fracture	1	(2.9)	1	0		0	1	(1.2)	1
Urinary tract infection	0		0	1	(2.0)	1	1	(1.2)	1
Viral myositis	1	(2.9)	1	0		0	1	(1.2)	1
Viral upper respiratory tract infection	1	(2.9)	1	0		0	1	(1.2)	1
Wound	1	(2.9)	1	0		0	1	(1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[3] Adverse Events were coded using MedDRA Version 16.1

Table 14.3.2.1.1 Local Tolerability - Subject Assessment
(Safety Population)

	<6 years (N=35)				>=6 to <12 years (N=49)				Overall (N=84)			
	n	(%)	E	(%)	n	(%)	E	(%)	n	(%)	E	(%)
>=1 Assessment	34	(97.1)	1797		49	(100.0)	2977		83	(98.8)	4774	
Reaction												
None	34	(100.0)	1789	(99.6)	49	(100.0)	2958	(99.4)	83	(100.0)	4747	(99.4)
Very Slight	1	(2.9)	4	(0.2)	3	(6.1)	6	(0.2)	4	(4.8)	10	(0.2)
Slight	0				1	(2.0)	5	(0.2)	1	(1.2)	5	(0.1)
Moderate	2	(5.9)	4	(0.2)	3	(6.1)	8	(0.3)	5	(6.0)	12	(0.3)
Severe	0				0				0			

Source: Listing 16.2.7.4.1
Notes: [1] Table presents number and percentage of subjects [n (%)] and number and percentage of assessments [E(%)].

Table 14.3.2.2.1 Local Tolerability - Investigator Assessment
(Safety Population)

	<6 years (N=35) n	(%)	E	(%)	>=6 to <12 years (N=49) n	(%)	E	(%)	Total (N=84) n	(%)	E	(%)
>=1 Assessment	35	(100.0)	161		49	(100.0)	148		84	(100.0)	309	
Erythema Assessment												
None	34	(97.1)	160	(99.4)	49	(100.0)	147	(99.3)	83	(98.8)	307	(99.4)
Very Slight (Barely Perceptible)	0				0				0			
Well-defined	1	(2.9)	1	(0.6)	1	(2.0)	1	(0.7)	2	(2.4)	2	(0.6)
Moderate to Severe	0				0				0			
Severe (Beet Redness) to Slight Eschar Formations (Injuries in Depth)	0				0				0			
Maximum Size of the Edema or Induration at Smallest Diameter (mm)												
n	1				0				1			
Mean (SD)	30.0								30.0			
Median	30.0								30.0			
Min, Max	30, 30								30, 30			
Maximum Size of the Edema or Induration at Largest Diameter (mm)												
n	1				0				1			
Mean (SD)	30.0								30.0			
Median	30.0								30.0			
Min, Max	30, 30								30, 30			

Source: Listing 16.2.7.4.2
Notes: [1] Maximum size of edema/induration over all assessments is summarized.
[2] Where indicated, table presents number and percentage of subjects [(n(%)] and number and percentage of assessments [E (%)].

Table 14.3.2.2.1 Local Tolerability - Investigator Assessment
(Safety Population)

	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	n (%)	E (%)	n (%)	E (%)	n (%)	E (%)
Itching Severity						
None	35 (100.0)	161 (100.0)	48 (98.0)	147 (99.3)	83 (98.8)	308 (99.7)
Very Slight	0		1 (2.0)	1 (0.7)	1 (1.2)	1 (0.3)
Slight	0		0		0	
Moderate	0		0		0	
Severe	0		0		0	
Pain Severity						
None	35 (100.0)	161 (100.0)	48 (98.0)	147 (99.3)	83 (98.8)	308 (99.7)
Very Slight	0		1 (2.0)	1 (0.7)	1 (1.2)	1 (0.3)
Slight	0		0		0	
Moderate	0		0		0	
Severe	0		0		0	
Heat Severity						
None	35 (100.0)	161 (100.0)	49 (100.0)	147 (99.3)	84 (100.0)	308 (99.7)
Very Slight	0		1 (2.0)	1 (0.7)	1 (1.2)	1 (0.3)
Slight	0		0		0	
Moderate	0		0		0	
Severe	0		0		0	

Source: Listing 16.2.7.4.2
Notes: [1] Maximum size of edema/induration over all assessments is summarized.
[2] Where indicated, table presents number and percentage of subjects [(n(%)] and number and percentage of assessments [E (%)].

Table 14.3.3.1.1 Summary of Inhibitors Verified Upon Re-Testing
(Safety Population, Excluding Subjects with Inhibitors at Baseline)

	Total (N=83) n (%)	95% CI [1] (N=64)	95% CI [2] (N=83)
Inhibitors to FVIII			
Positive [3]	0	(0.0, 5.6)	(0.0, 4.3)
Low-titre (<=5 BU/mL) [4]	0		
High-titre (>5 BU/mL) [4]	0		
Negative [3]	83 (100.0)		

Source: Listing 16.2.8.3
Notes: [1] Exact Clopper-Pearson 95% CI based on subjects in specified population with >=50 EDs.
[2] Exact Clopper-Pearson 95% CI based on subjects in specified population.
[3] Percentages are based on the number of subjects in specified population.
[4] Percentages are based on the number of subjects in specified population with inhibitors to FVIII during the study.

Table 14.3.3.1.2 Summary of Inhibitor Assay Tests by Visit
(Safety Population)

	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Screening			
Number Tested [2]	33 (94.3)	47 (95.9)	80 (95.2)
Positive [3]	0	1 (2.1)	1 (1.3)
Low-titre (<=5 BU/mL) [4]	0	1 (100.0)	1 (100.0)
High-titre (>5 BU/mL) [4]	0	0	0
Negative [3]	33 (100.0)	46 (97.9)	79 (98.8)
Month 1			
Number Tested [2]	27 (77.1)	33 (67.3)	60 (71.4)
Positive [3]	0	0	0
Low-titre (<=5 BU/mL) [4]	0	0	0
High-titre (>5 BU/mL) [4]	0	0	0
Negative [3]	27 (100.0)	33 (100.0)	60 (100.0)
Month 2			
Number Tested [2]	16 (45.7)	31 (63.3)	47 (56.0)
Positive [3]	0	1 (3.2)	1 (2.1)
Low-titre (<=5 BU/mL) [4]	0	1 (100.0)	1 (100.0)
High-titre (>5 BU/mL) [4]	0	0	0
Negative [3]	16 (100.0)	30 (96.8)	46 (97.9)

Source: Listing 16.2.8.3
Notes: [1] Percentages are based on the number of subjects in specified population.
[2] Percentages are based on the number of subjects in specified population tested for inhibitors.
[3] Percentages are based on the number of subjects in specified population with inhibitors to FVIII during the study.
[4] Four subjects, 7920007-2001, 7920008-2001, 7920008-2002 and 7920008-2003 did not have a test at the screening visit; however at an unscheduled visit prior to dosing with CSL627.
[5] Positive titre tests needed confirmation in a second independent sample for the subject to be diagnosed as Inhibitor positive.
[6] See page 4 for individual titre values for subjects with a positive inhibitor titre during the study.

Table 14.3.3.1.2 Summary of Inhibitor Assay Tests by Visit
(Safety Population)

	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Month 3			
Number Tested [2]	10 (28.6)	12 (24.5)	22 (26.2)
Positive [3]	0	1 (8.3)	1 (4.5)
Low-titre (<=5 BU/mL) [4]	0	1 (100.0)	1 (100.0)
High-titre (>5 BU/mL) [4]	0	0	0
Negative [3]	10 (100.0)	11 (91.7)	21 (95.5)
Month 4			
Number Tested [2]	7 (20.0)	13 (26.5)	20 (23.8)
Positive [3]	0	0	0
Low-titre (<=5 BU/mL) [4]	0	0	0
High-titre (>5 BU/mL) [4]	0	0	0
Negative [3]	7 (100.0)	13 (100.0)	20 (100.0)
Month 5			
Number Tested [2]	7 (20.0)	10 (20.4)	17 (20.2)
Positive [3]	0	0	0
Low-titre (<=5 BU/mL) [4]	0	0	0
High-titre (>5 BU/mL) [4]	0	0	0
Negative [3]	7 (100.0)	10 (100.0)	17 (100.0)

Source: Listing 16.2.8.3
Notes: [1] Percentages are based on the number of subjects in specified population.
[2] Percentages are based on the number of subjects in specified population tested for inhibitors.
[3] Percentages are based on the number of subjects in specified population with inhibitors to FVIII during the study.
[4] Four subjects, 7920007-2001, 7920008-2001, 7920008-2002 and 7920008-2003 did not have a test at the screening visit; however at an unscheduled visit prior to dosing with CSL627.
[5] Positive titre tests needed confirmation in a second independent sample for the subject to be diagnosed as Inhibitor positive.
[6] See page 4 for individual titre values for subjects with a positive inhibitor titre during the study.

Table 14.3.3.1.2 Summary of Inhibitor Assay Tests by Visit
(Safety Population)

	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Month 6			
Number Tested [2]	4 (11.4)	9 (18.4)	13 (15.5)
Positive [3]	0	0	0
Low-titre (<=5 BU/mL) [4]	0	0	0
High-titre (>5 BU/mL) [4]	0	0	0
Negative [3]	4 (100.0)	9 (100.0)	13 (100.0)
Month 9			
Number Tested [2]	1 (2.9)	0	1 (1.2)
Positive [3]	0	0	0
Low-titre (<=5 BU/mL) [4]	0	0	0
High-titre (>5 BU/mL) [4]	0	0	0
Negative [3]	1 (100.0)	0	1 (100.0)
End of Study			
Number Tested [2]	35 (100.0)	47 (95.9)	82 (97.6)
Positive [3]	0	1 (2.1)	1 (1.2)
Low-titre (<=5 BU/mL) [4]	0	1 (100.0)	1 (100.0)
High-titre (>5 BU/mL) [4]	0	0	0
Negative [3]	35 (100.0)	46 (97.9)	81 (98.8)

Notes: [1] Percentages are based on the number of subjects in specified population.
[2] Percentages are based on the number of subjects in specified population tested for inhibitors.
[3] Percentages are based on the number of subjects in specified population with inhibitors to FVIII during the study.
[4] Four subjects, 7920007-2001, 7920008-2001, 7920008-2002 and 7920008-2003 did not have a test at the screening visit; however at an unscheduled visit prior to dosing with CSL627.
[5] Positive titre tests needed confirmation in a second independent sample for the subject to be diagnosed as Inhibitor positive.
[6] See page 4 for individual titre values for subjects with a positive inhibitor titre during the study.

Table 14.3.3.1.2 Summary of Inhibitor Assay Tests by Visit
(Safety Population)

Age Group	Subject	Visit	Date:Time	FVIII Inhibitor Titre (BU/mL)	Titre Category
>=6 to <12 years	6080002-2004	Screening	21FEB2015:10:05	3.46	Positive - Low-titre
		Unscheduled	09APR2015:08:00	0.90	Positive - Low-titre
		Unscheduled	27APR2015:07:50	0.65	Positive - Low-titre
		Month 2	14MAY2015:07:07	1.20	Positive - Low-titre
		Month 3	16JUN2015:07:30	0.83	Positive - Low-titre
		Month 4	14JUL2015:07:50	0.55	Negative
		End of Study	11AUG2015:07:20	0.47	Negative
	8040005-2005	Screening	19FEB2015:12:00	<0.4	Negative
		Month 2	13MAY2015:10:50	<0.4	Negative
		End of Study	24JUL2015:12:00	0.64	Positive - Low-titre

Notes: [1] Percentages are based on the number of subjects in specified population.
[2] Percentages are based on the number of subjects in specified population tested for inhibitors.
[3] Percentages are based on the number of subjects in specified population with inhibitors to FVIII during the study.
[4] Four subjects, 7920007-2001, 7920008-2001, 7920008-2002 and 7920008-2003 did not have a test at the screening visit; however at an unscheduled visit prior to dosing with CSL627.
[5] Positive titre tests needed confirmation in a second independent sample for the subject to be diagnosed as Inhibitor positive.
[6] See page 4 for individual titre values for subjects with a positive inhibitor titre during the study.

Table 14.3.3.2.2 Summary of Anti-rFVIII Antibodies
(Safety Population, Age 0 to <6 Years)

Visit	Anti-rFVIII Antibodies (N=35) n	(%)	Anti-rFVIII Antibodies IgG (N=35) n	(%)	Anti-rFVIII Antibodies IgM (N=35) n	(%)	Final (b) Anti-rFVIII Antibodies (N=35) n	(%)
Screening								
Number Tested	33		14		14		33	
Positive	14	(42.4)	6	(42.9)	0		6	(18.2)
Negative	19	(57.6)	8	(57.1)	14	(100.0)	27	(81.8)
Month 1								
Number Tested	27		13		13		27	
Positive	13	(48.1)	8	(61.5)	0		8	(29.6)
Negative	14	(51.9)	5	(38.5)	13	(100.0)	19	(70.4)
Month 2								
Number Tested	16		9		9		16	
Positive	9	(56.3)	5	(55.6)	0		5	(31.3)
Negative	7	(43.8)	4	(44.4)	9	(100.0)	11	(68.8)
Month 3								
Number Tested	9		7		7		9	
Positive	7	(77.8)	3	(42.9)	0		3	(33.3)
Negative	2	(22.2)	4	(57.1)	7	(100.0)	6	(66.7)

Source: Listing 16.2.8.3
Notes: [1] (a) A subject's result is positive if the subject's tests results were positive anytime during the study, including at screening. Otherwise, the subject's result is negative.
[2] (b) = A subject's result is positive if the result from Anti-rFVII antibodies is positive and one of test result from IgG and IgM is positive, otherwise the subject's result is negative.

Table 14.3.3.2.2 Summary of Anti-rFVIII Antibodies
(Safety Population, Age 0 to <6 Years)

Visit	Anti-rFVIII Antibodies (N=35) n (%)	Anti-rFVIII Antibodies IgG (N=35) n (%)	Anti-rFVIII Antibodies IgM (N=35) n (%)	Final (b) Anti-rFVIII Antibodies (N=35) n (%)
Month 4				
Number Tested	7	3	3	7
Positive	3 (42.9)	2 (66.7)	0	2 (28.6)
Negative	4 (57.1)	1 (33.3)	3 (100.0)	5 (71.4)
Month 5				
Number Tested	7	4	4	7
Positive	4 (57.1)	2 (50.0)	0	2 (28.6)
Negative	3 (42.9)	2 (50.0)	4 (100.0)	5 (71.4)
Month 6				
Number Tested	4	2	2	4
Positive	2 (50.0)	1 (50.0)	0	1 (25.0)
Negative	2 (50.0)	1 (50.0)	2 (100.0)	3 (75.0)
Month 9				
Number Tested	1	1	1	1
Positive	1 (100.0)	0	0	0
Negative	0	1 (100.0)	1 (100.0)	1 (100.0)

Source: Listing 16.2.8.3
Notes: [1] (a) A subject's result is positive if the subject's tests results were positive anytime during the study, including at screening. Otherwise, the subject's result is negative.
[2] (b) = A subject's result is positive if the result from Anti-rFVII antibodies is positive and one of test result from IgG and IgM is positive, otherwise the subject's result is negative.

Table 14.3.3.2.2 Summary of Anti-rFVIII Antibodies
(Safety Population, Age 0 to <6 Years)

Visit	Anti-rFVIII Antibodies (N=35) n	(%)	Anti-rFVIII Antibodies IgG (N=35) n	(%)	Anti-rFVIII Antibodies IgM (N=35) n	(%)	Final (b) Anti-rFVIII Antibodies (N=35) n	(%)
End of Study								
Number Tested	35		18		18		35	
Positive	18	(51.4)	12	(66.7)	0		12	(34.3)
Negative	17	(48.6)	6	(33.3)	18	(100.0)	23	(65.7)
Final (a)								
Number Tested	35		25		25		35	
Positive	25	(71.4)	16	(64.0)	0		16	(45.7)
Negative	10	(28.6)	9	(36.0)	25	(100.0)	19	(54.3)

CSL Behring GmbH: CSL627_3002/CIL-MJ/FINAL/ANTI01P.SAS
Produced: [redacted] 20[redacted], 9:58
Source: Listing 16.2.8.3
Notes: [1] (a) A subject's result is positive if the subject's tests results were positive anytime during the study, including at screening. Otherwise, the subject's result is negative.
[2] (b) = A subject's result is positive if the result from Anti-rFVII antibodies is positive and one of test result from IgG and IgM is positive, otherwise the subject's result is negative.

Table 14.3.3.2.3 Summary of Anti-rFVIII Antibodies
(Safety Population, Age >=6 to <12 Years)

Visit	Anti-rFVIII Antibodies (N=49) n	(%)	Anti-rFVIII Antibodies IgG (N=49) n	(%)	Anti-rFVIII Antibodies IgM (N=49) n	(%)	Final (b) Anti-rFVIII Antibodies (N=49) n	(%)
Screening								
Number Tested	47		11		11		47	
Positive	11	(23.4)	4	(36.4)	1	(9.1)	4	(8.5)
Negative	36	(76.6)	7	(63.6)	10	(90.9)	43	(91.5)
Month 1								
Number Tested	33		6		6		33	
Positive	6	(18.2)	2	(33.3)	1	(16.7)	2	(6.1)
Negative	27	(81.8)	4	(66.7)	5	(83.3)	31	(93.9)
Month 2								
Number Tested	29		9		9		29	
Positive	9	(31.0)	1	(11.1)	0		1	(3.4)
Negative	20	(69.0)	8	(88.9)	9	(100.0)	28	(96.6)
Month 3								
Number Tested	11		2		2		11	
Positive	2	(18.2)	0		0		0	
Negative	9	(81.8)	2	(100.0)	2	(100.0)	11	(100.0)

Source: Listing 16.2.8.3
Notes: [1] (a) A subject's result is positive if the subject's tests results were positive anytime during the study, including at screening. Otherwise, the subject's result is negative.
[2] (b) = A subject's result is positive if the result from Anti-rFVII antibodies is positive and one of test result from IgG and IgM is positive, otherwise the subject's result is negative.

Table 14.3.3.2.3 Summary of Anti-rFVIII Antibodies
(Safety Population, Age >=6 to <12 Years)

Visit	Anti-rFVIII Antibodies (N=49) n	(%)	Anti-rFVIII Antibodies IgG (N=49) n	(%)	Anti-rFVIII Antibodies IgM (N=49) n	(%)	Final (b) Anti-rFVIII Antibodies (N=49) n	(%)
Month 4								
Number Tested	12		2		2		12	
Positive	2	(16.7)	1	(50.0)	0		1	(8.3)
Negative	10	(83.3)	1	(50.0)	2	(100.0)	11	(91.7)
Month 5								
Number Tested	10		2		2		10	
Positive	2	(20.0)	0		0		0	
Negative	8	(80.0)	2	(100.0)	2	(100.0)	10	(100.0)
Month 6								
Number Tested	9		1		1		9	
Positive	1	(11.1)	1	(100.0)	0		1	(11.1)
Negative	8	(88.9)	0		1	(100.0)	8	(88.9)
Month 9								
Number Tested	0		0		0		0	
Positive	0		0		0		0	
Negative	0		0		0		0	

Source: Listing 16.2.8.3
Notes: [1] (a) A subject's result is positive if the subject's tests results were positive anytime during the study, including at screening. Otherwise, the subject's result is negative.
[2] (b) = A subject's result is positive if the result from Anti-rFVII antibodies is positive and one of test result from IgG and IgM is positive, otherwise the subject's result is negative.

Table 14.3.3.2.3 Summary of Anti-rFVIII Antibodies
(Safety Population, Age >=6 to <12 Years)

Visit	Anti-rFVIII Antibodies (N=49) n	(%)	Anti-rFVIII Antibodies IgG (N=49) n	(%)	Anti-rFVIII Antibodies IgM (N=49) n	(%)	Final (b) Anti-rFVIII Antibodies (N=49) n	(%)
End of Study								
Number Tested	47		8		8		47	
Positive	8	(17.0)	3	(37.5)	0		3	(6.4)
Negative	39	(83.0)	5	(62.5)	8	(100.0)	44	(93.6)
Final (a)								
Number Tested	49		21		21		49	
Positive	21	(42.9)	4	(19.0)	1	(4.8)	4	(8.2)
Negative	28	(57.1)	17	(81.0)	20	(95.2)	45	(91.8)

Source: Listing 16.2.8.3
Notes: [1] (a) A subject's result is positive if the subject's tests results were positive anytime during the study, including at screening. Otherwise, the subject's result is negative.
[2] (b) = A subject's result is positive if the result from Anti-rFVII antibodies is positive and one of test result from IgG and IgM is positive, otherwise the subject's result is negative.

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Hemoglobin (g/L)						
Screening						
n	34		49		83	
Mean (SD)	120.62 (7.154)		120.94 (13.380)		120.81 (11.199)	
Median	120.43		121.00		120.85	
Min, Max	104.0, 133.0		76.0, 147.0		76.0, 147.0	
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	117.41 (8.450)		123.08 (10.156)		120.18 (9.633)	
Median	116.50		123.00		119.24	
Min, Max	106.0, 138.0		106.0, 147.0		106.0, 147.0	
Day 1 Non-PK						
n	24	24	42	42	66	66
Mean (SD)	116.51 (10.175)	-1.87 (4.012)	120.53 (12.331)	-0.48 (2.606)	119.07 (11.676)	-0.98 (3.231)
Median	115.00	0.00	120.00	0.00	118.00	0.00
Min, Max	99.0, 144.0	-11.0, 6.0	80.0, 148.0	-9.0, 6.0	80.0, 148.0	-11.0, 6.0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Hemoglobin (g/L)						
Month 1						
n	35	35	47	47	82	82
Mean (SD)	119.49 (9.897)	1.28 (8.705)	122.80 (10.903)	1.70 (7.313)	121.39 (10.552)	1.53 (7.889)
Median	118.00	2.00	124.00	1.00	121.00	1.50
Min, Max	103.0, 143.0	-35.0, 18.0	97.0, 147.0	-11.0, 22.0	97.0, 147.0	-35.0, 22.0
Month 2						
n	34	34	48	48	82	82
Mean (SD)	118.99 (10.311)	0.81 (9.764)	123.54 (10.993)	2.41 (8.611)	121.65 (10.887)	1.75 (9.082)
Median	116.01	1.50	123.50	2.00	121.00	2.00
Min, Max	104.0, 153.0	-34.0, 20.0	95.0, 149.0	-14.0, 26.0	95.0, 153.0	-34.0, 26.0
Month 3						
n	34	34	47	47	81	81
Mean (SD)	118.56 (10.212)	0.38 (7.740)	123.02 (12.067)	1.57 (7.420)	121.15 (11.474)	1.07 (7.531)
Median	115.00	1.50	123.00	0.00	121.00	1.00
Min, Max	97.0, 140.0	-22.0, 15.0	82.0, 146.0	-18.0, 22.0	82.0, 146.0	-22.0, 22.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Hemoglobin (g/L)						
Month 4						
n	28	28	43	43	71	71
Mean (SD)	118.93 (10.403)	-0.57 (7.974)	122.35 (9.905)	0.09 (8.489)	121.00 (10.171)	-0.17 (8.239)
Median	118.00	0.50	122.00	1.00	121.00	1.00
Min, Max	101.0, 146.0	-21.0, 14.0	88.0, 148.0	-23.0, 15.0	88.0, 148.0	-23.0, 15.0
Month 5						
n	18	18	29	29	47	47
Mean (SD)	120.94 (8.271)	3.22 (5.663)	124.24 (9.568)	2.78 (7.338)	122.98 (9.145)	2.95 (6.684)
Median	120.50	3.50	123.00	1.00	123.00	2.00
Min, Max	109.0, 135.0	-7.0, 17.0	105.0, 140.0	-10.0, 19.0	105.0, 140.0	-10.0, 19.0
Month 6						
n	10	10	16	16	26	26
Mean (SD)	115.10 (10.126)	-2.10 (12.810)	123.81 (6.950)	5.81 (6.462)	120.46 (9.197)	2.77 (9.977)
Median	114.50	-1.00	123.50	4.50	122.00	3.50
Min, Max	98.0, 130.0	-23.0, 21.0	111.0, 138.0	-2.0, 20.0	98.0, 138.0	-23.0, 21.0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Hemoglobin (g/L)						
Month 9						
n	2	2	0	0	2	2
Mean (SD)	113.50 (9.192)	1.00 (14.142)			113.50 (9.192)	1.00 (14.142)
Median	113.50	1.00			113.50	1.00
Min, Max	107.0, 120.0	-9.0, 11.0			107.0, 120.0	-9.0, 11.0
End of Study						
n	35	35	49	49	84	84
Mean (SD)	118.68 (11.854)	0.47 (7.993)	124.46 (9.488)	3.34 (11.310)	122.05 (10.856)	2.14 (10.108)
Median	116.00	2.00	123.00	2.00	121.00	2.00
Min, Max	97.0, 151.0	-19.0, 17.0	102.0, 149.0	-20.0, 46.0	97.0, 151.0	-20.0, 46.0
Hematocrit (L/L)						
Screening						
n	34		49		83	
Mean (SD)	0.36 (0.024)		0.36 (0.032)		0.36 (0.029)	
Median	0.36		0.36		0.36	
Min, Max	0.3, 0.4		0.2, 0.4		0.2, 0.4	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Hematocrit (L/L)						
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	0.35 (0.026)		0.36 (0.027)		0.36 (0.028)	
Median	0.34		0.37		0.35	
Min, Max	0.3, 0.4		0.3, 0.4		0.3, 0.4	
Day 1 Non-PK						
n	24	24	42	42	66	66
Mean (SD)	0.34 (0.027)	-0.01 (0.014)	0.36 (0.030)	-0.00 (0.008)	0.35 (0.030)	-0.00 (0.011)
Median	0.34	0.00	0.36	0.00	0.35	0.00
Min, Max	0.3, 0.4	-0.0, 0.0	0.3, 0.4	-0.0, 0.0	0.3, 0.4	-0.0, 0.0
Month 1						
n	35	35	48	48	83	83
Mean (SD)	0.36 (0.034)	0.01 (0.023)	0.37 (0.030)	0.01 (0.026)	0.36 (0.032)	0.01 (0.025)
Median	0.36	0.01	0.37	0.01	0.36	0.01
Min, Max	0.3, 0.4	-0.0, 0.1	0.3, 0.4	-0.0, 0.1	0.3, 0.4	-0.0, 0.1

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Hematocrit (L/L)						
Month 2						
n	34	34	48	48	82	82
Mean (SD)	0.35 (0.035)	0.00 (0.026)	0.37 (0.029)	0.01 (0.029)	0.36 (0.033)	0.01 (0.028)
Median	0.34	0.00	0.37	0.01	0.36	0.01
Min, Max	0.3, 0.5	-0.1, 0.1	0.3, 0.4	-0.0, 0.1	0.3, 0.5	-0.1, 0.1
Month 3						
n	34	34	47	47	81	81
Mean (SD)	0.35 (0.031)	0.00 (0.023)	0.37 (0.033)	0.01 (0.024)	0.36 (0.033)	0.00 (0.024)
Median	0.35	0.00	0.37	0.01	0.36	0.01
Min, Max	0.3, 0.4	-0.0, 0.1	0.3, 0.4	-0.1, 0.1	0.3, 0.4	-0.1, 0.1
Month 4						
n	28	28	43	43	71	71
Mean (SD)	0.35 (0.033)	-0.00 (0.019)	0.36 (0.031)	0.00 (0.025)	0.36 (0.032)	0.00 (0.022)
Median	0.35	-0.00	0.36	0.01	0.36	0.00
Min, Max	0.3, 0.4	-0.0, 0.0	0.3, 0.4	-0.1, 0.0	0.3, 0.4	-0.1, 0.0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Hematocrit (L/L)						
Month 5						
n	18	18	29	29	47	47
Mean (SD)	0.36 (0.019)	0.01 (0.015)	0.37 (0.028)	0.01 (0.023)	0.36 (0.025)	0.01 (0.020)
Median	0.36	0.01	0.37	0.01	0.36	0.01
Min, Max	0.3, 0.4	-0.0, 0.0	0.3, 0.4	-0.0, 0.1	0.3, 0.4	-0.0, 0.1
Month 6						
n	10	10	16	16	26	26
Mean (SD)	0.35 (0.030)	-0.00 (0.029)	0.36 (0.021)	0.01 (0.023)	0.36 (0.026)	0.01 (0.026)
Median	0.35	-0.00	0.36	0.01	0.36	0.01
Min, Max	0.3, 0.4	-0.1, 0.1	0.3, 0.4	-0.0, 0.1	0.3, 0.4	-0.1, 0.1
Month 9						
n	2	2	0	0	2	2
Mean (SD)	0.36 (0.008)	0.03 (0.018)			0.36 (0.008)	0.03 (0.018)
Median	0.36	0.03			0.36	0.03
Min, Max	0.4, 0.4	0.0, 0.0			0.4, 0.4	0.0, 0.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Hematocrit (L/L)						
End of Study						
n	34	34	49	49	83	83
Mean (SD)	0.35 (0.032)	0.00 (0.020)	0.37 (0.028)	0.01 (0.030)	0.36 (0.031)	0.01 (0.026)
Median	0.35	0.00	0.37	0.00	0.36	0.00
Min, Max	0.3, 0.4	-0.0, 0.1	0.3, 0.4	-0.0, 0.1	0.3, 0.4	-0.0, 0.1
Erythrocytes (10^12/L)						
Screening						
n	34		49		83	
Mean (SD)	4.65 (0.355)		4.61 (0.362)		4.63 (0.357)	
Median	4.67		4.55		4.60	
Min, Max	3.9, 5.5		3.8, 5.6		3.8, 5.6	
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	4.66 (0.578)		4.57 (0.340)		4.62 (0.473)	
Median	4.50		4.61		4.54	
Min, Max	4.1, 6.6		3.8, 5.2		3.8, 6.6	

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Erythrocytes (10^12/L)						
Day 1 Non-PK						
n	24	24	42	42	66	66
Mean (SD)	4.43 (0.481)	-0.14 (0.271)	4.64 (0.400)	-0.02 (0.096)	4.57 (0.440)	-0.06 (0.188)
Median	4.46	0.00	4.68	0.00	4.59	0.00
Min, Max	3.7, 5.5	-1.1, 0.0	3.9, 5.4	-0.4, 0.3	3.7, 5.5	-1.1, 0.3
Month 1						
n	35	35	48	48	83	83
Mean (SD)	4.59 (0.501)	-0.00 (0.531)	4.71 (0.433)	0.06 (0.321)	4.66 (0.463)	0.03 (0.421)
Median	4.55	0.10	4.64	0.07	4.61	0.07
Min, Max	3.9, 5.8	-2.7, 0.7	3.9, 5.9	-1.3, 0.6	3.9, 5.9	-2.7, 0.7
Month 2						
n	34	34	48	48	82	82
Mean (SD)	4.59 (0.473)	-0.01 (0.569)	4.69 (0.448)	0.04 (0.341)	4.65 (0.458)	0.02 (0.447)
Median	4.50	0.01	4.61	0.08	4.56	0.08
Min, Max	3.9, 5.8	-2.7, 0.8	3.8, 5.6	-1.3, 0.6	3.8, 5.8	-2.7, 0.8

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Erythrocytes (10^12/L)						
Month 3						
n	34	34	47	47	81	81
Mean (SD)	4.59 (0.395)	-0.01 (0.533)	4.69 (0.426)	0.04 (0.295)	4.65 (0.414)	0.02 (0.410)
Median	4.65	0.10	4.65	0.00	4.65	0.02
Min, Max	3.8, 5.5	-2.6, 0.6	3.8, 5.5	-0.8, 0.8	3.8, 5.5	-2.6, 0.8
Month 4						
n	28	28	43	43	71	71
Mean (SD)	4.59 (0.423)	-0.07 (0.581)	4.62 (0.436)	-0.01 (0.330)	4.61 (0.428)	-0.03 (0.443)
Median	4.56	0.02	4.61	0.07	4.60	0.05
Min, Max	3.6, 5.5	-2.7, 0.5	3.4, 5.5	-1.5, 0.4	3.4, 5.5	-2.7, 0.5
Month 5						
n	18	18	29	29	47	47
Mean (SD)	4.74 (0.358)	-0.01 (0.658)	4.65 (0.451)	0.05 (0.266)	4.69 (0.416)	0.03 (0.451)
Median	4.75	0.10	4.72	0.01	4.73	0.04
Min, Max	4.1, 5.5	-2.5, 0.7	3.8, 5.4	-0.5, 0.6	3.8, 5.5	-2.5, 0.7

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Erythrocytes (10^12/L)						
Month 6						
n	10	10	16	16	26	26
Mean (SD)	4.59 (0.520)	-0.33 (0.963)	4.58 (0.337)	0.14 (0.294)	4.58 (0.407)	-0.04 (0.664)
Median	4.56	-0.13	4.63	0.11	4.59	-0.05
Min, Max	3.9, 5.5	-2.7, 0.8	3.8, 5.1	-0.2, 0.8	3.8, 5.5	-2.7, 0.8
Month 9						
n	2	2	0	0	2	2
Mean (SD)	4.61 (0.764)	0.41 (0.057)			4.61 (0.764)	0.41 (0.057)
Median	4.61	0.41			4.61	0.41
Min, Max	4.1, 5.2	0.4, 0.5			4.1, 5.2	0.4, 0.5
End of Study						
n	34	34	49	49	83	83
Mean (SD)	4.60 (0.410)	0.00 (0.590)	4.70 (0.451)	0.05 (0.362)	4.66 (0.435)	0.03 (0.466)
Median	4.63	0.10	4.66	0.01	4.63	0.03
Min, Max	3.8, 5.5	-2.8, 1.1	3.7, 5.8	-1.3, 0.8	3.7, 5.8	-2.8, 1.1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Erythrocyte Mean Corpuscular Volume (fL)						
Screening						
n	34		46		80	
Mean (SD)	77.10 (3.644)		77.87 (5.847)		77.55 (5.016)	
Median	77.10		78.95		78.15	
Min, Max	70.0, 85.0		53.0, 87.0		53.0, 87.0	
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	76.59 (2.821)		79.97 (4.221)		78.24 (3.919)	
Median	77.00		80.00		78.00	
Min, Max	71.0, 81.3		71.1, 87.2		71.0, 87.2	
Day 1 Non-PK						
n	24	24	40	40	64	64
Mean (SD)	78.28 (4.914)	0.11 (1.190)	77.78 (6.531)	-0.01 (0.327)	77.97 (5.940)	0.04 (0.766)
Median	77.95	0.00	78.90	0.00	78.80	0.00
Min, Max	70.5, 91.0	-3.4, 4.2	51.0, 87.3	-1.0, 1.0	51.0, 91.0	-3.4, 4.2

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Erythrocyte Mean Corpuscular Volume (fL)						
Month 1						
n	35	35	46	46	81	81
Mean (SD)	77.13 (3.949)	-0.33 (2.987)	78.82 (4.205)	0.77 (4.519)	78.09 (4.157)	0.30 (3.947)
Median	77.90	0.30	79.00	-0.20	78.00	-0.20
Min, Max	67.0, 83.0	-11.0, 3.9	70.0, 87.8	-4.8, 24.0	67.0, 87.8	-11.0, 24.0
Month 2						
n	34	34	46	46	80	80
Mean (SD)	76.38 (3.851)	-1.01 (3.450)	78.73 (4.137)	0.68 (4.678)	77.73 (4.160)	-0.04 (4.259)
Median	76.65	-0.35	78.45	-0.10	77.60	-0.30
Min, Max	66.0, 85.0	-16.0, 5.0	67.8, 87.3	-7.2, 24.0	66.0, 87.3	-16.0, 24.0
Month 3						
n	34	34	45	45	79	79
Mean (SD)	76.42 (3.999)	-0.97 (3.572)	78.40 (5.307)	0.24 (2.960)	77.55 (4.861)	-0.28 (3.271)
Median	76.85	-0.40	78.90	-0.10	77.70	-0.40
Min, Max	67.0, 84.0	-15.0, 5.0	55.0, 87.7	-7.5, 9.0	55.0, 87.7	-15.0, 9.0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Erythrocyte Mean Corpuscular Volume (fL)						
Month 4						
n	28	28	41	41	69	69
Mean (SD)	76.18 (4.101)	-1.36 (3.801)	79.11 (4.298)	0.37 (2.710)	77.92 (4.432)	-0.33 (3.285)
Median	75.65	-0.75	79.50	-0.10	78.10	-0.30
Min, Max	68.0, 85.0	-16.0, 4.0	70.7, 89.1	-7.6, 7.5	68.0, 89.1	-16.0, 7.5
Month 5						
n	18	18	27	27	45	45
Mean (SD)	75.89 (4.150)	-0.89 (2.973)	79.56 (4.374)	0.81 (4.289)	78.09 (4.611)	0.13 (3.873)
Median	75.00	0.15	80.00	0.00	77.80	0.00
Min, Max	69.0, 83.0	-8.3, 4.0	69.6, 88.4	-9.9, 11.0	69.0, 88.4	-9.9, 11.0
Month 6						
n	10	10	16	16	26	26
Mean (SD)	76.05 (5.129)	0.28 (3.033)	79.86 (4.187)	-0.07 (2.108)	78.39 (4.853)	0.07 (2.451)
Median	75.80	0.55	80.40	0.00	78.90	0.05
Min, Max	68.0, 83.2	-5.0, 6.1	72.2, 86.1	-5.0, 4.0	68.0, 86.1	-5.0, 6.1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Erythrocyte Mean Corpuscular Volume (fL)						
Month 9						
n	2	2	0	0	2	2
Mean (SD)	78.65 (11.243)	-1.05 (4.031)			78.65 (11.243)	-1.05 (4.031)
Median	78.65	-1.05			78.65	-1.05
Min, Max	70.7, 86.6	-3.9, 1.8			70.7, 86.6	-3.9, 1.8
End of Study						
n	34	34	49	47	83	81
Mean (SD)	76.81 (4.227)	-0.64 (3.268)	78.86 (5.386)	1.27 (7.095)	78.02 (5.020)	0.47 (5.852)
Median	77.00	-0.70	79.70	0.00	78.30	-0.30
Min, Max	69.0, 84.5	-7.0, 8.5	61.7, 95.0	-9.4, 34.0	61.7, 95.0	-9.4, 34.0
Leukocytes (10^9/L)						
Screening						
n	34		49		83	
Mean (SD)	8.39 (2.860)		7.47 (2.023)		7.84 (2.428)	
Median	8.00		7.00		7.20	
Min, Max	4.6, 17.0		2.0, 11.9		2.0, 17.0	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Leukocytes (10^9/L)						
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	7.27 (2.066)		7.08 (1.443)		7.18 (1.769)	
Median	6.50		6.80		6.80	
Min, Max	4.7, 11.8		5.1, 11.0		4.7, 11.8	
Day 1 Non-PK						
n	24	24	42	42	66	66
Mean (SD)	7.62 (2.391)	-0.08 (0.756)	7.09 (1.902)	0.06 (0.315)	7.28 (2.091)	0.01 (0.519)
Median	7.05	0.00	6.95	0.00	7.00	0.00
Min, Max	4.2, 12.3	-2.2, 1.7	3.3, 11.3	-0.9, 1.4	3.3, 12.3	-2.2, 1.7
Month 1						
n	35	35	48	48	83	83
Mean (SD)	8.30 (2.481)	0.53 (2.063)	7.25 (2.151)	0.19 (2.368)	7.69 (2.340)	0.34 (2.238)
Median	7.84	0.04	6.90	0.05	7.23	0.04
Min, Max	4.9, 15.1	-4.0, 6.9	3.4, 14.0	-5.9, 6.4	3.4, 15.1	-5.9, 6.9

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Leukocytes (10^9/L)						
Month 2						
n	34	34	48	48	82	82
Mean (SD)	7.88 (2.590)	0.07 (1.793)	7.12 (1.614)	0.06 (2.102)	7.43 (2.094)	0.07 (1.968)
Median	7.06	-0.35	6.73	-0.01	6.88	-0.16
Min, Max	4.8, 16.6	-3.1, 7.0	3.3, 11.1	-5.7, 4.5	3.3, 16.6	-5.7, 7.0
Month 3						
n	34	34	47	47	81	81
Mean (SD)	7.74 (1.683)	-0.06 (2.262)	7.09 (1.856)	-0.01 (2.107)	7.37 (1.803)	-0.03 (2.160)
Median	7.79	0.10	6.82	0.20	7.43	0.14
Min, Max	5.1, 11.3	-6.4, 3.9	3.5, 11.6	-7.1, 4.8	3.5, 11.6	-7.1, 4.8
Month 4						
n	28	28	43	43	71	71
Mean (SD)	8.51 (2.571)	0.83 (2.212)	7.10 (1.891)	-0.02 (2.243)	7.66 (2.275)	0.32 (2.254)
Median	8.19	0.25	6.80	-0.10	7.40	0.10
Min, Max	4.7, 14.2	-2.4, 7.3	2.9, 11.5	-6.4, 4.9	2.9, 14.2	-6.4, 7.3

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Leukocytes (10^9/L)						
Month 5						
n	18	18	29	29	47	47
Mean (SD)	7.51 (2.679)	-0.26 (1.853)	7.12 (1.625)	0.00 (2.192)	7.27 (2.073)	-0.10 (2.052)
Median	7.01	-0.77	6.96	-0.14	6.96	-0.20
Min, Max	3.9, 13.0	-2.7, 3.4	5.1, 11.3	-5.9, 3.7	3.9, 13.0	-5.9, 3.7
Month 6						
n	10	10	16	16	26	26
Mean (SD)	7.48 (2.154)	-0.19 (1.802)	7.18 (2.118)	0.13 (2.644)	7.30 (2.094)	0.01 (2.321)
Median	7.02	0.10	6.75	0.45	6.90	0.20
Min, Max	4.7, 11.8	-2.9, 2.2	4.0, 11.9	-7.0, 4.2	4.0, 11.9	-7.0, 4.2
Month 9						
n	2	2	0	0	2	2
Mean (SD)	6.41 (0.955)	-0.97 (0.191)			6.41 (0.955)	-0.97 (0.191)
Median	6.41	-0.97			6.41	-0.97
Min, Max	5.7, 7.1	-1.1, -0.8			5.7, 7.1	-1.1, -0.8

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Leukocytes (10^9/L)						
End of Study						
n	35	35	49	49	84	84
Mean (SD)	7.80 (2.616)	0.03 (1.935)	6.77 (1.776)	-0.34 (2.054)	7.20 (2.210)	-0.18 (2.002)
Median	7.30	0.20	6.39	-0.10	6.75	0.04
Min, Max	3.6, 14.2	-4.8, 5.3	4.3, 11.3	-5.3, 5.5	3.6, 14.2	-5.3, 5.5
Neutrophils (10^9/L)						
Screening						
n	33		49		82	
Mean (SD)	3.32 (1.363)		3.68 (1.844)		3.53 (1.667)	
Median	3.10		3.75		3.40	
Min, Max	0.5, 7.4		0.3, 9.0		0.3, 9.0	
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	2.89 (1.038)		3.56 (1.398)		3.22 (1.257)	
Median	2.54		3.46		2.72	
Min, Max	1.7, 4.9		2.0, 8.4		1.7, 8.4	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Neutrophils (10^9/L)						
Day 1 Non-PK						
n	24	24	42	42	66	66
Mean (SD)	2.96 (1.236)	-0.10 (0.440)	3.31 (1.668)	0.05 (0.174)	3.19 (1.524)	-0.01 (0.305)
Median	3.05	0.00	3.32	0.00	3.21	0.00
Min, Max	0.4, 5.5	-1.5, 0.8	0.3, 8.2	-0.2, 0.7	0.3, 8.2	-1.5, 0.8
Month 1						
n	35	35	48	48	83	83
Mean (SD)	3.56 (1.480)	0.43 (1.470)	3.50 (1.866)	0.21 (1.985)	3.52 (1.704)	0.30 (1.780)
Median	3.70	0.09	3.20	0.08	3.20	0.09
Min, Max	0.3, 7.6	-2.1, 4.1	0.3, 10.0	-6.8, 6.0	0.3, 10.0	-6.8, 6.0
Month 2						
n	34	34	48	48	82	82
Mean (SD)	3.38 (1.603)	0.24 (1.547)	3.43 (1.504)	0.14 (1.680)	3.41 (1.536)	0.18 (1.617)
Median	3.00	0.10	3.41	0.10	3.24	0.10
Min, Max	0.3, 8.8	-2.4, 5.7	0.4, 6.7	-6.2, 3.8	0.3, 8.8	-6.2, 5.7

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Neutrophils (10^9/L)						
Month 3						
n	33	33	46	46	79	79
Mean (SD)	3.36 (1.374)	0.17 (1.261)	3.45 (1.780)	0.12 (1.824)	3.41 (1.614)	0.14 (1.604)
Median	3.07	-0.00	3.49	-0.05	3.30	-0.03
Min, Max	0.3, 6.9	-2.3, 3.0	0.3, 7.9	-6.8, 3.5	0.3, 7.9	-6.8, 3.5
Month 4						
n	28	28	42	42	70	70
Mean (SD)	4.02 (2.257)	0.91 (2.067)	3.18 (1.737)	-0.16 (1.772)	3.52 (1.989)	0.27 (1.954)
Median	4.06	0.37	2.99	-0.07	3.19	-0.03
Min, Max	0.5, 11.8	-1.7, 8.1	0.2, 7.7	-6.7, 4.2	0.2, 11.8	-6.7, 8.1
Month 5						
n	18	18	29	29	47	47
Mean (SD)	3.09 (1.864)	0.05 (1.655)	3.55 (1.752)	0.01 (1.905)	3.38 (1.790)	0.03 (1.795)
Median	2.83	-0.14	3.42	0.05	3.10	-0.03
Min, Max	0.5, 6.3	-2.2, 3.3	0.4, 8.0	-6.7, 3.5	0.4, 8.0	-6.7, 3.5

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Neutrophils (10^9/L)						
Month 6						
n	10	10	16	16	26	26
Mean (SD)	3.45 (1.217)	0.59 (1.030)	3.82 (1.882)	0.06 (2.361)	3.68 (1.641)	0.27 (1.948)
Median	3.18	0.43	3.90	0.64	3.48	0.53
Min, Max	1.8, 5.7	-1.4, 1.9	1.1, 8.4	-7.3, 3.4	1.1, 8.4	-7.3, 3.4
Month 9						
n	2	2	0	0	2	2
Mean (SD)	3.36 (1.119)	0.18 (1.505)			3.36 (1.119)	0.18 (1.505)
Median	3.36	0.18			3.36	0.18
Min, Max	2.6, 4.1	-0.9, 1.2			2.6, 4.1	-0.9, 1.2
End of Study						
n	33	33	49	49	82	82
Mean (SD)	3.36 (1.713)	0.17 (1.563)	3.20 (1.690)	-0.14 (1.669)	3.26 (1.690)	-0.02 (1.625)
Median	3.30	0.18	2.96	-0.05	2.98	0.02
Min, Max	0.4, 9.3	-3.1, 5.6	0.3, 8.1	-5.4, 4.3	0.3, 9.3	-5.4, 5.6

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Lymphocytes (10^9/L)						
Screening						
n	33		49		82	
Mean (SD)	3.97 (2.072)		2.28 (0.916)		2.96 (1.700)	
Median	3.41		2.28		2.65	
Min, Max	0.4, 10.7		0.2, 4.5		0.2, 10.7	
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	3.51 (1.171)		2.60 (0.593)		3.07 (1.032)	
Median	3.19		2.48		2.88	
Min, Max	2.0, 6.4		1.6, 3.7		1.6, 6.4	
Day 1 Non-PK						
n	24	24	42	42	66	66
Mean (SD)	3.46 (1.781)	-0.01 (0.432)	2.28 (0.927)	0.00 (0.156)	2.71 (1.411)	-0.00 (0.285)
Median	2.91	0.00	2.30	0.00	2.39	0.00
Min, Max	0.5, 7.2	-0.8, 1.7	0.3, 4.4	-0.4, 0.8	0.3, 7.2	-0.8, 1.7

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Lymphocytes (10^9/L)						
Month 1						
n	35	35	48	48	83	83
Mean (SD)	3.66 (1.902)	0.08 (0.969)	2.33 (0.843)	-0.00 (0.527)	2.89 (1.531)	0.03 (0.741)
Median	3.12	0.07	2.24	0.04	2.47	0.07
Min, Max	0.6, 7.8	-2.7, 3.0	0.4, 4.0	-1.6, 1.3	0.4, 7.8	-2.7, 3.0
Month 2						
n	34	34	48	48	82	82
Mean (SD)	3.38 (1.378)	-0.22 (0.713)	2.38 (0.915)	0.05 (0.639)	2.79 (1.227)	-0.06 (0.679)
Median	3.20	-0.25	2.30	-0.00	2.60	-0.03
Min, Max	0.6, 6.3	-1.9, 1.0	0.4, 5.0	-1.8, 2.0	0.4, 6.3	-1.9, 2.0
Month 3						
n	33	33	46	46	79	79
Mean (SD)	3.31 (1.066)	-0.29 (1.207)	2.26 (0.916)	-0.08 (0.532)	2.70 (1.104)	-0.17 (0.879)
Median	3.24	-0.10	2.24	0.01	2.62	-0.03
Min, Max	0.6, 5.4	-4.4, 1.5	0.2, 4.2	-1.4, 1.4	0.2, 5.4	-4.4, 1.5

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Lymphocytes (10^9/L)						
Month 4						
n	28	28	42	42	70	70
Mean (SD)	3.33 (1.262)	-0.20 (0.894)	2.42 (0.945)	0.12 (0.498)	2.78 (1.165)	-0.01 (0.696)
Median	3.39	-0.27	2.41	0.06	2.71	-0.01
Min, Max	0.4, 6.0	-2.1, 1.8	0.3, 4.1	-1.0, 1.4	0.3, 6.0	-2.1, 1.8
Month 5						
n	18	18	29	29	47	47
Mean (SD)	3.15 (1.351)	-0.30 (0.814)	2.45 (0.812)	0.12 (0.580)	2.72 (1.094)	-0.04 (0.701)
Median	2.90	-0.12	2.40	0.09	2.65	0.03
Min, Max	0.4, 6.1	-1.7, 0.9	0.4, 3.8	-1.5, 1.5	0.4, 6.1	-1.7, 1.5
Month 6						
n	10	10	16	16	26	26
Mean (SD)	3.08 (1.242)	-0.77 (1.269)	2.56 (0.557)	0.07 (0.616)	2.76 (0.899)	-0.25 (0.991)
Median	2.89	-0.23	2.52	0.03	2.57	-0.02
Min, Max	1.3, 5.4	-3.2, 0.5	1.7, 3.7	-1.3, 1.1	1.3, 5.4	-3.2, 1.1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35) Result	<6 years (N=35) Change	>=6 to <12 years (N=49) Result	>=6 to <12 years (N=49) Change	Total (N=84) Result	Total (N=84) Change
Lymphocytes (10^9/L)						
Month 9						
n	2	2	0	0	2	2
Mean (SD)	2.40 (0.063)	-0.83 (1.554)			2.40 (0.063)	-0.83 (1.554)
Median	2.40	-0.83			2.40	-0.83
Min, Max	2.4, 2.4	-1.9, 0.3			2.4, 2.4	-1.9, 0.3
End of Study						
n	33	33	49	49	82	82
Mean (SD)	3.29 (1.585)	-0.30 (0.656)	2.31 (0.779)	-0.03 (0.631)	2.71 (1.259)	-0.14 (0.651)
Median	3.06	-0.20	2.47	-0.07	2.58	-0.13
Min, Max	0.5, 7.0	-2.2, 1.1	0.4, 3.6	-1.6, 1.9	0.4, 7.0	-2.2, 1.9
Monocytes (10^9/L)						
Screening						
n	33		49		82	
Mean (SD)	0.55 (0.193)		0.50 (0.234)		0.52 (0.218)	
Median	0.56		0.50		0.54	
Min, Max	0.1, 0.9		0.0, 1.0		0.0, 1.0	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Monocytes (10^9/L)						
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	0.55 (0.185)		0.55 (0.173)		0.55 (0.177)	
Median	0.52		0.55		0.53	
Min, Max	0.3, 1.1		0.3, 0.8		0.3, 1.1	
Day 1 Non-PK						
n	24	24	42	42	66	66
Mean (SD)	0.52 (0.202)	-0.00 (0.088)	0.45 (0.221)	0.00 (0.057)	0.47 (0.215)	-0.00 (0.069)
Median	0.51	0.00	0.43	0.00	0.50	0.00
Min, Max	0.1, 0.8	-0.2, 0.3	0.1, 0.9	-0.2, 0.2	0.1, 0.9	-0.2, 0.3
Month 1						
n	35	35	48	48	83	83
Mean (SD)	0.58 (0.351)	0.05 (0.370)	0.48 (0.231)	0.01 (0.179)	0.52 (0.290)	0.03 (0.275)
Median	0.50	0.00	0.47	0.01	0.48	0.01
Min, Max	0.1, 2.0	-0.6, 1.6	0.1, 1.1	-0.4, 0.4	0.1, 2.0	-0.6, 1.6

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Monocytes (10^9/L)						
Month 2						
n	34	34	48	48	82	82
Mean (SD)	0.58 (0.253)	0.06 (0.214)	0.47 (0.202)	0.00 (0.189)	0.52 (0.231)	0.03 (0.200)
Median	0.60	0.06	0.53	0.00	0.54	0.02
Min, Max	0.1, 1.3	-0.5, 0.6	0.1, 0.9	-0.4, 0.4	0.1, 1.3	-0.5, 0.6
Month 3						
n	33	33	46	46	79	79
Mean (SD)	0.51 (0.184)	-0.01 (0.182)	0.46 (0.235)	-0.00 (0.204)	0.48 (0.216)	-0.01 (0.194)
Median	0.53	-0.01	0.49	-0.01	0.50	-0.01
Min, Max	0.1, 0.9	-0.5, 0.3	0.1, 1.2	-0.4, 0.6	0.1, 1.2	-0.5, 0.6
Month 4						
n	28	28	42	42	70	70
Mean (SD)	0.55 (0.221)	0.05 (0.202)	0.48 (0.199)	0.03 (0.175)	0.51 (0.210)	0.03 (0.185)
Median	0.60	0.01	0.49	0.03	0.51	0.03
Min, Max	0.1, 1.2	-0.3, 0.7	0.1, 0.8	-0.3, 0.4	0.1, 1.2	-0.3, 0.7

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Monocytes (10^9/L)						
Month 5						
n	18	18	29	29	47	47
Mean (SD)	0.47 (0.157)	-0.07 (0.155)	0.42 (0.199)	-0.02 (0.220)	0.44 (0.184)	-0.04 (0.197)
Median	0.49	-0.02	0.46	0.01	0.46	0.00
Min, Max	0.1, 0.8	-0.4, 0.2	0.0, 0.7	-0.5, 0.4	0.0, 0.8	-0.5, 0.4
Month 6						
n	10	10	16	16	26	26
Mean (SD)	0.59 (0.226)	0.05 (0.170)	0.50 (0.180)	0.02 (0.278)	0.53 (0.199)	0.03 (0.239)
Median	0.52	0.09	0.50	-0.04	0.50	0.00
Min, Max	0.3, 0.9	-0.3, 0.3	0.2, 0.8	-0.4, 0.5	0.2, 0.9	-0.4, 0.5
Month 9						
n	2	2	0	0	2	2
Mean (SD)	0.24 (0.058)	-0.04 (0.076)			0.24 (0.058)	-0.04 (0.076)
Median	0.24	-0.04			0.24	-0.04
Min, Max	0.2, 0.3	-0.1, 0.0			0.2, 0.3	-0.1, 0.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Monocytes (10^9/L)						
End of Study						
n	33	33	49	49	82	82
Mean (SD)	0.52 (0.241)	-0.01 (0.218)	0.43 (0.206)	-0.04 (0.171)	0.46 (0.224)	-0.03 (0.191)
Median	0.50	0.03	0.41	0.00	0.43	0.01
Min, Max	0.1, 1.2	-0.5, 0.6	0.1, 0.9	-0.4, 0.3	0.1, 1.2	-0.5, 0.6
Eosinophils (10^9/L)						
Screening						
n	33		49		82	
Mean (SD)	0.30 (0.230)		0.49 (1.180)		0.41 (0.925)	
Median	0.26		0.23		0.24	
Min, Max	0.0, 1.1		0.0, 8.1		0.0, 8.1	
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	0.29 (0.295)		0.85 (1.833)		0.56 (1.310)	
Median	0.19		0.33		0.27	
Min, Max	0.0, 1.3		0.1, 8.1		0.0, 8.1	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Eosinophils (10^9/L)						
Day 1 Non-PK						
n	24	24	42	42	66	66
Mean (SD)	0.37 (0.423)	0.03 (0.130)	0.54 (1.570)	0.08 (0.334)	0.48 (1.275)	0.06 (0.277)
Median	0.20	0.00	0.20	0.00	0.20	0.00
Min, Max	0.0, 1.9	-0.1, 0.6	0.0, 9.7	-0.0, 1.6	0.0, 9.7	-0.1, 1.6
Month 1						
n	35	35	48	48	83	83
Mean (SD)	0.35 (0.602)	0.04 (0.642)	0.75 (2.221)	0.28 (1.119)	0.58 (1.736)	0.18 (0.950)
Median	0.24	0.00	0.22	0.03	0.23	0.01
Min, Max	0.0, 3.6	-1.0, 3.5	0.0, 13.8	-0.5, 5.7	0.0, 13.8	-1.0, 5.7
Month 2						
n	34	34	48	48	82	82
Mean (SD)	0.32 (0.210)	0.01 (0.191)	0.71 (2.050)	0.24 (1.041)	0.55 (1.579)	0.15 (0.810)
Median	0.30	0.02	0.23	0.02	0.29	0.02
Min, Max	0.0, 0.9	-0.6, 0.5	0.0, 11.8	-0.5, 6.1	0.0, 11.8	-0.6, 6.1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Eosinophils (10^9/L)						
Month 3						
n	33	33	46	46	79	79
Mean (SD)	0.27 (0.175)	-0.05 (0.261)	0.69 (2.125)	0.22 (1.169)	0.52 (1.632)	0.11 (0.913)
Median	0.21	-0.01	0.23	0.00	0.23	0.00
Min, Max	0.0, 0.9	-1.0, 0.6	0.0, 11.2	-0.5, 7.3	0.0, 11.2	-1.0, 7.3
Month 4						
n	28	28	42	42	70	70
Mean (SD)	0.32 (0.264)	0.06 (0.209)	0.85 (2.624)	0.38 (1.558)	0.64 (2.046)	0.25 (1.218)
Median	0.24	0.01	0.21	0.03	0.23	0.02
Min, Max	0.0, 1.2	-0.3, 0.7	0.0, 13.6	-0.5, 8.6	0.0, 13.6	-0.5, 8.6
Month 5						
n	18	18	29	29	47	47
Mean (SD)	0.31 (0.231)	-0.02 (0.296)	0.23 (0.156)	0.02 (0.162)	0.26 (0.190)	0.00 (0.220)
Median	0.23	-0.02	0.21	0.00	0.21	0.00
Min, Max	0.1, 0.8	-0.7, 0.7	0.0, 0.5	-0.3, 0.4	0.0, 0.8	-0.7, 0.7

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Eosinophils (10^9/L)						
Month 6						
n	10	10	16	16	26	26
Mean (SD)	0.29 (0.255)	-0.06 (0.165)	0.27 (0.134)	0.00 (0.233)	0.28 (0.185)	-0.02 (0.209)
Median	0.23	0.00	0.26	0.05	0.25	0.04
Min, Max	0.1, 1.0	-0.4, 0.1	0.1, 0.6	-0.6, 0.5	0.1, 1.0	-0.6, 0.5
Month 9						
n	2	2	0	0	2	2
Mean (SD)	0.18 (0.112)	-0.18 (0.168)			0.18 (0.112)	-0.18 (0.168)
Median	0.18	-0.18			0.18	-0.18
Min, Max	0.1, 0.3	-0.3, -0.1			0.1, 0.3	-0.3, -0.1
End of Study						
n	33	33	49	49	82	82
Mean (SD)	0.35 (0.393)	0.06 (0.334)	0.65 (1.925)	0.19 (1.017)	0.53 (1.510)	0.14 (0.813)
Median	0.23	0.01	0.19	0.01	0.21	0.01
Min, Max	0.0, 1.7	-0.5, 1.4	0.0, 10.5	-0.6, 6.6	0.0, 10.5	-0.6, 6.6

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Basophils (10^9/L)						
Screening						
n	32		48		80	
Mean (SD)	0.06 (0.058)		0.05 (0.078)		0.05 (0.070)	
Median	0.04		0.03		0.03	
Min, Max	0.0, 0.2		0.0, 0.5		0.0, 0.5	
Day 1 CSL627 PK						
n	20		18		38	
Mean (SD)	0.04 (0.038)		0.03 (0.031)		0.03 (0.035)	
Median	0.04		0.02		0.02	
Min, Max	0.0, 0.1		0.0, 0.1		0.0, 0.1	
Day 1 Non-PK						
n	24	24	41	41	65	65
Mean (SD)	0.07 (0.179)	-0.00 (0.015)	0.03 (0.032)	-0.00 (0.016)	0.05 (0.112)	-0.00 (0.015)
Median	0.04	0.00	0.02	0.00	0.03	0.00
Min, Max	0.0, 0.9	-0.1, 0.0	0.0, 0.1	-0.1, 0.0	0.0, 0.9	-0.1, 0.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Basophils (10^9/L)						
Month 1						
n	35	35	48	47	83	82
Mean (SD)	0.05 (0.076)	-0.01 (0.160)	0.04 (0.037)	0.01 (0.033)	0.04 (0.057)	-0.00 (0.107)
Median	0.03	0.00	0.03	0.00	0.03	0.00
Min, Max	0.0, 0.4	-0.8, 0.4	0.0, 0.2	-0.1, 0.1	0.0, 0.4	-0.8, 0.4
Month 2						
n	34	34	48	47	82	81
Mean (SD)	0.05 (0.042)	-0.02 (0.154)	0.04 (0.040)	0.01 (0.035)	0.05 (0.041)	-0.00 (0.103)
Median	0.04	0.00	0.03	0.00	0.04	0.00
Min, Max	0.0, 0.2	-0.9, 0.1	0.0, 0.2	-0.1, 0.1	0.0, 0.2	-0.9, 0.1
Month 3						
n	32	32	45	45	77	77
Mean (SD)	0.05 (0.045)	0.01 (0.044)	0.04 (0.054)	0.01 (0.053)	0.05 (0.050)	0.01 (0.049)
Median	0.04	0.00	0.03	0.01	0.03	0.00
Min, Max	0.0, 0.2	-0.1, 0.1	0.0, 0.3	-0.1, 0.3	0.0, 0.3	-0.1, 0.3

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Basophils (10^9/L)						
Month 4						
n	28	28	42	41	70	69
Mean (SD)	0.04 (0.038)	-0.04 (0.163)	0.04 (0.032)	0.01 (0.040)	0.04 (0.035)	-0.01 (0.110)
Median	0.03	0.00	0.04	0.00	0.03	0.00
Min, Max	0.0, 0.1	-0.9, 0.1	0.0, 0.1	-0.1, 0.1	0.0, 0.1	-0.9, 0.1
Month 5						
n	18	18	29	28	47	46
Mean (SD)	0.05 (0.038)	-0.04 (0.205)	0.03 (0.031)	0.00 (0.039)	0.04 (0.034)	-0.01 (0.132)
Median	0.05	0.01	0.02	0.00	0.03	0.00
Min, Max	0.0, 0.1	-0.9, 0.1	0.0, 0.1	-0.1, 0.1	0.0, 0.1	-0.9, 0.1
Month 6						
n	10	10	16	15	26	25
Mean (SD)	0.03 (0.036)	-0.09 (0.279)	0.04 (0.026)	0.01 (0.030)	0.04 (0.030)	-0.03 (0.180)
Median	0.02	0.00	0.04	0.00	0.03	0.00
Min, Max	0.0, 0.1	-0.9, 0.0	0.0, 0.1	-0.0, 0.1	0.0, 0.1	-0.9, 0.1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Basophils (10^9/L)						
Month 9						
n	2	2	0	0	2	2
Mean (SD)	0.02 (0.002)	-0.01 (0.016)			0.02 (0.002)	-0.01 (0.016)
Median	0.02	-0.01			0.02	-0.01
Min, Max	0.0, 0.0	-0.0, 0.0			0.0, 0.0	-0.0, 0.0
End of Study						
n	33	33	49	48	82	81
Mean (SD)	0.06 (0.155)	-0.01 (0.217)	0.03 (0.035)	-0.00 (0.035)	0.04 (0.102)	-0.00 (0.140)
Median	0.02	0.00	0.03	0.00	0.02	0.00
Min, Max	0.0, 0.9	-0.8, 0.9	0.0, 0.2	-0.1, 0.1	0.0, 0.9	-0.8, 0.9
Platelets (10^9/L)						
Screening						
n	34		49		83	
Mean (SD)	345.82 (83.397)		301.32 (64.065)		319.55 (75.408)	
Median	336.50		291.00		313.00	
Min, Max	219.0, 504.0		172.0, 444.0		172.0, 504.0	

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Platelets (10^9/L)						
Day 1 CSL627 PK						
n	20		18		38	
Mean (SD)	312.56 (75.802)		293.22 (58.310)		303.40 (67.886)	
Median	297.00		290.00		293.50	
Min, Max	187.0, 423.0		172.0, 451.0		172.0, 451.0	
Day 1 Non-PK						
n	24	24	42	42	66	66
Mean (SD)	325.69 (83.197)	-3.39 (33.909)	313.64 (72.791)	6.38 (24.138)	318.02 (76.325)	2.83 (28.228)
Median	317.00	0.00	298.00	0.00	301.50	0.00
Min, Max	221.0, 529.0	-121.4, 76.0	196.0, 498.0	-8.0, 126.0	196.0, 529.0	-121.4, 126.0
Month 1						
n	35	35	48	48	83	83
Mean (SD)	329.62 (72.140)	-1.86 (86.992)	303.56 (61.131)	-3.04 (59.586)	314.55 (66.839)	-2.54 (71.925)
Median	317.00	7.00	306.00	-4.00	311.00	1.00
Min, Max	222.0, 531.0	-256.0, 155.0	185.0, 433.0	-150.0, 120.0	185.0, 531.0	-256.0, 155.0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Platelets (10^9/L)						
Month 2						
n	34	34	48	48	82	82
Mean (SD)	321.96 (76.160)	-12.22 (71.768)	301.46 (55.246)	-5.14 (54.850)	309.96 (65.095)	-8.08 (62.100)
Median	309.00	-3.00	292.00	6.00	303.00	3.50
Min, Max	182.0, 466.0	-188.0, 144.0	187.0, 460.0	-182.0, 101.0	182.0, 466.0	-188.0, 144.0
Month 3						
n	34	34	47	47	81	81
Mean (SD)	339.00 (94.557)	4.83 (76.546)	299.78 (59.708)	-6.62 (68.351)	316.24 (78.215)	-1.82 (71.663)
Median	318.50	7.00	292.00	-3.00	299.00	-2.00
Min, Max	207.0, 635.0	-146.0, 205.0	209.0, 494.0	-164.0, 204.0	207.0, 635.0	-164.0, 205.0
Month 4						
n	28	28	43	43	71	71
Mean (SD)	324.34 (73.411)	-10.41 (82.605)	292.12 (67.381)	-16.76 (64.849)	304.83 (71.094)	-14.26 (71.868)
Median	321.80	13.00	281.00	2.00	296.00	3.00
Min, Max	172.0, 448.0	-181.0, 128.0	191.0, 511.0	-216.0, 152.0	172.0, 511.0	-216.0, 152.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Platelets (10^9/L)						
Month 5						
n	18	18	29	29	47	47
Mean (SD)	347.46 (102.280)	-5.61 (96.404)	287.93 (53.556)	-19.44 (65.582)	310.73 (80.421)	-14.14 (78.095)
Median	336.50	-11.50	301.00	1.00	302.00	1.00
Min, Max	226.0, 672.0	-147.0, 242.0	167.0, 365.0	-240.0, 52.0	167.0, 672.0	-240.0, 242.0
Month 6						
n	10	10	16	16	26	26
Mean (SD)	348.50 (91.923)	9.10 (91.116)	308.41 (60.649)	19.24 (38.255)	323.83 (75.130)	15.34 (62.387)
Median	318.00	-13.50	299.80	10.50	305.00	6.50
Min, Max	231.0, 542.0	-94.0, 137.0	208.0, 427.0	-31.0, 112.0	208.0, 542.0	-94.0, 137.0
Month 9						
n	2	2	0	0	2	2
Mean (SD)	315.50 (43.134)	-4.00 (97.581)			315.50 (43.134)	-4.00 (97.581)
Median	315.50	-4.00			315.50	-4.00
Min, Max	285.0, 346.0	-73.0, 65.0			285.0, 346.0	-73.0, 65.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.1 Hematology Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Platelets (10^9/L)						
End of Study						
n	35	35	49	49	84	84
Mean (SD)	332.67 (95.802)	1.19 (84.351)	285.28 (61.839)	-21.53 (62.366)	305.03 (80.770)	-12.07 (72.739)
Median	315.00	6.00	277.00	-16.00	296.00	-13.50
Min, Max	164.0, 613.0	-146.0, 236.0	171.0, 423.0	-208.0, 126.0	164.0, 613.0	-208.0, 236.0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Sodium (mmol/L)						
Screening						
n	34		48		82	
Mean (SD)	138.95 (2.324)		139.63 (2.634)		139.35 (2.518)	
Median	139.00		139.00		139.00	
Min, Max	136.0, 145.0		134.5, 147.0		134.5, 147.0	
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	138.90 (1.832)		140.71 (1.710)		139.78 (1.976)	
Median	139.00		140.00		140.00	
Min, Max	136.0, 143.0		138.0, 144.0		136.0, 144.0	
Day 1 Non-PK						
n	24	24	40	40	64	64
Mean (SD)	138.09 (1.909)	-0.42 (1.139)	139.71 (3.364)	-0.25 (0.954)	139.10 (2.994)	-0.31 (1.022)
Median	138.00	0.00	140.00	0.00	139.00	0.00
Min, Max	135.0, 142.0	-3.0, 2.0	134.0, 153.3	-5.0, 1.0	134.0, 153.3	-5.0, 2.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Sodium (mmol/L)						
Month 1						
n	34	34	47	47	81	81
Mean (SD)	138.84 (2.154)	0.10 (2.690)	139.79 (2.194)	-0.22 (3.444)	139.39 (2.215)	-0.09 (3.135)
Median	138.50	0.00	140.00	0.00	140.00	0.00
Min, Max	135.0, 144.0	-5.0, 7.0	130.0, 143.0	-14.2, 7.0	130.0, 144.0	-14.2, 7.0
Month 2						
n	32	32	48	48	80	80
Mean (SD)	138.98 (2.380)	0.16 (2.158)	139.80 (2.034)	-0.16 (3.007)	139.47 (2.202)	-0.03 (2.689)
Median	139.00	0.00	140.00	0.00	139.40	0.00
Min, Max	134.0, 144.2	-3.0, 5.0	136.0, 146.0	-10.6, 9.0	134.0, 146.0	-10.6, 9.0
Month 3						
n	34	34	47	47	81	81
Mean (SD)	138.82 (2.065)	0.06 (2.382)	139.54 (2.120)	-0.39 (3.129)	139.24 (2.114)	-0.20 (2.832)
Median	139.00	0.00	139.10	0.00	139.00	0.00
Min, Max	133.0, 144.0	-5.0, 6.0	134.0, 146.0	-10.0, 7.0	133.0, 146.0	-10.0, 7.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Sodium (mmol/L)						
Month 4						
n	27	27	43	43	70	70
Mean (SD)	138.59 (1.910)	-0.20 (2.210)	139.33 (2.005)	-0.61 (3.135)	139.04 (1.988)	-0.45 (2.804)
Median	139.00	0.00	139.10	-0.10	139.00	0.00
Min, Max	135.0, 142.0	-4.0, 5.0	135.0, 145.0	-11.9, 7.0	135.0, 145.0	-11.9, 7.0
Month 5						
n	18	18	29	29	47	47
Mean (SD)	138.82 (2.901)	-0.07 (2.188)	140.50 (2.795)	0.71 (3.791)	139.85 (2.924)	0.41 (3.265)
Median	138.50	0.00	140.00	1.00	140.00	0.60
Min, Max	134.0, 144.0	-4.0, 5.0	135.9, 150.0	-10.0, 8.0	134.0, 150.0	-10.0, 8.0
Month 6						
n	10	10	15	15	25	25
Mean (SD)	138.10 (2.331)	-1.20 (2.530)	140.06 (2.283)	-0.35 (4.538)	139.28 (2.457)	-0.69 (3.820)
Median	138.00	-1.50	140.00	1.00	139.00	0.60
Min, Max	135.0, 143.0	-6.0, 2.0	136.0, 144.0	-10.9, 8.0	135.0, 144.0	-10.9, 8.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Sodium (mmol/L)						
Month 9						
n	2	2	0	0	2	2
Mean (SD)	138.00 (0.000)	-1.00 (1.414)			138.00 (0.000)	-1.00 (1.414)
Median	138.00	-1.00			138.00	-1.00
Min, Max	138.0, 138.0	-2.0, 0.0			138.0, 138.0	-2.0, 0.0
End of Study						
n	34	34	48	48	82	82
Mean (SD)	138.44 (2.113)	-0.30 (2.393)	139.38 (2.293)	-0.57 (3.432)	138.99 (2.256)	-0.46 (3.031)
Median	138.00	0.00	139.00	0.00	139.00	0.00
Min, Max	135.0, 143.2	-5.0, 6.1	133.0, 145.0	-11.5, 9.9	133.0, 145.0	-11.5, 9.9
Potassium (mmol/L)						
Screening						
n	34		48		82	
Mean (SD)	3.93 (0.359)		4.00 (0.583)		3.97 (0.501)	
Median	3.92		4.00		3.97	
Min, Max	3.1, 4.7		3.0, 6.8		3.0, 6.8	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Potassium (mmol/L)						
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	4.04 (0.347)		3.97 (0.228)		4.01 (0.293)	
Median	3.97		4.00		4.00	
Min, Max	3.5, 4.9		3.6, 4.5		3.5, 4.9	
Day 1 Non-PK						
n	24	24	40	40	64	64
Mean (SD)	4.02 (0.376)	-0.03 (0.179)	4.03 (0.449)	0.03 (0.122)	4.02 (0.420)	0.01 (0.148)
Median	4.10	0.00	3.95	0.00	4.00	0.00
Min, Max	3.2, 4.7	-0.5, 0.5	3.3, 5.9	-0.2, 0.6	3.2, 5.9	-0.5, 0.6
Month 1						
n	34	34	47	47	81	81
Mean (SD)	4.07 (0.347)	0.01 (0.462)	3.98 (0.423)	-0.01 (0.516)	4.02 (0.393)	-0.00 (0.491)
Median	4.10	-0.06	4.05	0.10	4.10	0.00
Min, Max	3.3, 4.8	-1.0, 1.6	2.9, 4.9	-1.7, 1.3	2.9, 4.9	-1.7, 1.6

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Potassium (mmol/L)						
Month 2						
n	32	32	48	48	80	80
Mean (SD)	4.06 (0.380)	-0.00 (0.529)	3.99 (0.299)	0.00 (0.447)	4.02 (0.333)	0.00 (0.478)
Median	4.00	-0.04	4.10	0.00	4.02	0.00
Min, Max	3.4, 5.2	-1.3, 1.5	3.3, 4.5	-1.6, 1.0	3.3, 5.2	-1.6, 1.5
Month 3						
n	34	34	47	47	81	81
Mean (SD)	4.12 (0.367)	0.06 (0.421)	4.08 (0.334)	0.11 (0.488)	4.10 (0.347)	0.09 (0.459)
Median	4.10	0.00	4.10	0.10	4.10	0.10
Min, Max	3.3, 5.1	-0.6, 1.6	3.3, 4.9	-1.8, 1.3	3.3, 5.1	-1.8, 1.6
Month 4						
n	28	28	43	43	71	71
Mean (SD)	4.11 (0.333)	0.11 (0.482)	4.00 (0.314)	0.02 (0.529)	4.05 (0.324)	0.06 (0.509)
Median	4.05	0.00	4.00	0.00	4.00	0.00
Min, Max	3.6, 5.0	-0.6, 1.8	3.1, 4.6	-1.8, 1.3	3.1, 5.0	-1.8, 1.8

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Potassium (mmol/L)						
Month 5						
n	18	18	29	29	47	47
Mean (SD)	4.06 (0.363)	0.04 (0.401)	3.94 (0.357)	-0.09 (0.503)	3.99 (0.360)	-0.04 (0.467)
Median	4.00	0.00	4.00	-0.10	4.00	0.00
Min, Max	3.2, 4.9	-0.5, 1.0	3.4, 4.9	-1.5, 0.8	3.2, 4.9	-1.5, 1.0
Month 6						
n	10	10	15	15	25	25
Mean (SD)	3.83 (0.368)	-0.23 (0.503)	4.00 (0.474)	0.11 (0.457)	3.93 (0.434)	-0.03 (0.496)
Median	3.80	-0.12	4.00	0.00	3.83	0.00
Min, Max	3.3, 4.5	-1.2, 0.3	3.1, 4.7	-0.6, 1.0	3.1, 4.7	-1.2, 1.0
Month 9						
n	2	2	0	0	2	2
Mean (SD)	4.15 (0.354)	0.55 (0.495)			4.15 (0.354)	0.55 (0.495)
Median	4.15	0.55			4.15	0.55
Min, Max	3.9, 4.4	0.2, 0.9			3.9, 4.4	0.2, 0.9

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Potassium (mmol/L)						
End of Study						
n	34	34	49	49	83	83
Mean (SD)	4.01 (0.296)	-0.03 (0.425)	3.96 (0.370)	-0.04 (0.443)	3.98 (0.341)	-0.03 (0.433)
Median	4.08	0.00	3.97	-0.05	4.00	0.00
Min, Max	3.4, 4.9	-1.1, 0.8	3.3, 5.0	-1.5, 0.9	3.3, 5.0	-1.5, 0.9
Chloride (mmol/L)						
Screening						
n	32		48		80	
Mean (SD)	103.74 (2.902)		103.06 (3.000)		103.33 (2.962)	
Median	103.50		103.00		103.00	
Min, Max	97.0, 109.0		95.0, 111.0		95.0, 111.0	
Day 1 CSL627 PK						
n	20		18		38	
Mean (SD)	104.00 (2.865)		104.09 (2.683)		104.04 (2.744)	
Median	103.50		104.50		104.00	
Min, Max	100.0, 109.0		99.0, 109.0		99.0, 109.0	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Chloride (mmol/L)						
Day 1 Non-PK						
n	23	23	40	40	63	63
Mean (SD)	103.56 (3.139)	-0.52 (1.310)	103.55 (3.228)	-0.13 (1.017)	103.55 (3.170)	-0.27 (1.139)
Median	103.00	0.00	104.00	0.00	104.00	0.00
Min, Max	98.0, 110.4	-6.0, 0.0	98.0, 111.1	-6.0, 1.0	98.0, 111.1	-6.0, 1.0
Month 1						
n	33	33	46	46	79	79
Mean (SD)	103.84 (2.836)	0.09 (1.922)	103.88 (2.656)	0.07 (3.176)	103.86 (2.715)	0.07 (2.708)
Median	104.00	0.00	104.00	0.00	104.00	0.00
Min, Max	99.0, 110.9	-4.0, 5.0	98.0, 109.0	-8.7, 6.2	98.0, 110.9	-8.7, 6.2
Month 2						
n	32	31	48	48	80	79
Mean (SD)	103.78 (2.975)	-0.22 (1.963)	103.81 (2.347)	-0.10 (3.148)	103.80 (2.598)	-0.15 (2.731)
Median	104.00	0.00	104.00	0.00	104.00	0.00
Min, Max	99.0, 112.0	-4.0, 5.0	99.0, 109.0	-7.9, 9.0	99.0, 112.0	-7.9, 9.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Chloride (mmol/L)						
Month 3						
n	34	33	47	47	81	80
Mean (SD)	103.46 (3.163)	-0.61 (2.827)	103.73 (2.913)	-0.25 (3.130)	103.61 (3.004)	-0.40 (2.996)
Median	103.00	-1.10	104.00	0.00	103.00	-1.00
Min, Max	98.0, 110.0	-4.0, 7.9	98.0, 110.0	-8.3, 6.0	98.0, 110.0	-8.3, 7.9
Month 4						
n	28	27	43	43	71	70
Mean (SD)	103.38 (3.176)	-0.64 (2.729)	103.87 (2.729)	0.10 (2.937)	103.68 (2.902)	-0.18 (2.861)
Median	103.00	-1.00	104.00	1.00	103.20	0.00
Min, Max	99.0, 110.0	-6.0, 5.0	99.0, 110.0	-7.3, 5.0	99.0, 110.0	-7.3, 5.0
Month 5						
n	17	17	29	29	46	46
Mean (SD)	103.41 (3.527)	-0.97 (2.197)	104.24 (3.429)	0.24 (3.611)	103.93 (3.451)	-0.21 (3.190)
Median	103.00	-1.00	105.00	0.00	104.35	0.00
Min, Max	99.0, 108.9	-6.0, 4.0	99.0, 115.0	-10.4, 9.0	99.0, 115.0	-10.4, 9.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Chloride (mmol/L)						
Month 6						
n	10	10	14	14	24	24
Mean (SD)	104.70 (4.572)	0.10 (4.606)	102.37 (3.027)	-0.62 (4.898)	103.34 (3.838)	-0.32 (4.689)
Median	104.50	-1.50	102.00	0.60	103.10	0.00
Min, Max	99.0, 115.0	-5.0, 10.0	97.0, 107.0	-10.0, 6.0	97.0, 115.0	-10.0, 10.0
Month 9						
n	2	2	0	0	2	2
Mean (SD)	107.00 (0.000)	0.00 (2.828)			107.00 (0.000)	0.00 (2.828)
Median	107.00	0.00			107.00	0.00
Min, Max	107.0, 107.0	-2.0, 2.0			107.0, 107.0	-2.0, 2.0
End of Study						
n	34	33	49	49	83	82
Mean (SD)	103.76 (3.204)	-0.21 (2.536)	103.76 (3.087)	-0.11 (2.698)	103.76 (3.116)	-0.15 (2.618)
Median	103.00	0.00	104.00	0.00	104.00	0.00
Min, Max	99.0, 110.0	-6.0, 5.0	96.0, 109.4	-6.0, 5.0	96.0, 110.0	-6.0, 5.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Blood Urea Nitrogen (umol/L)						
Screening						
n	19		25		44	
Mean (SD)	4.24 (1.011)		3.91 (1.353)		4.05 (1.215)	
Median	4.10		3.90		4.05	
Min, Max	2.8, 6.4		0.4, 6.0		0.4, 6.4	
Day 1 CSL627 PK						
n	8		8		16	
Mean (SD)	3.85 (0.848)		4.40 (0.873)		4.12 (0.878)	
Median	3.86		4.20		4.01	
Min, Max	2.9, 5.4		3.5, 5.7		2.9, 5.7	
Day 1 Non-PK						
n	16	16	21	21	37	37
Mean (SD)	4.01 (1.004)	-0.10 (0.367)	3.88 (1.012)	0.01 (0.215)	3.93 (0.997)	-0.04 (0.291)
Median	3.93	0.00	3.80	0.00	3.93	0.00
Min, Max	2.5, 5.6	-1.4, 0.2	2.5, 5.7	-0.6, 0.8	2.5, 5.7	-1.4, 0.8

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Blood Urea Nitrogen (umol/L)						
Month 1						
n	18	18	23	23	41	41
Mean (SD)	3.99 (1.133)	-0.14 (0.959)	3.90 (1.096)	-0.12 (0.887)	3.94 (1.099)	-0.13 (0.907)
Median	4.07	0.10	4.07	0.00	4.07	0.00
Min, Max	2.2, 6.1	-1.8, 1.4	2.0, 6.2	-1.6, 1.7	2.0, 6.2	-1.8, 1.7
Month 2						
n	19	19	24	24	43	43
Mean (SD)	3.99 (0.915)	-0.07 (1.029)	4.20 (1.294)	0.25 (1.165)	4.11 (1.135)	0.11 (1.106)
Median	3.90	0.00	4.15	0.15	4.10	0.10
Min, Max	2.5, 6.2	-2.1, 1.7	1.6, 6.5	-2.1, 3.5	1.6, 6.5	-2.1, 3.5
Month 3						
n	19	19	23	23	42	42
Mean (SD)	3.83 (1.155)	-0.23 (1.027)	3.93 (0.972)	-0.04 (0.970)	3.89 (1.047)	-0.13 (0.988)
Median	3.70	-0.29	4.10	0.00	4.08	-0.07
Min, Max	1.8, 6.8	-2.0, 1.8	1.9, 5.2	-2.5, 2.0	1.8, 6.8	-2.5, 2.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Blood Urea Nitrogen (umol/L)						
Month 4						
n	19	19	22	22	41	41
Mean (SD)	4.04 (1.029)	-0.02 (1.062)	3.89 (1.395)	0.04 (0.779)	3.96 (1.226)	0.01 (0.909)
Median	4.28	0.00	3.75	0.05	4.10	0.00
Min, Max	2.1, 5.4	-2.2, 2.1	1.7, 7.1	-1.5, 1.4	1.7, 7.1	-2.2, 2.1
Month 5						
n	12	12	16	16	28	28
Mean (SD)	4.14 (1.402)	0.34 (0.988)	3.97 (1.146)	0.12 (0.849)	4.04 (1.240)	0.21 (0.900)
Median	3.69	0.15	4.07	0.00	4.02	0.00
Min, Max	2.5, 6.8	-1.2, 2.1	1.9, 5.5	-1.3, 1.8	1.9, 6.8	-1.3, 2.1
Month 6						
n	7	7	7	7	14	14
Mean (SD)	4.82 (1.094)	0.71 (0.456)	3.73 (0.776)	-0.09 (0.928)	4.28 (1.073)	0.31 (0.816)
Median	4.64	0.71	3.75	-0.36	3.96	0.54
Min, Max	3.6, 6.8	0.0, 1.4	2.5, 5.1	-1.4, 1.2	2.5, 6.8	-1.4, 1.4

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Blood Urea Nitrogen (umol/L)						
Month 9						
n	2	2	0	0	2	2
Mean (SD)	5.71 (0.000)	0.36 (0.000)			5.71 (0.000)	0.36 (0.000)
Median	5.71	0.36			5.71	0.36
Min, Max	5.7, 5.7	0.4, 0.4			5.7, 5.7	0.4, 0.4
End of Study						
n	19	19	25	24	44	43
Mean (SD)	3.77 (1.136)	-0.29 (0.997)	4.16 (1.569)	-0.02 (0.932)	3.99 (1.398)	-0.14 (0.959)
Median	3.93	0.00	4.10	-0.34	3.93	-0.33
Min, Max	0.7, 5.7	-2.2, 1.4	2.2, 9.6	-1.6, 2.4	0.7, 9.6	-2.2, 2.4
Creatinine (umol/L)						
Screening						
n	35		48		83	
Mean (SD)	33.26 (12.226)		44.29 (11.558)		39.64 (12.983)	
Median	29.17		44.10		37.00	
Min, Max	17.7, 70.7		31.0, 81.4		17.7, 81.4	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Creatinine (umol/L)						
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	30.98 (10.073)		40.36 (7.773)		35.55 (10.095)	
Median	28.00		39.00		36.00	
Min, Max	19.4, 60.1		25.0, 56.0		19.4, 60.1	
Day 1 Non-PK						
n	24	24	42	42	66	66
Mean (SD)	35.11 (19.244)	0.42 (3.740)	43.71 (13.930)	0.13 (2.681)	40.58 (16.456)	0.24 (3.083)
Median	31.47	0.00	40.39	0.00	36.12	0.00
Min, Max	15.9, 108.3	-13.0, 7.0	26.0, 82.5	-10.0, 10.6	15.9, 108.3	-13.0, 10.6
Month 1						
n	34	34	47	47	81	81
Mean (SD)	34.61 (18.610)	0.10 (6.450)	44.63 (10.923)	1.07 (7.238)	40.43 (15.369)	0.66 (6.893)
Median	30.00	0.44	42.43	1.00	40.00	0.88
Min, Max	17.7, 107.4	-15.0, 19.0	22.0, 79.2	-27.1, 15.0	17.7, 107.4	-27.1, 19.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Creatinine (umol/L)						
Month 2						
n	34	34	48	48	82	82
Mean (SD)	34.64 (16.346)	-0.08 (5.993)	44.63 (10.433)	1.31 (8.529)	40.49 (14.019)	0.74 (7.571)
Median	32.00	0.44	43.00	1.00	37.60	0.94
Min, Max	17.7, 105.4	-15.0, 10.6	26.5, 75.4	-22.9, 19.0	17.7, 105.4	-22.9, 19.0
Month 3						
n	34	34	47	47	81	81
Mean (SD)	35.02 (18.053)	0.30 (6.892)	45.62 (10.330)	2.28 (7.568)	41.17 (14.949)	1.45 (7.314)
Median	30.50	0.00	43.32	4.00	40.00	2.65
Min, Max	14.1, 109.0	-15.9, 15.3	33.0, 77.3	-19.0, 17.7	14.1, 109.0	-19.0, 17.7
Month 4						
n	28	28	43	43	71	71
Mean (SD)	36.99 (18.052)	1.41 (8.249)	44.28 (11.534)	1.69 (6.331)	41.40 (14.777)	1.58 (7.093)
Median	33.74	3.09	44.00	1.77	39.78	2.00
Min, Max	17.7, 99.5	-20.3, 17.2	19.0, 76.3	-10.6, 17.7	17.7, 99.5	-20.3, 17.7

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Creatinine (umol/L)						
Month 5						
n	18	18	29	29	47	47
Mean (SD)	35.90 (11.233)	3.80 (8.738)	46.84 (12.702)	2.21 (10.315)	42.65 (13.180)	2.82 (9.674)
Median	32.50	2.77	47.00	3.54	40.66	3.54
Min, Max	23.9, 72.5	-7.0, 29.2	12.0, 75.2	-31.0, 17.7	12.0, 75.2	-31.0, 29.2
Month 6						
n	10	10	15	15	25	25
Mean (SD)	33.73 (6.984)	0.76 (7.230)	45.13 (8.037)	5.27 (6.772)	40.57 (9.403)	3.47 (7.173)
Median	34.24	2.83	44.20	6.00	40.00	5.00
Min, Max	22.1, 44.2	-14.0, 8.8	30.9, 59.0	-4.4, 16.0	22.1, 59.0	-14.0, 16.0
Month 9						
n	2	2	0	0	2	2
Mean (SD)	31.82 (6.251)	-7.96 (0.000)			31.82 (6.251)	-7.96 (0.000)
Median	31.82	-7.96			31.82	-7.96
Min, Max	27.4, 36.2	-8.0, -8.0			27.4, 36.2	-8.0, -8.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Creatinine (umol/L)						
End of Study						
n	35	35	49	49	84	84
Mean (SD)	35.28 (16.525)	0.92 (8.770)	45.10 (11.204)	1.77 (6.401)	41.01 (14.429)	1.42 (7.442)
Median	32.71	0.00	43.32	2.00	39.50	0.94
Min, Max	16.8, 92.5	-15.8, 19.4	25.0, 76.2	-12.4, 17.7	16.8, 92.5	-15.8, 19.4
Gamma Glutamyl Transferase (U/L)						
Screening						
n	33		47		80	
Mean (SD)	11.47 (4.511)		15.99 (8.453)		14.12 (7.407)	
Median	11.00		13.00		12.00	
Min, Max	5.9, 27.5		8.0, 44.5		5.9, 44.5	
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	10.80 (3.458)		15.68 (6.775)		13.18 (5.817)	
Median	10.50		13.00		11.00	
Min, Max	6.0, 19.0		8.0, 31.0		6.0, 31.0	

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Gamma Glutamyl Transferase (U/L)						
Day 1 Non-PK						
n	22	22	39	39	61	61
Mean (SD)	11.17 (3.843)	0.05 (1.046)	17.14 (10.681)	-0.03 (0.707)	14.99 (9.261)	0.00 (0.837)
Median	10.50	0.00	13.00	0.00	12.00	0.00
Min, Max	8.0, 25.0	-2.0, 3.0	8.0, 51.4	-2.0, 3.0	8.0, 51.4	-2.0, 3.0
Month 1						
n	35	35	45	44	80	79
Mean (SD)	12.33 (7.864)	0.91 (4.985)	14.22 (6.172)	-2.21 (8.290)	13.40 (6.980)	-0.83 (7.152)
Median	11.00	0.00	12.50	0.00	12.00	0.00
Min, Max	5.0, 52.3	-5.0, 27.3	8.0, 34.0	-41.6, 3.0	5.0, 52.3	-41.6, 27.3
Month 2						
n	34	34	48	47	82	81
Mean (SD)	11.15 (3.371)	-0.29 (2.013)	14.29 (7.684)	-2.43 (9.101)	12.99 (6.428)	-1.53 (7.102)
Median	11.00	0.00	13.00	0.00	12.00	0.00
Min, Max	6.0, 20.0	-5.4, 3.0	7.0, 56.0	-41.4, 15.0	6.0, 56.0	-41.4, 15.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Gamma Glutamyl Transferase (U/L)						
Month 3						
n	34	34	45	44	79	78
Mean (SD)	10.95 (3.154)	-0.49 (3.049)	14.49 (7.425)	-2.42 (8.862)	12.97 (6.199)	-1.58 (6.983)
Median	10.00	0.00	12.00	-0.50	11.00	0.00
Min, Max	7.0, 20.1	-8.0, 3.0	8.0, 45.0	-39.7, 7.0	7.0, 45.0	-39.7, 7.0
Month 4						
n	28	28	43	42	71	70
Mean (SD)	11.20 (2.893)	-0.86 (3.681)	14.61 (5.916)	-2.54 (8.848)	13.26 (5.200)	-1.87 (7.246)
Median	10.00	0.00	13.00	0.00	12.00	0.00
Min, Max	8.0, 18.3	-10.0, 4.0	8.0, 37.0	-38.5, 5.0	8.0, 37.0	-38.5, 5.0
Month 5						
n	18	18	29	28	47	46
Mean (SD)	12.08 (3.051)	0.70 (3.378)	13.30 (4.483)	-3.15 (10.503)	12.83 (4.004)	-1.64 (8.608)
Median	12.20	1.00	12.00	0.00	12.00	1.00
Min, Max	7.0, 17.0	-8.0, 6.0	8.0, 26.0	-41.4, 4.0	7.0, 26.0	-41.4, 6.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Gamma Glutamyl Transferase (U/L)						
Month 6						
n	10	10	14	14	24	24
Mean (SD)	11.20 (2.860)	0.40 (1.838)	13.79 (4.742)	0.43 (3.345)	12.71 (4.196)	0.42 (2.765)
Median	10.00	1.00	12.50	0.50	12.00	1.00
Min, Max	8.0, 16.0	-3.0, 3.0	8.0, 24.0	-7.0, 5.0	8.0, 24.0	-7.0, 5.0
Month 9						
n	2	2	0	0	2	2
Mean (SD)	13.50 (2.121)	1.00 (0.000)			13.50 (2.121)	1.00 (0.000)
Median	13.50	1.00			13.50	1.00
Min, Max	12.0, 15.0	1.0, 1.0			12.0, 15.0	1.0, 1.0
End of Study						
n	30	30	47	46	77	76
Mean (SD)	10.81 (2.670)	-0.99 (3.951)	14.01 (5.496)	-2.78 (8.306)	12.76 (4.846)	-2.07 (6.943)
Median	11.00	0.50	12.00	-1.00	12.00	0.00
Min, Max	6.0, 17.0	-13.2, 4.0	8.0, 34.0	-38.7, 6.0	6.0, 34.0	-38.7, 6.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Alkaline Phosphatase (U/L)						
Screening						
n	34		45		79	
Mean (SD)	257.26 (105.858)		226.07 (84.125)		239.49 (94.734)	
Median	228.00		219.00		221.00	
Min, Max	101.0, 584.2		13.0, 541.2		13.0, 584.2	
Day 1 CSL627 PK						
n	19		19		38	
Mean (SD)	225.42 (44.939)		235.84 (63.487)		230.63 (54.508)	
Median	227.00		223.00		226.50	
Min, Max	126.0, 312.0		149.0, 436.0		126.0, 436.0	
Day 1 Non-PK						
n	22	22	41	41	63	63
Mean (SD)	227.34 (96.494)	-2.77 (20.584)	228.48 (89.409)	-1.02 (6.916)	228.08 (91.167)	-1.63 (13.232)
Median	200.50	0.00	199.00	0.00	199.00	0.00
Min, Max	83.0, 574.8	-76.0, 50.0	117.0, 570.0	-39.0, 7.0	83.0, 574.8	-76.0, 50.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Alkaline Phosphatase (U/L)						
Month 1						
n	34	34	43	41	77	75
Mean (SD)	228.17 (62.665)	-11.11 (82.760)	245.75 (95.007)	14.05 (39.402)	237.99 (82.284)	2.64 (63.660)
Median	229.00	2.50	218.00	15.00	221.00	7.00
Min, Max	122.0, 394.0	-332.7, 83.0	131.0, 662.2	-118.1, 118.2	122.0, 662.2	-332.7, 118.2
Month 2						
n	34	34	47	45	81	79
Mean (SD)	236.79 (80.530)	-0.64 (61.839)	243.60 (87.872)	14.86 (49.416)	240.74 (84.418)	8.19 (55.272)
Median	216.00	1.50	233.00	15.00	228.00	10.00
Min, Max	131.0, 580.7	-304.0, 112.8	35.0, 578.6	-161.0, 127.7	35.0, 580.7	-304.0, 127.7
Month 3						
n	34	34	47	45	81	79
Mean (SD)	228.35 (74.590)	-9.07 (61.014)	251.16 (80.455)	20.90 (43.828)	241.58 (78.392)	8.00 (53.682)
Median	212.00	-1.50	230.00	16.00	225.00	8.00
Min, Max	124.0, 548.4	-284.0, 70.0	137.0, 532.2	-73.1, 123.3	124.0, 548.4	-284.0, 123.3

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Alkaline Phosphatase (U/L)						
Month 4						
n	28	28	43	42	71	70
Mean (SD)	238.99 (79.496)	-5.53 (79.303)	253.67 (84.830)	23.98 (52.674)	247.88 (82.507)	12.18 (65.739)
Median	219.00	-2.00	234.00	17.00	231.00	8.00
Min, Max	132.0, 537.2	-345.0, 152.3	150.0, 503.1	-71.5, 199.3	132.0, 537.2	-345.0, 199.3
Month 5						
n	18	18	29	29	47	47
Mean (SD)	223.64 (47.110)	-19.24 (77.728)	255.86 (90.408)	21.55 (46.087)	243.52 (77.757)	5.93 (62.668)
Median	225.00	-1.00	238.00	17.00	235.00	8.00
Min, Max	142.0, 307.1	-281.0, 61.0	122.0, 552.4	-110.9, 141.0	122.0, 552.4	-281.0, 141.0
Month 6						
n	10	10	14	14	24	24
Mean (SD)	274.90 (165.763)	8.30 (215.143)	238.50 (48.820)	30.64 (33.550)	253.67 (111.513)	21.33 (137.386)
Median	236.00	-15.00	232.50	25.50	232.50	15.50
Min, Max	168.0, 724.0	-350.0, 530.0	173.0, 348.0	-39.0, 94.0	168.0, 724.0	-350.0, 530.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Alkaline Phosphatase (U/L)						
Month 9						
n	2	2	0	0	2	2
Mean (SD)	195.50 (16.263)	-47.50 (53.033)			195.50 (16.263)	-47.50 (53.033)
Median	195.50	-47.50			195.50	-47.50
Min, Max	184.0, 207.0	-85.0, -10.0			184.0, 207.0	-85.0, -10.0
End of Study						
n	32	32	49	47	81	79
Mean (SD)	238.55 (112.697)	0.78 (82.342)	246.66 (81.803)	15.93 (47.853)	243.45 (94.618)	9.79 (64.040)
Median	216.00	1.40	235.00	11.00	229.00	8.00
Min, Max	142.0, 796.8	-306.0, 222.0	132.0, 518.5	-108.0, 155.7	132.0, 796.8	-306.0, 222.0
Alanine Aminotransferase (U/L)						
Screening						
n	35		49		84	
Mean (SD)	19.57 (7.330)		17.69 (6.758)		18.47 (7.021)	
Median	17.00		16.50		16.75	
Min, Max	10.0, 37.0		7.0, 33.0		7.0, 37.0	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Alanine Aminotransferase (U/L)						
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	19.05 (7.803)		22.84 (7.841)		20.90 (7.953)	
Median	17.50		21.00		19.00	
Min, Max	10.0, 40.0		11.0, 41.0		10.0, 41.0	
Day 1 Non-PK						
n	24	24	43	43	67	67
Mean (SD)	18.99 (8.445)	-0.38 (1.013)	19.17 (11.504)	-0.05 (1.413)	19.11 (10.445)	-0.16 (1.286)
Median	16.00	0.00	15.00	0.00	15.00	0.00
Min, Max	9.0, 36.0	-4.0, 1.0	8.0, 65.4	-6.0, 4.0	8.0, 65.4	-6.0, 4.0
Month 1						
n	34	34	47	47	81	81
Mean (SD)	20.26 (8.199)	1.06 (6.437)	21.00 (16.851)	0.83 (9.271)	20.69 (13.825)	0.93 (8.157)
Median	18.00	1.00	16.00	0.00	17.00	0.00
Min, Max	10.0, 38.0	-8.0, 21.0	8.1, 119.9	-14.9, 54.5	8.1, 119.9	-14.9, 54.5

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Alanine Aminotransferase (U/L)						
Month 2						
n	34	34	48	48	82	82
Mean (SD)	20.37 (7.190)	1.38 (5.160)	18.89 (8.132)	-1.08 (8.746)	19.50 (7.744)	-0.06 (7.531)
Median	18.00	1.00	18.00	-1.00	18.00	0.00
Min, Max	11.7, 37.0	-9.0, 18.0	5.8, 38.0	-40.3, 14.0	5.8, 38.0	-40.3, 18.0
Month 3						
n	34	34	47	47	81	81
Mean (SD)	19.58 (9.447)	0.59 (8.175)	20.99 (12.728)	1.18 (9.923)	20.40 (11.422)	0.93 (9.180)
Median	17.00	-0.50	17.00	0.30	17.00	0.00
Min, Max	9.0, 53.0	-12.0, 32.0	7.0, 76.0	-37.1, 31.0	7.0, 76.0	-37.1, 32.0
Month 4						
n	28	28	43	43	71	71
Mean (SD)	18.95 (7.281)	0.31 (5.065)	20.03 (7.194)	-0.27 (9.194)	19.61 (7.196)	-0.04 (7.791)
Median	17.00	1.00	20.00	0.40	18.00	1.00
Min, Max	9.0, 36.0	-13.0, 15.0	8.0, 36.0	-40.3, 19.0	8.0, 36.0	-40.3, 19.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Alanine Aminotransferase (U/L)						
Month 5						
n	18	18	29	29	47	47
Mean (SD)	18.14 (7.111)	1.46 (6.627)	21.33 (10.777)	2.21 (6.782)	20.11 (9.582)	1.92 (6.661)
Median	16.00	1.50	19.00	1.00	18.00	1.00
Min, Max	8.0, 31.0	-8.0, 14.0	9.0, 60.6	-14.3, 16.0	8.0, 60.6	-14.3, 16.0
Month 6						
n	10	10	15	15	25	25
Mean (SD)	15.40 (5.929)	0.10 (4.383)	20.27 (10.925)	1.53 (11.032)	18.32 (9.419)	0.96 (8.872)
Median	14.00	1.00	14.00	0.00	14.00	0.00
Min, Max	7.0, 26.0	-6.0, 8.0	10.0, 47.0	-11.0, 37.0	7.0, 47.0	-11.0, 37.0
Month 9						
n	2	2	0	0	2	2
Mean (SD)	13.00 (2.828)	0.00 (4.243)			13.00 (2.828)	0.00 (4.243)
Median	13.00	0.00			13.00	0.00
Min, Max	11.0, 15.0	-3.0, 3.0			11.0, 15.0	-3.0, 3.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Alanine Aminotransferase (U/L)						
End of Study						
n	33	33	49	49	82	82
Mean (SD)	19.80 (8.980)	0.63 (7.167)	20.93 (9.980)	1.20 (6.437)	20.47 (9.549)	0.97 (6.703)
Median	17.00	1.90	18.00	0.70	17.50	1.00
Min, Max	7.0, 42.0	-11.0, 23.0	7.3, 53.1	-14.0, 21.0	7.0, 53.1	-14.0, 23.0
Aspartate Aminotransferase (U/L)						
Screening						
n	35		49		84	
Mean (SD)	36.17 (9.928)		27.74 (6.924)		31.25 (9.252)	
Median	34.40		28.00		31.00	
Min, Max	20.0, 79.0		17.0, 55.0		17.0, 79.0	
Day 1 CSL627 PK						
n	20		19		39	
Mean (SD)	35.45 (10.551)		31.16 (4.180)		33.36 (8.286)	
Median	34.00		30.00		32.00	
Min, Max	26.0, 75.0		24.0, 37.0		24.0, 75.0	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Aspartate Aminotransferase (U/L)						
Day 1 Non-PK						
n	24	24	41	41	65	65
Mean (SD)	34.41 (9.710)	-0.25 (1.294)	27.53 (6.022)	-0.37 (1.178)	30.07 (8.231)	-0.32 (1.213)
Median	33.45	0.00	26.70	0.00	29.00	0.00
Min, Max	21.0, 72.0	-3.0, 4.0	18.0, 47.0	-5.0, 1.0	18.0, 72.0	-5.0, 4.0
Month 1						
n	33	33	47	47	80	80
Mean (SD)	34.20 (8.835)	0.11 (8.033)	28.62 (8.526)	0.35 (5.321)	30.92 (9.033)	0.25 (6.530)
Median	32.00	0.00	29.00	-1.00	30.00	-0.50
Min, Max	15.0, 65.0	-26.0, 24.0	18.2, 70.1	-9.0, 23.1	15.0, 70.1	-26.0, 24.0
Month 2						
n	34	34	48	48	82	82
Mean (SD)	32.75 (7.174)	-1.21 (6.614)	29.16 (8.835)	1.03 (6.097)	30.65 (8.333)	0.10 (6.375)
Median	33.00	-0.50	27.00	0.00	31.00	0.00
Min, Max	12.0, 54.0	-23.0, 8.0	14.9, 63.3	-9.0, 25.0	12.0, 63.3	-23.0, 25.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Aspartate Aminotransferase (U/L)						
Month 3						
n	34	34	45	45	79	79
Mean (SD)	32.99 (10.350)	-0.98 (5.176)	27.67 (6.631)	-0.40 (4.685)	29.96 (8.784)	-0.65 (4.879)
Median	32.40	-1.40	27.00	-0.50	29.00	-1.00
Min, Max	11.0, 72.0	-14.0, 9.0	12.1, 43.0	-9.0, 10.0	11.0, 72.0	-14.0, 10.0
Month 4						
n	28	28	43	43	71	71
Mean (SD)	30.58 (4.344)	-1.13 (4.318)	28.23 (5.835)	0.04 (5.103)	29.16 (5.388)	-0.42 (4.812)
Median	30.00	0.55	28.00	0.90	29.00	0.60
Min, Max	23.0, 38.0	-14.0, 4.0	12.0, 40.0	-17.0, 12.0	12.0, 40.0	-17.0, 12.0
Month 5						
n	18	18	29	29	47	47
Mean (SD)	30.80 (5.032)	-0.62 (4.716)	28.34 (7.885)	0.63 (5.411)	29.28 (6.976)	0.15 (5.140)
Median	32.00	-1.00	28.00	0.00	29.00	0.00
Min, Max	22.0, 39.0	-10.0, 8.0	13.0, 45.0	-10.0, 13.0	13.0, 45.0	-10.0, 13.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Aspartate Aminotransferase (U/L)						
Month 6						
n	10	10	15	15	25	25
Mean (SD)	29.20 (5.095)	-2.30 (6.237)	29.27 (9.823)	0.80 (7.580)	29.24 (8.125)	-0.44 (7.107)
Median	30.00	-1.00	30.00	-1.00	30.00	-1.00
Min, Max	20.0, 36.0	-15.0, 6.0	15.0, 55.0	-6.0, 24.0	15.0, 55.0	-15.0, 24.0
Month 9						
n	2	2	0	0	2	2
Mean (SD)	30.00 (1.414)	-4.00 (2.828)			30.00 (1.414)	-4.00 (2.828)
Median	30.00	-4.00			30.00	-4.00
Min, Max	29.0, 31.0	-6.0, -2.0			29.0, 31.0	-6.0, -2.0
End of Study						
n	33	33	47	47	80	80
Mean (SD)	31.69 (7.080)	-2.24 (6.248)	28.49 (7.622)	0.53 (5.599)	29.81 (7.527)	-0.61 (5.997)
Median	30.00	-1.00	29.00	0.00	30.00	-0.65
Min, Max	19.0, 57.0	-22.0, 14.0	12.0, 45.0	-14.0, 13.0	12.0, 57.0	-22.0, 14.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Albumin (g/dL)						
Screening						
n	34		47		81	
Mean (SD)	42.19 (4.454)		42.95 (4.745)		42.63 (4.612)	
Median	42.10		44.00		43.00	
Min, Max	29.5, 52.0		27.2, 50.0		27.2, 52.0	
Day 1 CSL627 PK						
n	18		19		37	
Mean (SD)	41.49 (2.116)		42.36 (2.804)		41.94 (2.498)	
Median	42.00		43.00		42.30	
Min, Max	38.0, 45.0		37.0, 47.2		37.0, 47.2	
Day 1 Non-PK						
n	23	23	42	42	65	65
Mean (SD)	41.36 (3.533)	-0.07 (0.621)	42.38 (4.113)	-0.05 (0.767)	42.02 (3.920)	-0.06 (0.714)
Median	41.00	0.00	43.00	0.00	43.00	0.00
Min, Max	34.4, 47.1	-2.4, 1.0	31.2, 49.4	-2.5, 3.0	31.2, 49.4	-2.5, 3.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Albumin (g/dL)						
Month 1						
n	33	33	46	46	79	79
Mean (SD)	42.34 (3.450)	1.01 (2.155)	41.99 (4.043)	-0.49 (2.872)	42.13 (3.788)	0.14 (2.687)
Median	43.00	0.60	43.00	-0.85	43.00	0.00
Min, Max	34.6, 47.0	-2.0, 6.0	27.9, 48.0	-7.3, 8.6	27.9, 48.0	-7.3, 8.6
Month 2						
n	33	33	45	45	78	78
Mean (SD)	41.66 (3.836)	0.39 (2.579)	42.80 (3.913)	0.12 (3.620)	42.32 (3.897)	0.24 (3.205)
Median	41.20	0.00	43.00	0.00	42.44	0.00
Min, Max	31.9, 51.0	-3.6, 6.0	31.2, 52.0	-9.0, 10.0	31.2, 52.0	-9.0, 10.0
Month 3						
n	32	32	44	44	76	76
Mean (SD)	41.60 (3.719)	0.20 (2.806)	43.17 (3.562)	0.71 (3.263)	42.51 (3.687)	0.50 (3.069)
Median	41.40	0.66	43.50	0.55	43.00	0.66
Min, Max	34.7, 51.0	-7.3, 5.0	32.6, 49.7	-4.0, 8.0	32.6, 51.0	-7.3, 8.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Albumin (g/dL)						
Month 4						
n	28	28	41	41	69	69
Mean (SD)	41.60 (3.816)	0.57 (2.491)	42.60 (3.640)	-0.02 (3.139)	42.19 (3.717)	0.22 (2.889)
Median	42.00	1.00	43.00	0.00	43.00	0.30
Min, Max	34.7, 49.0	-4.3, 5.7	29.4, 49.0	-6.2, 9.0	29.4, 49.0	-6.2, 9.0
Month 5						
n	17	17	28	28	45	45
Mean (SD)	42.67 (3.475)	0.94 (2.410)	42.62 (4.262)	0.24 (3.085)	42.64 (3.942)	0.50 (2.840)
Median	43.00	1.00	44.00	0.00	43.16	0.82
Min, Max	36.0, 49.0	-3.0, 6.0	31.9, 49.0	-4.4, 7.0	31.9, 49.0	-4.4, 7.0
Month 6						
n	10	10	14	14	24	24
Mean (SD)	42.00 (5.077)	0.20 (3.967)	44.57 (2.709)	-0.29 (3.384)	43.50 (3.989)	-0.08 (3.562)
Median	44.00	1.50	44.50	-1.50	44.00	0.00
Min, Max	28.0, 45.0	-9.0, 4.0	40.0, 48.0	-5.0, 6.0	28.0, 48.0	-9.0, 6.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Albumin (g/dL)						
Month 9						
n	2	2	0	0	2	2
Mean (SD)	41.50 (2.121)	-0.50 (0.707)			41.50 (2.121)	-0.50 (0.707)
Median	41.50	-0.50			41.50	-0.50
Min, Max	40.0, 43.0	-1.0, 0.0			40.0, 43.0	-1.0, 0.0
End of Study						
n	33	33	49	49	82	82
Mean (SD)	41.84 (2.988)	0.60 (2.437)	43.33 (3.444)	0.86 (3.500)	42.73 (3.331)	0.76 (3.102)
Median	42.00	0.17	44.00	1.00	43.00	0.55
Min, Max	38.0, 50.0	-4.0, 5.4	30.0, 49.0	-5.2, 11.6	30.0, 50.0	-5.2, 11.6
Bilirubin (umol/L)						
Screening						
n	34		49		83	
Mean (SD)	7.26 (5.185)		7.75 (4.667)		7.55 (4.861)	
Median	5.52		6.84		5.99	
Min, Max	2.9, 28.8		0.0, 23.0		0.0, 28.8	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Bilirubin (umol/L)						
Day 1 CSL627 PK						
n	20		18		38	
Mean (SD)	6.70 (4.633)		6.51 (3.926)		6.61 (4.256)	
Median	5.38		5.85		5.73	
Min, Max	2.4, 22.6		0.9, 17.0		0.9, 22.6	
Day 1 Non-PK						
n	23	23	43	43	66	66
Mean (SD)	6.71 (4.456)	0.18 (1.689)	7.04 (3.861)	-0.75 (2.228)	6.92 (4.047)	-0.42 (2.092)
Median	5.13	0.00	6.50	0.00	6.15	0.00
Min, Max	1.0, 16.4	-5.1, 5.1	0.0, 19.1	-10.6, 0.0	0.0, 19.1	-10.6, 5.1
Month 1						
n	33	33	45	45	78	78
Mean (SD)	6.84 (4.652)	0.17 (2.358)	7.44 (3.945)	-0.41 (3.057)	7.18 (4.240)	-0.16 (2.781)
Median	5.13	0.00	6.84	0.00	6.16	0.00
Min, Max	1.0, 22.6	-4.6, 7.4	2.4, 21.9	-10.5, 9.1	1.0, 22.6	-10.5, 9.1

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Bilirubin (umol/L)						
Month 2						
n	34	34	48	48	82	82
Mean (SD)	7.51 (6.764)	0.77 (3.836)	6.94 (3.499)	-0.55 (3.398)	7.17 (5.082)	-0.00 (3.623)
Median	5.00	0.21	6.76	-0.46	5.85	0.00
Min, Max	1.7, 31.8	-3.9, 14.5	0.0, 16.2	-10.7, 6.0	0.0, 31.8	-10.7, 14.5
Month 3						
n	34	34	46	46	80	80
Mean (SD)	7.18 (6.209)	0.44 (3.793)	7.08 (4.024)	-0.50 (3.647)	7.13 (5.033)	-0.10 (3.716)
Median	4.36	0.00	5.91	0.00	5.13	0.00
Min, Max	1.7, 31.1	-6.2, 14.4	1.9, 24.0	-11.8, 7.0	1.7, 31.1	-11.8, 14.4
Month 4						
n	28	28	42	42	70	70
Mean (SD)	7.89 (5.805)	0.83 (3.064)	6.98 (4.085)	-0.49 (3.515)	7.34 (4.828)	0.04 (3.382)
Median	6.00	0.00	5.39	0.00	5.99	0.00
Min, Max	2.1, 23.8	-3.1, 10.3	1.0, 23.4	-13.3, 10.6	1.0, 23.8	-13.3, 10.6

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Bilirubin (umol/L)						
Month 5						
n	18	18	29	29	47	47
Mean (SD)	7.82 (6.425)	1.01 (5.615)	7.45 (3.329)	0.16 (3.010)	7.59 (4.694)	0.49 (4.164)
Median	5.39	0.68	7.10	0.51	6.84	0.51
Min, Max	1.5, 23.1	-6.6, 14.9	0.0, 13.9	-8.7, 6.5	0.0, 23.1	-8.7, 14.9
Month 6						
n	10	10	14	14	24	24
Mean (SD)	9.56 (8.633)	1.70 (4.633)	6.48 (3.126)	0.59 (2.470)	7.77 (6.090)	1.05 (3.487)
Median	6.50	0.00	6.25	0.84	6.33	0.34
Min, Max	1.0, 27.5	-2.0, 14.0	1.0, 12.0	-3.1, 6.8	1.0, 27.5	-3.1, 14.0
Month 9						
n	2	2	0	0	2	2
Mean (SD)	12.40 (4.959)	3.34 (1.330)			12.40 (4.959)	3.34 (1.330)
Median	12.40	3.34			12.40	3.34
Min, Max	8.9, 15.9	2.4, 4.3			8.9, 15.9	2.4, 4.3

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Bilirubin (umol/L)						
End of Study						
n	33	33	49	49	82	82
Mean (SD)	7.35 (6.804)	0.71 (3.652)	7.50 (4.278)	0.14 (4.017)	7.44 (5.398)	0.37 (3.862)
Median	5.13	0.51	6.84	0.00	6.45	0.17
Min, Max	1.9, 38.6	-5.1, 16.0	0.2, 24.6	-13.1, 11.8	0.2, 38.6	-13.1, 16.0
Protein (g/L)						
Screening						
n	35		48		83	
Mean (SD)	69.28 (5.426)		73.04 (5.506)		71.45 (5.751)	
Median	69.00		73.55		71.50	
Min, Max	57.0, 81.0		57.0, 82.0		57.0, 82.0	
Day 1 CSL627 PK						
n	20		18		38	
Mean (SD)	67.69 (4.623)		72.40 (5.428)		69.92 (5.494)	
Median	67.00		73.40		69.70	
Min, Max	62.0, 79.0		59.0, 80.0		59.0, 80.0	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Protein (g/L)						
Day 1 Non-PK						
n	23	23	42	42	65	65
Mean (SD)	68.29 (6.309)	-0.30 (1.893)	73.87 (5.593)	-0.14 (0.993)	71.89 (6.399)	-0.20 (1.368)
Median	68.00	0.00	74.00	0.00	72.30	0.00
Min, Max	60.0, 81.0	-5.0, 6.0	62.0, 83.0	-4.0, 3.0	60.0, 83.0	-5.0, 6.0
Month 1						
n	33	33	44	44	77	77
Mean (SD)	68.72 (5.991)	0.02 (4.009)	71.79 (4.641)	-1.91 (4.030)	70.47 (5.444)	-1.08 (4.109)
Median	69.00	-1.00	72.35	-1.80	70.90	-1.00
Min, Max	59.3, 82.0	-11.8, 6.0	62.0, 80.0	-18.0, 6.0	59.3, 82.0	-18.0, 6.0
Month 2						
n	34	34	46	46	80	80
Mean (SD)	68.15 (5.422)	-0.62 (3.893)	72.89 (4.843)	-0.91 (4.854)	70.87 (5.585)	-0.79 (4.447)
Median	68.50	-1.00	72.65	0.00	71.00	-0.85
Min, Max	58.0, 78.0	-9.6, 6.8	64.0, 82.0	-10.0, 10.4	58.0, 82.0	-10.0, 10.4

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Protein (g/L)						
Month 3						
n	33	33	44	44	77	77
Mean (SD)	68.92 (4.941)	-0.20 (3.486)	73.26 (5.230)	-0.27 (4.803)	71.40 (5.515)	-0.24 (4.263)
Median	70.00	0.00	72.00	-1.00	71.10	0.00
Min, Max	57.0, 77.0	-8.9, 8.0	66.0, 84.0	-9.5, 10.0	57.0, 84.0	-9.5, 10.0
Month 4						
n	28	28	40	40	68	68
Mean (SD)	67.91 (6.155)	-0.91 (3.576)	72.20 (5.557)	-1.22 (5.866)	70.44 (6.145)	-1.09 (5.020)
Median	66.50	-1.60	72.00	-1.75	71.05	-1.75
Min, Max	59.0, 78.0	-8.9, 7.0	61.0, 83.0	-17.0, 13.0	59.0, 83.0	-17.0, 13.0
Month 5						
n	17	17	28	28	45	45
Mean (SD)	70.30 (6.776)	1.34 (4.083)	72.21 (4.426)	-1.35 (5.179)	71.49 (5.440)	-0.33 (4.925)
Median	69.00	1.00	72.05	-1.85	72.00	-1.00
Min, Max	58.0, 80.0	-4.0, 11.0	62.0, 81.0	-9.0, 12.0	58.0, 81.0	-9.0, 12.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Protein (g/L)						
Month 6						
n	10	10	14	14	24	24
Mean (SD)	67.90 (8.373)	-0.50 (4.197)	74.45 (3.275)	-0.94 (4.705)	71.72 (6.661)	-0.75 (4.410)
Median	70.00	1.50	74.50	-2.00	73.50	-1.00
Min, Max	48.0, 77.0	-9.0, 4.0	68.0, 79.0	-9.0, 9.0	48.0, 79.0	-9.0, 9.0
Month 9						
n	2	2	0	0	2	2
Mean (SD)	74.00 (7.071)	2.00 (1.414)			74.00 (7.071)	2.00 (1.414)
Median	74.00	2.00			74.00	2.00
Min, Max	69.0, 79.0	1.0, 3.0			69.0, 79.0	1.0, 3.0
End of Study						
n	35	35	49	49	84	84
Mean (SD)	68.00 (4.934)	-0.60 (3.691)	73.07 (5.044)	-0.37 (5.361)	70.96 (5.569)	-0.47 (4.713)
Median	68.00	0.00	72.10	-1.00	71.00	0.00
Min, Max	59.0, 76.0	-8.0, 7.0	61.0, 84.0	-11.9, 13.0	59.0, 84.0	-11.9, 13.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Glucose (mmol/L)						
Screening						
n	33		43		76	
Mean (SD)	5.03 (0.892)		4.87 (0.783)		4.94 (0.830)	
Median	4.84		4.83		4.83	
Min, Max	3.2, 7.1		2.7, 6.6		2.7, 7.1	
Day 1 CSL627 PK						
n	19		19		38	
Mean (SD)	4.91 (0.517)		5.19 (0.728)		5.05 (0.638)	
Median	5.05		5.04		5.04	
Min, Max	4.1, 5.7		4.4, 7.4		4.1, 7.4	
Day 1 Non-PK						
n	24	24	41	41	65	65
Mean (SD)	4.86 (0.896)	-0.02 (0.582)	4.79 (0.597)	-0.04 (0.225)	4.81 (0.716)	-0.03 (0.392)
Median	4.69	0.00	4.77	0.00	4.77	0.00
Min, Max	3.3, 6.8	-1.9, 1.9	3.4, 6.5	-1.1, 0.2	3.3, 6.8	-1.9, 1.9

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Glucose (mmol/L)						
Month 1						
n	34	34	47	47	81	81
Mean (SD)	5.08 (0.612)	0.23 (0.798)	4.92 (0.812)	-0.04 (0.955)	4.98 (0.735)	0.07 (0.897)
Median	5.08	0.08	4.72	-0.09	4.89	0.00
Min, Max	4.0, 7.0	-1.7, 1.8	3.3, 7.1	-2.6, 1.8	3.3, 7.1	-2.6, 1.8
Month 2						
n	33	33	48	48	81	81
Mean (SD)	4.94 (0.731)	0.06 (0.910)	4.86 (0.787)	-0.09 (0.930)	4.89 (0.761)	-0.03 (0.919)
Median	4.77	0.10	4.76	-0.08	4.77	-0.06
Min, Max	3.8, 7.3	-1.4, 2.0	2.6, 6.8	-2.3, 2.1	2.6, 7.3	-2.3, 2.1
Month 3						
n	33	33	47	47	80	80
Mean (SD)	4.63 (0.536)	-0.24 (0.758)	4.98 (0.861)	0.05 (0.937)	4.84 (0.760)	-0.07 (0.874)
Median	4.60	-0.27	4.86	0.10	4.66	-0.03
Min, Max	3.2, 6.2	-1.7, 1.3	3.4, 8.4	-1.7, 2.7	3.2, 8.4	-1.7, 2.7

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Glucose (mmol/L)						
Month 4						
n	28	28	43	43	71	71
Mean (SD)	4.78 (0.643)	-0.12 (0.626)	4.89 (0.729)	0.01 (0.863)	4.84 (0.694)	-0.04 (0.775)
Median	4.71	0.08	4.90	0.06	4.77	0.07
Min, Max	3.4, 6.7	-1.8, 0.8	3.2, 6.9	-1.9, 2.1	3.2, 6.9	-1.9, 2.1
Month 5						
n	18	18	29	29	47	47
Mean (SD)	4.58 (0.692)	-0.38 (0.822)	4.69 (0.705)	-0.10 (0.960)	4.65 (0.695)	-0.21 (0.911)
Median	4.47	-0.17	4.77	-0.22	4.66	-0.22
Min, Max	3.8, 6.4	-2.1, 0.7	2.6, 6.8	-1.9, 2.4	2.6, 6.8	-2.1, 2.4
Month 6						
n	10	10	14	14	24	24
Mean (SD)	4.76 (0.633)	-0.35 (1.039)	5.03 (0.741)	0.18 (0.959)	4.92 (0.697)	-0.04 (1.007)
Median	4.77	-0.46	4.77	-0.01	4.77	-0.18
Min, Max	4.1, 6.0	-1.8, 1.2	4.3, 6.6	-1.6, 1.9	4.1, 6.6	-1.8, 1.9

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Glucose (mmol/L)						
Month 9						
n	2	2	0	0	2	2
Mean (SD)	4.69 (0.196)	-0.69 (0.510)			4.69 (0.196)	-0.69 (0.510)
Median	4.69	-0.69			4.69	-0.69
Min, Max	4.6, 4.8	-1.1, -0.3			4.6, 4.8	-1.1, -0.3
End of Study						
n	33	33	49	49	82	82
Mean (SD)	4.62 (0.632)	-0.25 (0.903)	4.89 (0.786)	-0.04 (1.004)	4.78 (0.736)	-0.13 (0.965)
Median	4.66	-0.39	4.70	-0.10	4.68	-0.20
Min, Max	3.0, 6.5	-2.1, 2.4	3.4, 6.8	-2.9, 2.7	3.0, 6.8	-2.9, 2.7
Calcium (mmol/L)						
Screening						
n	32		40		72	
Mean (SD)	2.35 (0.261)		2.44 (0.548)		2.40 (0.443)	
Median	2.40		2.37		2.37	
Min, Max	1.0, 2.6		1.2, 4.7		1.0, 4.7	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Calcium (mmol/L)						
Day 1 CSL627 PK						
n	20		16		36	
Mean (SD)	2.37 (0.123)		2.37 (0.083)		2.37 (0.106)	
Median	2.34		2.35		2.34	
Min, Max	2.2, 2.7		2.3, 2.5		2.2, 2.7	
Day 1 Non-PK						
n	23	23	36	36	59	59
Mean (SD)	2.35 (0.326)	0.01 (0.060)	2.19 (0.476)	0.01 (0.028)	2.25 (0.428)	0.01 (0.043)
Median	2.40	0.00	2.35	0.00	2.39	0.00
Min, Max	0.9, 2.6	-0.2, 0.1	0.9, 2.6	-0.0, 0.1	0.9, 2.6	-0.2, 0.1
Month 1						
n	34	34	47	43	81	77
Mean (SD)	2.34 (0.258)	-0.01 (0.130)	2.32 (0.633)	-0.04 (0.194)	2.33 (0.508)	-0.03 (0.168)
Median	2.39	-0.01	2.35	0.00	2.36	-0.01
Min, Max	1.1, 2.6	-0.3, 0.3	1.0, 4.7	-1.2, 0.2	1.0, 4.7	-1.2, 0.3

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Calcium (mmol/L)						
Month 2						
n	32	32	48	44	80	76
Mean (SD)	2.33 (0.295)	-0.02 (0.171)	2.31 (0.639)	-0.02 (0.097)	2.32 (0.527)	-0.02 (0.132)
Median	2.40	-0.02	2.36	-0.00	2.37	-0.01
Min, Max	1.0, 2.7	-0.5, 0.3	1.0, 4.7	-0.3, 0.1	1.0, 4.7	-0.5, 0.3
Month 3						
n	33	33	46	42	79	75
Mean (SD)	2.32 (0.245)	-0.03 (0.157)	2.35 (0.658)	0.02 (0.100)	2.34 (0.524)	-0.00 (0.129)
Median	2.35	-0.04	2.37	0.03	2.37	-0.01
Min, Max	1.2, 2.7	-0.3, 0.3	1.0, 4.8	-0.2, 0.2	1.0, 4.8	-0.3, 0.3
Month 4						
n	26	26	43	39	69	65
Mean (SD)	2.32 (0.251)	-0.01 (0.137)	2.26 (0.537)	-0.00 (0.132)	2.28 (0.449)	-0.01 (0.133)
Median	2.39	-0.03	2.35	0.01	2.35	0.00
Min, Max	1.2, 2.5	-0.3, 0.3	1.1, 4.7	-0.5, 0.3	1.1, 4.7	-0.5, 0.3

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Calcium (mmol/L)						
Month 5						
n	18	18	29	27	47	45
Mean (SD)	2.29 (0.323)	-0.02 (0.153)	2.22 (0.369)	-0.01 (0.130)	2.24 (0.350)	-0.01 (0.138)
Median	2.36	-0.01	2.35	-0.02	2.35	-0.02
Min, Max	1.2, 2.6	-0.4, 0.3	1.1, 2.5	-0.2, 0.2	1.1, 2.6	-0.4, 0.3
Month 6						
n	10	10	15	14	25	24
Mean (SD)	2.35 (0.179)	-0.07 (0.196)	2.29 (0.305)	-0.00 (0.074)	2.31 (0.259)	-0.03 (0.139)
Median	2.38	-0.01	2.38	0.00	2.38	0.00
Min, Max	1.9, 2.5	-0.6, 0.1	1.2, 2.5	-0.1, 0.1	1.2, 2.5	-0.6, 0.1
Month 9						
n	2	2	0	0	2	2
Mean (SD)	2.41 (0.194)	-0.01 (0.018)			2.41 (0.194)	-0.01 (0.018)
Median	2.41	-0.01			2.41	-0.01
Min, Max	2.3, 2.5	-0.0, 0.0			2.3, 2.5	-0.0, 0.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Calcium (mmol/L)						
End of Study						
n	31	31	47	43	78	74
Mean (SD)	2.31 (0.236)	-0.03 (0.163)	2.32 (0.608)	-0.01 (0.120)	2.32 (0.493)	-0.02 (0.139)
Median	2.35	-0.02	2.37	-0.02	2.37	-0.02
Min, Max	1.2, 2.7	-0.4, 0.3	1.1, 4.5	-0.3, 0.3	1.1, 4.5	-0.4, 0.3
Urea (mmol/L)						
Screening						
n	22		33		55	
Mean (SD)	4.58 (1.193)		4.07 (1.211)		4.28 (1.219)	
Median	4.45		4.10		4.30	
Min, Max	2.8, 7.0		0.2, 6.2		0.2, 7.0	
Day 1 CSL627 PK						
n	14		13		27	
Mean (SD)	4.71 (1.216)		4.34 (0.957)		4.53 (1.094)	
Median	4.70		4.30		4.60	
Min, Max	2.6, 6.3		3.1, 5.8		2.6, 6.3	

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Urea (mmol/L)						
Day 1 Non-PK						
n	14	14	26	26	40	40
Mean (SD)	4.77 (2.245)	0.07 (0.498)	4.69 (1.328)	0.21 (0.715)	4.72 (1.677)	0.16 (0.644)
Median	4.45	0.00	4.60	0.00	4.55	0.00
Min, Max	2.2, 10.9	-1.0, 1.3	2.5, 8.1	-1.3, 2.5	2.2, 10.9	-1.3, 2.5
Month 1						
n	22	22	32	32	54	54
Mean (SD)	4.45 (1.274)	-0.26 (1.367)	4.30 (1.090)	-0.19 (1.426)	4.36 (1.159)	-0.22 (1.389)
Median	4.45	-0.20	4.08	0.05	4.31	-0.07
Min, Max	2.5, 8.0	-3.2, 1.8	2.2, 6.8	-5.1, 2.9	2.2, 8.0	-5.1, 2.9
Month 2						
n	21	21	32	32	53	53
Mean (SD)	4.71 (1.321)	0.07 (1.419)	4.50 (1.289)	0.02 (1.585)	4.58 (1.293)	0.04 (1.507)
Median	4.51	0.33	4.33	0.08	4.50	0.17
Min, Max	2.5, 7.9	-3.0, 2.6	2.3, 7.2	-5.3, 3.0	2.3, 7.9	-5.3, 3.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Urea (mmol/L)						
Month 3						
n	21	21	32	32	53	53
Mean (SD)	4.47 (1.156)	-0.17 (1.301)	4.60 (1.296)	0.12 (1.670)	4.55 (1.233)	0.01 (1.527)
Median	4.28	0.20	4.31	-0.10	4.30	0.10
Min, Max	2.9, 7.5	-3.4, 1.9	2.9, 8.5	-5.2, 3.7	2.9, 8.5	-5.2, 3.7
Month 4						
n	15	15	27	27	42	42
Mean (SD)	4.66 (1.217)	-0.00 (1.923)	4.49 (1.070)	0.07 (1.556)	4.55 (1.113)	0.04 (1.673)
Median	4.40	0.49	4.40	0.33	4.40	0.34
Min, Max	2.1, 6.9	-5.5, 2.1	2.6, 7.1	-5.0, 3.5	2.1, 7.1	-5.5, 3.5
Month 5						
n	8	8	18	18	26	26
Mean (SD)	4.47 (1.463)	0.60 (1.267)	3.84 (1.164)	-0.47 (1.594)	4.03 (1.269)	-0.14 (1.560)
Median	4.10	0.60	3.60	-0.51	3.75	-0.23
Min, Max	2.5, 6.5	-1.1, 2.1	2.1, 6.3	-4.7, 2.2	2.1, 6.5	-4.7, 2.2

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Urea (mmol/L)						
Month 6						
n	4	4	9	9	13	13
Mean (SD)	3.96 (0.382)	0.73 (0.763)	4.53 (1.271)	0.37 (1.436)	4.36 (1.090)	0.48 (1.245)
Median	3.85	0.87	4.30	0.70	4.00	0.70
Min, Max	3.7, 4.5	-0.3, 1.5	2.8, 6.6	-2.3, 3.0	2.8, 6.6	-2.3, 3.0
Month 9						
n	0	0	0	0	0	0
Mean (SD)						
Median						
Min, Max						
End of Study						
n	21	21	33	33	54	54
Mean (SD)	4.33 (1.129)	-0.35 (1.901)	4.50 (1.194)	0.03 (1.344)	4.43 (1.162)	-0.11 (1.577)
Median	4.33	-0.67	4.30	0.10	4.31	0.00
Min, Max	2.5, 7.2	-6.2, 2.2	2.5, 8.5	-4.2, 3.0	2.5, 8.5	-6.2, 3.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Lactate Dehydrogenase (U/L)						
Screening						
n	27		38		65	
Mean (SD)	369.05 (174.630)		380.03 (218.015)		375.47 (199.742)	
Median	317.00		294.50		310.00	
Min, Max	105.4, 814.0		124.2, 1170.0		105.4, 1170.0	
Day 1 CSL627 PK						
n	19		17		36	
Mean (SD)	366.11 (186.893)		427.41 (197.196)		395.06 (191.581)	
Median	306.00		336.00		306.50	
Min, Max	169.0, 977.0		229.0, 827.0		169.0, 977.0	
Day 1 Non-PK						
n	23	23	37	37	60	60
Mean (SD)	334.64 (165.746)	-14.35 (63.265)	348.19 (187.544)	-9.03 (28.457)	343.00 (178.183)	-11.07 (44.647)
Median	284.00	0.00	269.00	0.00	275.00	0.00
Min, Max	153.5, 735.0	-283.0, 84.0	98.0, 817.0	-129.0, 19.0	98.0, 817.0	-283.0, 84.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Lactate Dehydrogenase (U/L)						
Month 1						
n	34	34	43	40	77	74
Mean (SD)	364.12 (165.199)	10.01 (92.657)	355.74 (173.697)	-21.00 (80.305)	359.44 (168.940)	-6.75 (86.997)
Median	295.50	6.00	274.00	-12.00	282.00	-1.45
Min, Max	159.5, 739.0	-271.0, 216.0	112.2, 932.0	-303.0, 248.6	112.2, 932.0	-303.0, 248.6
Month 2						
n	32	32	45	42	77	74
Mean (SD)	350.40 (172.923)	-2.75 (63.471)	349.04 (175.626)	-9.96 (85.264)	349.60 (173.363)	-6.84 (76.202)
Median	283.00	-2.00	271.00	-5.50	279.00	-3.15
Min, Max	182.5, 903.0	-183.0, 187.0	127.6, 898.0	-286.0, 267.0	127.6, 903.0	-286.0, 267.0
Month 3						
n	33	33	46	42	79	75
Mean (SD)	338.10 (167.001)	-19.14 (75.015)	340.39 (172.006)	-22.84 (57.845)	339.43 (168.855)	-21.21 (65.503)
Median	279.00	-2.00	248.50	-17.50	259.00	-13.30
Min, Max	140.2, 830.0	-263.0, 137.0	125.0, 758.0	-229.0, 105.0	125.0, 830.0	-263.0, 137.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Lactate Dehydrogenase (U/L)						
Month 4						
n	26	26	43	40	69	66
Mean (SD)	319.96 (139.806)	-4.65 (40.511)	346.03 (173.258)	-17.24 (78.703)	336.20 (160.900)	-12.28 (66.228)
Median	276.00	-2.50	268.00	-6.50	268.00	-4.00
Min, Max	154.9, 685.0	-76.0, 99.0	130.6, 833.0	-260.0, 202.0	130.6, 833.0	-260.0, 202.0
Month 5						
n	17	17	29	27	46	44
Mean (SD)	338.10 (153.334)	11.31 (54.770)	357.41 (211.136)	-4.51 (93.964)	350.27 (190.227)	1.60 (80.718)
Median	280.74	5.00	270.00	10.40	271.00	5.50
Min, Max	193.0, 741.0	-57.0, 150.0	108.4, 1003.0	-200.0, 310.0	108.4, 1003.0	-200.0, 310.0
Month 6						
n	10	10	15	14	25	24
Mean (SD)	336.40 (142.417)	-1.80 (72.466)	465.67 (177.164)	-30.71 (107.694)	413.96 (173.472)	-18.67 (93.927)
Median	259.50	2.00	488.00	-26.00	417.00	-17.00
Min, Max	204.0, 601.0	-134.0, 125.0	198.0, 829.0	-256.0, 198.0	198.0, 829.0	-256.0, 198.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.2 Biochemistry Results and Changes from Baseline at Each Visit
(Safety Population)

Parameter (Unit) / Visit	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
	Result	Change	Result	Change	Result	Change
Lactate Dehydrogenase (U/L)						
Month 9						
n	2	2	0	0	2	2
Mean (SD)	240.00 (72.125)	-10.00 (24.042)			240.00 (72.125)	-10.00 (24.042)
Median	240.00	-10.00			240.00	-10.00
Min, Max	189.0, 291.0	-27.0, 7.0			189.0, 291.0	-27.0, 7.0
End of Study						
n	29	29	48	43	77	72
Mean (SD)	349.48 (174.979)	-8.89 (71.838)	359.10 (180.274)	15.15 (92.150)	355.47 (177.200)	5.47 (84.850)
Median	278.00	-11.00	284.00	13.00	283.00	6.00
Min, Max	152.4, 829.0	-198.0, 186.0	149.6, 784.0	-329.0, 253.0	149.6, 829.0	-329.0, 253.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Hemoglobin (g/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-6.94 (9.810)	-4.36 (6.788)	-5.43 (8.228)
Median	-6.00	-4.00	-4.00
Min, Max	-37.1, 6.0	-23.0, 8.0	-37.1, 8.0
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	6.52 (6.951)	8.54 (9.397)	7.70 (8.477)
Median	7.00	5.00	6.72
Min, Max	-9.0, 21.0	-10.0, 46.0	-10.0, 46.0
Change from Baseline to End-of-Study Value			
n	35	49	84
Mean (SD)	0.47 (7.993)	3.34 (11.310)	2.14 (10.108)
Median	2.00	2.00	2.00
Min, Max	-19.0, 17.0	-20.0, 46.0	-20.0, 46.0

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Hematocrit (L/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-0.02 (0.023)	-0.01 (0.022)	-0.02 (0.023)
Median	-0.02	-0.01	-0.01
Min, Max	-0.1, 0.0	-0.1, 0.0	-0.1, 0.0
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	0.02 (0.022)	0.03 (0.025)	0.02 (0.024)
Median	0.02	0.02	0.02
Min, Max	-0.0, 0.1	-0.0, 0.1	-0.0, 0.1
Change from Baseline to End-of-Study Value			
n	34	49	83
Mean (SD)	0.00 (0.020)	0.01 (0.030)	0.01 (0.026)
Median	0.00	0.00	0.00
Min, Max	-0.0, 0.1	-0.0, 0.1	-0.0, 0.1

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Erythrocytes (10^12/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-0.30 (0.540)	-0.20 (0.335)	-0.24 (0.432)
Median	-0.22	-0.16	-0.17
Min, Max	-2.8, 0.3	-1.5, 0.4	-2.8, 0.4
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	0.20 (0.554)	0.26 (0.304)	0.23 (0.424)
Median	0.24	0.25	0.24
Min, Max	-2.5, 1.1	-0.8, 0.8	-2.5, 1.1
Change from Baseline to End-of-Study Value			
n	34	49	83
Mean (SD)	0.00 (0.590)	0.05 (0.362)	0.03 (0.466)
Median	0.10	0.01	0.03
Min, Max	-2.8, 1.1	-1.3, 0.8	-2.8, 1.1

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Erythrocyte Mean Corpuscular Volume (fL)			
Change from Baseline to Lowest Post-baseline Value			
n	35	47	82
Mean (SD)	-2.70 (3.516)	-1.44 (2.727)	-1.98 (3.132)
Median	-1.70	-1.80	-1.75
Min, Max	-16.0, 2.3	-9.9, 7.0	-16.0, 7.0
Change from Baseline to Highest Post-baseline Value			
n	35	47	82
Mean (SD)	1.16 (2.549)	2.92 (6.367)	2.17 (5.150)
Median	1.30	1.10	1.15
Min, Max	-7.0, 8.5	-4.8, 34.0	-7.0, 34.0
Change from Baseline to End-of-Study Value			
n	34	47	81
Mean (SD)	-0.64 (3.268)	1.27 (7.095)	0.47 (5.852)
Median	-0.70	0.00	-0.30
Min, Max	-7.0, 8.5	-9.4, 34.0	-9.4, 34.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Leukocytes (10^9/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-1.51 (1.826)	-1.43 (1.727)	-1.46 (1.759)
Median	-1.26	-1.40	-1.40
Min, Max	-6.4, 2.4	-7.1, 2.1	-7.1, 2.4
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	2.32 (2.150)	2.09 (2.468)	2.19 (2.330)
Median	1.86	2.10	2.00
Min, Max	-1.7, 7.3	-5.3, 9.7	-5.3, 9.7
Change from Baseline to End-of-Study Value			
n	35	49	84
Mean (SD)	0.03 (1.935)	-0.34 (2.054)	-0.18 (2.002)
Median	0.20	-0.10	0.04
Min, Max	-4.8, 5.3	-5.3, 5.5	-5.3, 5.5

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Neutrophils (10^9/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-0.78 (1.050)	-0.97 (1.382)	-0.89 (1.251)
Median	-0.72	-0.66	-0.70
Min, Max	-3.1, 1.2	-7.3, 1.2	-7.3, 1.2
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	2.08 (1.936)	1.60 (1.936)	1.80 (1.939)
Median	1.55	1.60	1.58
Min, Max	-1.0, 8.1	-5.4, 6.0	-5.4, 8.1
Change from Baseline to End-of-Study Value			
n	33	49	82
Mean (SD)	0.17 (1.563)	-0.14 (1.669)	-0.02 (1.625)
Median	0.18	-0.05	0.02
Min, Max	-3.1, 5.6	-5.4, 4.3	-5.4, 5.6

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Lymphocytes (10^9/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-0.97 (1.067)	-0.47 (0.509)	-0.68 (0.824)
Median	-0.66	-0.41	-0.56
Min, Max	-4.4, 0.3	-1.8, 0.8	-4.4, 0.8
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	0.62 (0.739)	0.44 (0.555)	0.51 (0.640)
Median	0.60	0.30	0.42
Min, Max	-0.6, 3.0	-0.8, 2.0	-0.8, 3.0
Change from Baseline to End-of-Study Value			
n	33	49	82
Mean (SD)	-0.30 (0.656)	-0.03 (0.631)	-0.14 (0.651)
Median	-0.20	-0.07	-0.13
Min, Max	-2.2, 1.1	-1.6, 1.9	-2.2, 1.9

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Monocytes (10^9/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-0.16 (0.191)	-0.14 (0.180)	-0.15 (0.184)
Median	-0.13	-0.12	-0.13
Min, Max	-0.6, 0.3	-0.5, 0.2	-0.6, 0.3
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	0.23 (0.321)	0.14 (0.198)	0.18 (0.258)
Median	0.18	0.10	0.17
Min, Max	-0.4, 1.6	-0.2, 0.6	-0.4, 1.6
Change from Baseline to End-of-Study Value			
n	33	49	82
Mean (SD)	-0.01 (0.218)	-0.04 (0.171)	-0.03 (0.191)
Median	0.03	0.00	0.01
Min, Max	-0.5, 0.6	-0.4, 0.3	-0.5, 0.6

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Eosinophils (10^9/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-0.16 (0.245)	0.06 (0.830)	-0.03 (0.660)
Median	-0.10	-0.08	-0.10
Min, Max	-1.0, 0.3	-0.6, 5.1	-1.0, 5.1
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	0.27 (0.643)	0.47 (1.456)	0.39 (1.185)
Median	0.12	0.11	0.12
Min, Max	-0.6, 3.5	-0.3, 8.6	-0.6, 8.6
Change from Baseline to End-of-Study Value			
n	33	49	82
Mean (SD)	0.06 (0.334)	0.19 (1.017)	0.14 (0.813)
Median	0.01	0.01	0.01
Min, Max	-0.5, 1.4	-0.6, 6.6	-0.6, 6.6

Source: Listing 16.2.8.1
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Basophils (10^9/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	48	83
Mean (SD)	-0.05 (0.148)	-0.02 (0.032)	-0.03 (0.100)
Median	-0.01	-0.00	-0.01
Min, Max	-0.9, 0.0	-0.1, 0.1	-0.9, 0.1
Change from Baseline to Highest Post-baseline Value			
n	35	48	83
Mean (SD)	0.05 (0.216)	0.05 (0.104)	0.05 (0.160)
Median	0.03	0.02	0.02
Min, Max	-0.8, 0.9	-0.0, 0.7	-0.8, 0.9
Change from Baseline to End-of-Study Value			
n	33	48	81
Mean (SD)	-0.01 (0.217)	-0.00 (0.035)	-0.00 (0.140)
Median	0.00	0.00	0.00
Min, Max	-0.8, 0.9	-0.1, 0.1	-0.8, 0.9

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.3 Hematology Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Platelets (10^9/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-59.64 (78.207)	-50.83 (57.304)	-54.50 (66.510)
Median	-48.00	-37.00	-41.50
Min, Max	-256.0, 121.0	-240.0, 50.0	-256.0, 121.0
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	71.14 (73.413)	39.98 (62.287)	52.96 (68.484)
Median	62.00	34.00	47.50
Min, Max	-85.0, 242.0	-149.0, 204.0	-149.0, 242.0
Change from Baseline to End-of-Study Value			
n	35	49	84
Mean (SD)	1.19 (84.351)	-21.53 (62.366)	-12.07 (72.739)
Median	6.00	-16.00	-13.50
Min, Max	-146.0, 236.0	-208.0, 126.0	-208.0, 236.0

Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Sodium (mmol/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	48	83
Mean (SD)	-2.19 (1.846)	-2.39 (3.188)	-2.31 (2.692)
Median	-2.90	-2.00	-2.00
Min, Max	-6.0, 2.0	-14.2, 5.2	-14.2, 5.2
Change from Baseline to Highest Post-baseline Value			
n	35	48	83
Mean (SD)	1.89 (2.353)	1.66 (3.285)	1.76 (2.914)
Median	1.00	1.95	1.00
Min, Max	-1.0, 7.0	-10.0, 9.9	-10.0, 9.9
Change from Baseline to End-of-Study Value			
n	34	48	82
Mean (SD)	-0.30 (2.393)	-0.57 (3.432)	-0.46 (3.031)
Median	0.00	0.00	0.00
Min, Max	-5.0, 6.1	-11.5, 9.9	-11.5, 9.9

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Potassium (mmol/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-0.27 (0.390)	-0.26 (0.441)	-0.26 (0.418)
Median	-0.20	-0.20	-0.20
Min, Max	-1.3, 0.5	-1.8, 0.6	-1.8, 0.6
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	0.34 (0.511)	0.32 (0.456)	0.33 (0.477)
Median	0.30	0.30	0.30
Min, Max	-0.6, 1.8	-1.0, 1.3	-1.0, 1.8
Change from Baseline to End-of-Study Value			
n	34	49	83
Mean (SD)	-0.03 (0.425)	-0.04 (0.443)	-0.03 (0.433)
Median	0.00	-0.05	0.00
Min, Max	-1.1, 0.8	-1.5, 0.9	-1.5, 0.9

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Chloride (mmol/L)			
Change from Baseline to Lowest Post-baseline Value			
n	34	49	83
Mean (SD)	-2.58 (1.787)	-2.27 (2.762)	-2.40 (2.403)
Median	-2.50	-2.00	-2.00
Min, Max	-6.0, 2.0	-10.4, 2.2	-10.4, 2.2
Change from Baseline to Highest Post-baseline Value			
n	34	49	83
Mean (SD)	1.92 (2.741)	2.29 (2.959)	2.14 (2.860)
Median	1.00	2.00	2.00
Min, Max	-2.0, 10.0	-5.2, 9.0	-5.2, 10.0
Change from Baseline to End-of-Study Value			
n	33	49	82
Mean (SD)	-0.21 (2.536)	-0.11 (2.698)	-0.15 (2.618)
Median	0.00	0.00	0.00
Min, Max	-6.0, 5.0	-6.0, 5.0	-6.0, 5.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Blood Urea Nitrogen (umol/L)			
Change from Baseline to Lowest Post-baseline Value			
n	19	24	43
Mean (SD)	-1.01 (0.695)	-0.85 (0.575)	-0.92 (0.628)
Median	-1.07	-0.71	-0.73
Min, Max	-2.2, 0.0	-2.5, -0.1	-2.5, 0.0
Change from Baseline to Highest Post-baseline Value			
n	19	24	43
Mean (SD)	0.75 (0.902)	0.97 (0.948)	0.87 (0.923)
Median	0.71	0.78	0.71
Min, Max	-1.1, 2.1	-0.6, 3.5	-1.1, 3.5
Change from Baseline to End-of-Study Value			
n	19	24	43
Mean (SD)	-0.29 (0.997)	-0.02 (0.932)	-0.14 (0.959)
Median	0.00	-0.34	-0.33
Min, Max	-2.2, 1.4	-1.6, 2.4	-2.2, 2.4

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Creatinine (umol/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-4.35 (6.327)	-3.83 (7.968)	-4.05 (7.293)
Median	-2.65	-1.77	-2.21
Min, Max	-20.3, 6.2	-31.0, 8.8	-31.0, 8.8
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	6.89 (7.170)	6.61 (7.267)	6.73 (7.185)
Median	7.96	7.00	7.07
Min, Max	-7.0, 29.2	-10.1, 19.0	-10.1, 29.2
Change from Baseline to End-of-Study Value			
n	35	49	84
Mean (SD)	0.92 (8.770)	1.77 (6.401)	1.42 (7.442)
Median	0.00	2.00	0.94
Min, Max	-15.8, 19.4	-12.4, 17.7	-15.8, 19.4

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Gamma Glutamyl Transferase (U/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	48	83
Mean (SD)	-1.98 (3.463)	-4.40 (8.320)	-3.38 (6.790)
Median	-1.00	-2.00	-1.00
Min, Max	-13.2, 1.0	-41.6, 1.0	-41.6, 1.0
Change from Baseline to Highest Post-baseline Value			
n	35	48	83
Mean (SD)	2.51 (4.701)	0.28 (8.428)	1.22 (7.148)
Median	2.00	2.00	2.00
Min, Max	-2.4, 27.3	-38.5, 19.0	-38.5, 27.3
Change from Baseline to End-of-Study Value			
n	30	46	76
Mean (SD)	-0.99 (3.951)	-2.78 (8.306)	-2.07 (6.943)
Median	0.50	-1.00	0.00
Min, Max	-13.2, 4.0	-38.7, 6.0	-38.7, 6.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Alkaline Phosphatase (U/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	47	82
Mean (SD)	-42.32 (84.494)	-14.58 (47.356)	-26.42 (66.789)
Median	-24.00	-11.00	-16.00
Min, Max	-350.0, 70.0	-161.0, 95.6	-350.0, 95.6
Change from Baseline to Highest Post-baseline Value			
n	35	47	82
Mean (SD)	39.48 (112.707)	50.44 (45.682)	45.76 (80.914)
Median	24.00	40.00	34.50
Min, Max	-281.0, 530.0	-55.0, 199.3	-281.0, 530.0
Change from Baseline to End-of-Study Value			
n	32	47	79
Mean (SD)	0.78 (82.342)	15.93 (47.853)	9.79 (64.040)
Median	1.40	11.00	8.00
Min, Max	-306.0, 222.0	-108.0, 155.7	-306.0, 222.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Alanine Aminotransferase (U/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-3.13 (4.518)	-4.59 (7.459)	-3.98 (6.408)
Median	-3.00	-3.00	-3.00
Min, Max	-13.0, 7.0	-40.3, 8.0	-40.3, 8.0
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	6.35 (7.919)	8.32 (11.129)	7.50 (9.913)
Median	4.00	5.00	5.00
Min, Max	-6.0, 32.0	-11.1, 54.5	-11.1, 54.5
Change from Baseline to End-of-Study Value			
n	33	49	82
Mean (SD)	0.63 (7.167)	1.20 (6.437)	0.97 (6.703)
Median	1.90	0.70	1.00
Min, Max	-11.0, 23.0	-14.0, 21.0	-14.0, 23.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Aspartate Aminotransferase (U/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-5.54 (6.463)	-4.11 (4.081)	-4.71 (5.219)
Median	-4.00	-4.00	-4.00
Min, Max	-26.0, 4.0	-17.0, 4.0	-26.0, 4.0
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	3.93 (5.291)	6.51 (6.615)	5.43 (6.198)
Median	4.00	5.00	4.00
Min, Max	-6.0, 24.0	-4.0, 25.0	-6.0, 25.0
Change from Baseline to End-of-Study Value			
n	33	47	80
Mean (SD)	-2.24 (6.248)	0.53 (5.599)	-0.61 (5.997)
Median	-1.00	0.00	-0.65
Min, Max	-22.0, 14.0	-14.0, 13.0	-22.0, 14.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Albumin (g/dL)			
Change from Baseline to Lowest Post-baseline Value			
n	34	49	83
Mean (SD)	-2.10 (2.489)	-1.95 (2.862)	-2.01 (2.701)
Median	-2.00	-2.00	-2.00
Min, Max	-9.0, 3.0	-9.0, 6.0	-9.0, 6.0
Change from Baseline to Highest Post-baseline Value			
n	34	49	83
Mean (SD)	2.66 (1.797)	2.55 (3.258)	2.60 (2.741)
Median	2.00	2.00	2.00
Min, Max	0.0, 6.0	-3.0, 11.6	-3.0, 11.6
Change from Baseline to End-of-Study Value			
n	33	49	82
Mean (SD)	0.60 (2.437)	0.86 (3.500)	0.76 (3.102)
Median	0.17	1.00	0.55
Min, Max	-4.0, 5.4	-5.2, 11.6	-5.2, 11.6

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Bilirubin (umol/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-1.75 (1.979)	-2.35 (2.898)	-2.10 (2.559)
Median	-1.71	-1.54	-1.62
Min, Max	-6.6, 1.7	-13.3, 1.9	-13.3, 1.9
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	2.95 (4.417)	1.91 (3.479)	2.34 (3.906)
Median	1.71	2.00	1.71
Min, Max	-1.7, 16.0	-10.5, 11.8	-10.5, 16.0
Change from Baseline to End-of-Study Value			
n	33	49	82
Mean (SD)	0.71 (3.652)	0.14 (4.017)	0.37 (3.862)
Median	0.51	0.00	0.17
Min, Max	-5.1, 16.0	-13.1, 11.8	-13.1, 16.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Protein (g/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	49	84
Mean (SD)	-3.79 (2.998)	-4.44 (4.742)	-4.17 (4.098)
Median	-3.00	-4.00	-4.00
Min, Max	-11.8, 2.0	-18.0, 9.0	-18.0, 9.0
Change from Baseline to Highest Post-baseline Value			
n	35	49	84
Mean (SD)	3.51 (3.294)	2.49 (4.405)	2.91 (3.991)
Median	4.00	2.00	3.00
Min, Max	-5.8, 11.0	-6.0, 13.0	-6.0, 13.0
Change from Baseline to End-of-Study Value			
n	35	49	84
Mean (SD)	-0.60 (3.691)	-0.37 (5.361)	-0.47 (4.713)
Median	0.00	-1.00	0.00
Min, Max	-8.0, 7.0	-11.9, 13.0	-11.9, 13.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Glucose (mmol/L)			
Change from Baseline to Lowest Post-baseline Value			
n	34	49	83
Mean (SD)	-0.74 (0.665)	-0.75 (0.819)	-0.75 (0.755)
Median	-0.60	-0.72	-0.68
Min, Max	-2.1, 0.4	-2.9, 1.7	-2.9, 1.7
Change from Baseline to Highest Post-baseline Value			
n	34	49	83
Mean (SD)	0.63 (0.820)	0.79 (0.945)	0.72 (0.894)
Median	0.58	0.83	0.70
Min, Max	-1.3, 2.4	-1.4, 2.7	-1.4, 2.7
Change from Baseline to End-of-Study Value			
n	33	49	82
Mean (SD)	-0.25 (0.903)	-0.04 (1.004)	-0.13 (0.965)
Median	-0.39	-0.10	-0.20
Min, Max	-2.1, 2.4	-2.9, 2.7	-2.9, 2.7

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Calcium (mmol/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	45	80
Mean (SD)	-0.13 (0.169)	-0.13 (0.193)	-0.13 (0.182)
Median	-0.09	-0.10	-0.10
Min, Max	-0.6, 0.2	-1.2, 0.1	-1.2, 0.2
Change from Baseline to Highest Post-baseline Value			
n	35	45	80
Mean (SD)	0.07 (0.124)	0.08 (0.090)	0.07 (0.106)
Median	0.04	0.09	0.07
Min, Max	-0.1, 0.3	-0.1, 0.3	-0.1, 0.3
Change from Baseline to End-of-Study Value			
n	31	43	74
Mean (SD)	-0.03 (0.163)	-0.01 (0.120)	-0.02 (0.139)
Median	-0.02	-0.02	-0.02
Min, Max	-0.4, 0.3	-0.3, 0.3	-0.4, 0.3

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Urea (mmol/L)			
Change from Baseline to Lowest Post-baseline Value			
n	22	33	55
Mean (SD)	-1.08 (1.529)	-0.91 (1.248)	-0.98 (1.356)
Median	-0.85	-0.83	-0.83
Min, Max	-6.2, 0.7	-5.3, 1.3	-6.2, 1.3
Change from Baseline to Highest Post-baseline Value			
n	22	33	55
Mean (SD)	0.73 (1.367)	0.86 (1.444)	0.81 (1.402)
Median	0.94	0.83	0.83
Min, Max	-2.9, 2.6	-4.2, 3.7	-4.2, 3.7
Change from Baseline to End-of-Study Value			
n	21	33	54
Mean (SD)	-0.35 (1.901)	0.03 (1.344)	-0.11 (1.577)
Median	-0.67	0.10	0.00
Min, Max	-6.2, 2.2	-4.2, 3.0	-6.2, 3.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.4 Biochemistry Changes from Baseline to Lowest, Highest and Final Value (Safety Population)

Parameter (Unit)	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Lactate Dehydrogenase (U/L)			
Change from Baseline to Lowest Post-baseline Value			
n	35	44	79
Mean (SD)	-39.83 (68.502)	-53.87 (75.208)	-47.65 (72.201)
Median	-29.00	-41.00	-32.00
Min, Max	-271.0, 83.0	-329.0, 94.0	-329.0, 94.0
Change from Baseline to Highest Post-baseline Value			
n	35	44	79
Mean (SD)	46.09 (77.886)	60.83 (92.020)	54.30 (85.829)
Median	31.00	48.50	41.00
Min, Max	-183.0, 216.0	-200.0, 310.0	-200.0, 310.0
Change from Baseline to End-of-Study Value			
n	29	43	72
Mean (SD)	-8.89 (71.838)	15.15 (92.150)	5.47 (84.850)
Median	-11.00	13.00	6.00
Min, Max	-198.0, 186.0	-329.0, 253.0	-329.0, 253.0

Source: Listing 16.2.8.2
Notes: [1] Baseline is the last non-missing result prior to the first infusion

Table 14.3.4.5 Hematology Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Hemoglobin (g/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	1 (2.0)	1 (1.2)
Month 3	1 (2.9)	0	1 (1.2)
Month 4	1 (2.9)	0	1 (1.2)
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	1 (2.0)	1 (1.2)
Hematocrit (L/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	1 (2.0)	1 (1.2)
Month 3	1 (2.9)	0	1 (1.2)
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0

Source: Listing 16.2.8.1
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.4.5 Hematology Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Erythrocytes (10^12/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	1 (2.0)	1 (1.2)
Erythrocyte Mean Corpuscular Volume (fL)			
Day 1 Non-PK	0	0	0
Month 1	0	1 (2.0)	1 (1.2)
Month 2	0	1 (2.0)	1 (1.2)
Month 3	0	1 (2.0)	1 (1.2)
Month 4	0	1 (2.0)	1 (1.2)
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	2 (4.1)	2 (2.4)

Source: Listing 16.2.8.1
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.4.5 Hematology Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Leukocytes (10^9/L)			
Day 1 Non-PK	0	0	0
Month 1	0	2 (4.1)	2 (2.4)
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0
Neutrophils (10^9/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0

Source: Listing 16.2.8.1
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.4.5 Hematology Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Lymphocytes (10^9/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0
Monocytes (10^9/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0

Source: Listing 16.2.8.1
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.4.5 Hematology Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Eosinophils (10^9/L)			
Day 1 Non-PK	0	0	0
Month 1	0	1 (2.0)	1 (1.2)
Month 2	0	1 (2.0)	1 (1.2)
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0
Basophils (10^9/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0

Source: Listing 16.2.8.1
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.4.5 Hematology Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Platelets (10^9/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0

Source: Listing 16.2.8.1
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Sodium (mmol/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0
Potassium (mmol/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0

Source: Listing 16.2.8.2
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Chloride (mmol/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0
Blood Urea Nitrogen (umol/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0

Source: Listing 16.2.8.2
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Creatinine (umol/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0
Gamma Glutamyl Transferase (U/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0

Source: Listing 16.2.8.2
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Alkaline Phosphatase (U/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0
Alanine Aminotransferase (U/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0

Source: Listing 16.2.8.2
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Aspartate Aminotransferase (U/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0
Albumin (g/dL)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0

Source: Listing 16.2.8.2
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Bilirubin (umol/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0
Protein (g/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0

Source: Listing 16.2.8.2
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Glucose (mmol/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0
Calcium (mmol/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0

Source: Listing 16.2.8.2
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.4.6 Biochemistry Treatment-Emergent Clinically Significant Abnormal Results
(Safety Population)

Parameter (Unit) Visit	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Urea (mmol/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0
Lactate Dehydrogenase (U/L)			
Day 1 Non-PK	0	0	0
Month 1	0	0	0
Month 2	0	0	0
Month 3	0	0	0
Month 4	0	0	0
Month 5	0	0	0
Month 6	0	0	0
Month 9	0	0	0
End of Study	0	0	0

Source: Listing 16.2.8.2
Notes: [1] Table presents treatment-emergent clinically significant abnormal results as assessed by the investigator. These are those in which the baseline value is normal and post-baseline value is abnormal and clinically significant as assessed by the investigator.
[2] Table presents number and percentage of subjects [n (%)].

Table 14.3.5.2 Vital Signs Treatment-Emergent Potentially Clinically Significant Results
(Safety Population)

Parameter (Unit) Visit/Time Point Criterion	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
Systolic Blood Pressure (mmHg)						
Day 1 CSL627 PK: 1 h Post-infusion						
Low	0		0		0	
High	1	(2.9)	1	(2.0)	2	(2.4)
Day 1 CSL627 PK: 24 h Post-infusion						
Low	0		1	(2.0)	1	(1.2)
High	1	(2.9)	0		1	(1.2)
Day 1 CSL627 PK: 48 h Post-infusion						
Low	1	(2.9)	1	(2.0)	2	(2.4)
High	0		0		0	
Day 1 Non-PK						
Low	1	(2.9)	1	(2.0)	2	(2.4)
High	0		0		0	

Source: Listing 16.2.9.1
Notes: [1] Table presents number and percentage of subjects [(n (%)]

Table 14.3.5.2 Vital Signs Treatment-Emergent Potentially Clinically Significant Results
(Safety Population)

Parameter (Unit) Visit/Time Point Criterion	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Systolic Blood Pressure (mmHg)			
Month 1			
Low	2 (5.7)	5 (10.2)	7 (8.3)
High	3 (8.6)	1 (2.0)	4 (4.8)
Month 2			
Low	1 (2.9)	0	1 (1.2)
High	3 (8.6)	4 (8.2)	7 (8.3)
Month 3			
Low	1 (2.9)	2 (4.1)	3 (3.6)
High	1 (2.9)	1 (2.0)	2 (2.4)
Month 4			
Low	1 (2.9)	2 (4.1)	3 (3.6)
High	1 (2.9)	1 (2.0)	2 (2.4)

Source: Listing 16.2.9.1
Notes: [1] Table presents number and percentage of subjects [(n (%)]

Table 14.3.5.2 Vital Signs Treatment-Emergent Potentially Clinically Significant Results
(Safety Population)

Parameter (Unit) Visit/Time Point Criterion	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
Systolic Blood Pressure (mmHg)						
Month 5						
Low	0		0		0	
High	0		3	(6.1)	3	(3.6)
Month 6						
Low	0		0		0	
High	1	(2.9)	2	(4.1)	3	(3.6)
Month 9						
Low	1	(2.9)	0		1	(1.2)
High	0		0		0	
End of Study						
Low	1	(2.9)	1	(2.0)	2	(2.4)
High	3	(8.6)	2	(4.1)	5	(6.0)

Source: Listing 16.2.9.1
Notes: [1] Table presents number and percentage of subjects [(n (%)]

Table 14.3.5.2 Vital Signs Treatment-Emergent Potentially Clinically Significant Results
(Safety Population)

Parameter (Unit) Visit/Time Point Criterion	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Systolic Blood Pressure (mmHg)			
Anytime post-baseline			
Low	4 (11.4)	10 (20.4)	14 (16.7)
High	11 (31.4)	11 (22.4)	22 (26.2)
Diastolic Blood Pressure (mmHg)			
Day 1 CSL627 PK: 1 h Post-infusion			
Low	0	1 (2.0)	1 (1.2)
High	1 (2.9)	0	1 (1.2)
Day 1 CSL627 PK: 24 h Post-infusion			
Low	0	0	0
High	0	0	0
Day 1 CSL627 PK: 48 h Post-infusion			
Low	0	0	0
High	1 (2.9)	0	1 (1.2)

Notes: [1] Table presents number and percentage of subjects [(n (%)]

Table 14.3.5.2 Vital Signs Treatment-Emergent Potentially Clinically Significant Results
(Safety Population)

Parameter (Unit) Visit/Time Point Criterion	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Diastolic Blood Pressure (mmHg)			
Day 1 Non-PK			
Low	0	0	0
High	1 (2.9)	0	1 (1.2)
Month 1			
Low	0	0	0
High	1 (2.9)	0	1 (1.2)
Month 2			
Low	0	0	0
High	1 (2.9)	1 (2.0)	2 (2.4)
Month 3			
Low	0	0	0
High	1 (2.9)	0	1 (1.2)

Source: Listing 16.2.9.1
Notes: [1] Table presents number and percentage of subjects [(n (%)]

Table 14.3.5.2 Vital Signs Treatment-Emergent Potentially Clinically Significant Results
(Safety Population)

Parameter (Unit) Visit/Time Point Criterion	<6 years (N=35)		>=6 to <12 years (N=49)		Total (N=84)	
Diastolic Blood Pressure (mmHg)						
Month 4						
Low	0		1	(2.0)	1	(1.2)
High	1	(2.9)	0		1	(1.2)
Month 5						
Low	0		0		0	
High	1	(2.9)	1	(2.0)	2	(2.4)
Month 6						
Low	1	(2.9)	0		1	(1.2)
High	0		0		0	
Month 9						
Low	0		0		0	
High	0		0		0	

Source: Listing 16.2.9.1
Notes: [1] Table presents number and percentage of subjects [(n (%)]

Table 14.3.5.2 Vital Signs Treatment-Emergent Potentially Clinically Significant Results
(Safety Population)

Parameter (Unit) Visit/Time Point Criterion	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Diastolic Blood Pressure (mmHg)			
End of Study			
Low	0	2 (4.1)	2 (2.4)
High	2 (5.7)	0	2 (2.4)
Anytime post-baseline			
Low	1 (2.9)	4 (8.2)	5 (6.0)
High	7 (20.0)	2 (4.1)	9 (10.7)
Heart Rate (bpm)			
Day 1 CSL627 PK: 1 h Post-infusion			
Low	0	0	0
High	0	0	0
Day 1 CSL627 PK: 24 h Post-infusion			
Low	0	0	0
High	0	0	0

Notes: [1] Table presents number and percentage of subjects [(n (%)]

Table 14.3.5.2 Vital Signs Treatment-Emergent Potentially Clinically Significant Results
(Safety Population)

Parameter (Unit) Visit/Time Point Criterion	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Heart Rate (bpm)			
Day 1 CSL627 PK: 48 h Post-infusion			
Low	0	0	0
High	0	0	0
Day 1 Non-PK			
Low	0	0	0
High	0	0	0
Month 1			
Low	0	0	0
High	0	1 (2.0)	1 (1.2)
Month 2			
Low	0	0	0
High	0	0	0

Source: Listing 16.2.9.1
Notes: [1] Table presents number and percentage of subjects [(n (%)]

Table 14.3.5.2 Vital Signs Treatment-Emergent Potentially Clinically Significant Results
(Safety Population)

Parameter (Unit) Visit/Time Point Criterion	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Heart Rate (bpm)			
Month 3			
Low	0	0	0
High	0	0	0
Month 4			
Low	0	0	0
High	0	0	0
Month 5			
Low	0	0	0
High	0	0	0
Month 6			
Low	0	0	0
High	0	1 (2.0)	1 (1.2)

Source: Listing 16.2.9.1
Notes: [1] Table presents number and percentage of subjects [(n (%)]

Table 14.3.5.2 Vital Signs Treatment-Emergent Potentially Clinically Significant Results
(Safety Population)

Parameter (Unit) Visit/Time Point Criterion	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Heart Rate (bpm)			
Month 9			
Low	0	0	0
High	0	0	0
End of Study			
Low	0	0	0
High	0	0	0
Anytime post-baseline			
Low	0	0	0
High	0	2 (4.1)	2 (2.4)

Source: Listing 16.2.9.1
Notes: [1] Table presents number and percentage of subjects [(n (%)]

Table 14.3.6 Medical Events of Special Interest
(Safety Population)

	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Any Medical Events of Special Interest	2	(5.7)	2	2	(4.1)	2	4	(4.8)	4
Minor Surgery	2	(5.7)	2	1	(2.0)	1	3	(3.6)	3
Dental caries	1	(2.9)	1				1	(1.2)	1
Device related infection	1	(2.9)	1				1	(1.2)	1
Laceration				1	(2.0)	1	1	(1.2)	1
Hospital admission for less than 24 hours for events not considered as SAEs	0		0	0		0	0		0
Any AE related to CSL627 associated with double or higher dose than prescribed	0		0	0		0	0		0
Positive test result for inhibitors performed at local laboratory	0		0	0		0	0		0
Hypersensitivity Reactions	0		0	1	(2.0)	1	1	(1.2)	1
Hypersensitivity				1	(2.0)	1	1	(1.2)	1
Thrombotic Events	0		0	0		0	0		0

Source: Listing 16.2.7.6
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified of events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.

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2.7.5　参考文献

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略語・略号一覧

略語・略号	略していない表現（英語）	略していない表現（日本語）
λ_z (Lambda z)	Terminal first-order rate constant	終末相消失速度定数
ABR	Annualized bleeding rate	年間出血回数
ADA	Anti-drug antibody	抗薬物抗体
AE	Adverse event	有害事象
ALT	Alanine aminotransferase	アラニンアミノトランスフェラーゼ
AsBR	Annualized spontaneous bleeding rate	年換算の自然出血回数
AST	Aspartate aminotransferase	アスパラギン酸アミノトランスフェラーゼ
AUC	Area under the activity / concentration curve	活性／濃度曲線下面積
AUC_{0-t}	Area under the activity / concentration curve to the last sample with quantifiable drug concentration	定量化可能な最終検体採取時刻までの活性／濃度曲線下面積
$AUC_{0-\infty}$	Area under the activity / concentration curve extrapolated to infinity	無限大時間まで外挿した活性／濃度曲線下面積
AUMC	Area under the first moment versus time curve	血中濃度時間曲線の 1 次モーメント下面積
$AUMC_{0-\infty}$	Area under the first moment versus time curve extrapolated to infinity	0 時間から無限時間までの血中濃度時間曲線の 1 次モーメント下面積
BMI	Body mass index	体格指数
BU	Bethesda Units	ベセスダ単位
CHO	Chinese hamster ovary	チャイニーズハムスター卵巣
ChS	Chromogenic substrate (assay)	発色合成基質法
CI	Confidence interval	信頼区間
CL	Clearance	クリアランス
C_{max}	Observed maximum plasma concentration	最高血漿中濃度
CSR	Clinical Study Report	治験総括報告書
CT	Computerized tomography	コンピュータ断層（撮影）
CV	Coefficient of variation	変動係数
CV%	Percent coefficient of variation	変動係数%
ED	Exposure day	投与日数
FVIII	Factor VIII	血液凝固第 VIII 因子
HIV	Human immunodeficiency virus	ヒト免疫不全ウイルス
INN	International nonproprietary name	（医薬品）国際一般名称
IR	Incremental recovery	回収率
IU	International Units	国際単位
IV	Intravenous(ly)	静脈内
LLOQ	Lower limit of quantification	定量下限
MC	Multicenter	多施設共同
MedDRA	Medical Dictionary for Regulatory	ICH 国際医薬用語集

略語・略号	略していない表現（英語）	略していない表現（日本語）
	Activities	
MRT	Mean residence time	平均滞留時間
N/A	Not applicable	該当せず
OL	Open-label	非盲検
OS	One-stage clotting (assay)	凝固一段法
PK	Pharmacokinetic(s)	薬物動態
PP	Per protocol	治験実施計画書に適合した
PT	Preferred Term	基本語
Q1	First quartile	第 1 四分位
Q3	Third quartile	第 3 四分位
rFVIII	Recombinant coagulation factor VIII	遺伝子組換え血液凝固第 VIII 因子
rVIII-SingleChain	Recombinant single-chain factor VIII (CSL627)	遺伝子組換え単鎖血液凝固第 VIII 因子（CSL627）
SAE	Serious adverse event	重篤な有害事象
SD	Standard deviation	標準偏差
SOC	System Organ Class	器官別大分類
Study 1001	Study CSL627_1001 (adolescent/adult pivotal study)	CSL627-1001 試験（1001 試験）
Study 3002	Study CSL627_3002 (pediatric pivotal study)	CSL627-3002 試験（3002 試験）
Study 3001	Study CSL627_3001 (extension study to Studies 1001 and 3002)	CSL627-3001 試験（3001 試験）
TEAE	Treatment-emergent adverse event	治験治療下で発現した有害事象
TESAE	Treatment-emergent serious adverse event	治験治療下で発現した重篤な有害事象
t_{max}	Time to C_{max}	最高血漿中濃度までの時間
$t_{1/2}$	Half-life	半減期
V_{ss}	Volume of distribution at steady-state	定常状態での分布容積
V_z	Volume of distribution at terminal phase	終末期の分布容積
WFH	World Federation of Hemophilia	世界血友病連盟

2.7.6　個々の試験のまとめ

本項では、評価資料とした CSL627_1001 試験（1001 試験）及び CSL627_3002 試験（3002 試験）について、臨床試験一覧表と個々の試験の概要を記載した。

試験の有害事象（Adverse event：AE）名は、治験総括報告書の作成に用いた ICH 国際医薬用語集（Medical dictionary for regulatory activities：MedDRA）（バージョンは試験ごとに規定）を MedDRA/J Ver.12.0 で和訳し表記した。

全臨床試験一覧表

試験番号	試験の種類	試験の主要目的	試験デザイン／対照の種類	治験薬／レジメン／投与経路	被験者数	対象	投与期間	進行状況／報告書の種類	添付資料番号
CSL627_1001	PK、有効性、安全性	主試験： 本剤の PK プロファイルの特徴を明らかにする。 出血エピソードの抑制及び治療における有効性を示す。 オンデマンド療法に対する定期的な投与の有効性を示す。 インヒビター産生率を調べる。 外科的 substudy： 外科手術時の補充療法における本剤の有効性を示す。	第 I／III 相、プロスペクティブ、MC、OL、3 部構成（青年／成人を対象としたピボタル試験）	本剤、IV Part 1 PK（クロスオーバー）： ルリオクトコグアルファ、IV、50 IU/kg 単回投与 本剤、IV、50 IU/kg 単回投与 Part 2 及び 3（50 ED 以上に達するまで投与）： *オンデマンド療法*: 組入れ前に同じ種類の出血エピソードに使用していた FVIII 製剤と同程度の用量で治験責任医師の裁量で行う。 *定期的な投与*： 20～40 IU/kg を隔日、又は 20～50 IU/kg を週 2～3 回投与、若しくは治験責任医師が判断した用量、頻度で投与 *外科的 substudy*： FVIII 活性が WFH ガイドラインの推奨レベルに到達し、維持できるように手術の種類及び被験者の臨床状況に基づき個別に用量を決定する。 Part 3 PK 評価： 初回及び反復 PK 評価のため本剤（IV）50 IU/kg 単回投与	グローバル患者集団：175 名（日本人患者集団[a]：10 名）	血友病 A FVIII 活性 1%未満：治療歴のある患者	平均（SD）：8.5（5.37）箇月（実際） 投与日数中央値：64 ED	完了 CSR 最終版	5.3.5.1 項

試験番号	試験の種類	試験の主要目的	試験デザイン／対照の種類	治験薬／レジメン／投与経路	被験者数	対象	投与期間	進行状況／報告書の種類	添付資料番号
CSL627_3002[b]	PK、有効性、安全性	治験責任医師による 4 点評価スケールに基づき、大出血及び小出血エピソードの治療における本剤の有効性を評価する。	第 III 相、プロスペクティブ、MC、OL（小児試験）	本剤、IV 単回投与 PK 評価： 本剤、IV、50 IU/kg 単回投与 投与期間（50 ED 以上に達するまで投与）： *オンデマンド療法*： 組入れ前に同じ種類の出血エピソードに使用していた FVIII 製剤と同程度の用量で治験責任医師の裁量で行う。出血エピソードの治療における望ましい FVIII レベルは、WFH が推奨する最小用量 15 IU/kg（WFH, 2012）に基づく。 *定期的な投与*： 15～50 IU/kg を隔日、又は週 2～3 回投与、若しくは治験責任医師が判断した用量、頻度で投与	84 名[b]	血友病 A FVIII 活性 1%未満：治療歴のある患者	平均値（SD）：6.0（2.01）箇月 （実際）投与日数中央値：58.5 ED	完了 CSR 最終版	5.3.5.2 項

略語：CSR、治験総括報告書；ED、投与日数；FVIII、血液凝固第 VIII 因子；IU、国際単位：IV、静脈内；MC、多施設共同； OL、非盲検；PK、薬物動態；本剤、遺伝子組換え単鎖血液凝固第 VIII 因子；SD、標準偏差；WFH、世界血友病連盟

[a] 1001 試験では、日本人被験者は Part 3 にのみ参加し、外科的 substudy に参加した日本人被験者はいなかった。

[b] 3002 試験に参加した日本人被験者はいなかった。

引用：1001 試験 CSR；3002 試験 CSR

2.7.6.1　第 I/III 相試験（試験番号　CSL627_1001　評価資料：5.3.1.1.1）

標題：血友病 A 患者を対象とし、遺伝子組換え血液凝固第 VIII 因子製剤（rFVIII；JAN：ルリオクトコグアルファ）との比較において遺伝子組換え単鎖血液凝固第 VIII 因子（rFVIII）の安全性、有効性及び薬物動態を検討し、さらに薬物動態を再検討し、安全性及び有効性を検討する、多施設共同、非盲検、クロスオーバー比較、第 I/III 相試験

（1）　試験方法

試験方法の概要を以下に示す。

項目	内容
治験調整医師	Prof. Dr. med. Ingrid Pabinger, Division of Hematology and Hemostaseology, Department of Internal Medicine I, Medical University Vienna
実施国及び実施施設数	米国、欧州、日本（8 施設）、その他の地域の 53 施設
公表文献	• Klamroth R, Simpson M, von Depka-Prondzinski M, et al. Comparative pharmacokinetics of rVIII-SingleChain and octocog alfa (Advate®) in patients with severe haemophilia A. Haemophilia. 2016:1-9 [Klamroth et al, 2016] • Mahlangu J, Kuliczkowski K, Karim FA, et al. Efficacy and safety of rVIII-SingleChain: results of a phase 1/3 multicenter clinical trial in severe hemophilia A. Blood. 2016;128(5):630-7 [Mahlangu et al, 2016]
実施期間	20[redacted]年[redacted]月[redacted]5 日～20[redacted]年[redacted]月[redacted]日
開発のフェーズ	第 I/III 相
試験の目的	主要目的： - インヒビター産生率の特性を明らかにする - 遺伝子組換え単鎖血液凝固第 VIII 因子 rVIII（Recombinant single-chain factor VIII：rVIII-SingleChain）（以下、本剤）の薬物動態［Pharmacokinetic(s)：PK］プロファイルを明らかにする - 出血イベントの抑制及び治療の有効性を立証する - オンデマンド療法に優る定期的な投与の有効性を立証する - 外科手術時の補充療法における本剤の有効性を立証する 副次的目的： - 本剤の安全性プロファイルを明らかにする - 本剤の PK をルリオクトコグアルファと比較する
試験デザイン	本治験は、本剤の PK、有効性、及び安全性を評価することを目的とし、3 つのパートに分けて行われた非盲検試験であった。治験の目的は 1）出血エピソードのコントロールと抑制（オンデマンド療法）、2）出血エピソードの抑制と頻度減少のための定期的な投与、3）重度血友病 A 患者を対象とした周術期の

	補充療法（外科手術時の補充療法）を調査することであった。 主要試験は、スクリーニング期間とその後の 3 つのパートから構成された（図 2.7.6.1-1）。 **Part 1**： 適格被験者は、18 歳以上の男性で、血液凝固第 VIII 因子（Factor VIII：FVIII）補充療法を受けていない時の FVIII 活性が 1%未満の重度血友病 A 患者であった。本パートでは、ルリオクトコグアルファと本剤の 1 シークエンス・クロスオーバー比較試験を行った。被験者は、ルリオクトコグアルファ 50 国際単位（International Units：IU）/kg の単回静脈内［Intravenous(ly)：IV］投与を受け、その後 4 日間の休薬期間を経て、同用量の本剤投与を受けた。 本パートでは、PK 評価可能な最終被験者から最終の PK サンプル採取を完了後、PK 及び安全性データの中間解析を行った。Part 1 の PK データから［世界血友病連盟（World Federation of Hemophilia：WFH）ガイドラインに基づく］Part 3 の用量選択及び投与スケジュールを求めることとした。 **Part 2**： 本パートでは、Part 1 からの本剤の継続投与について、有効性及び安全性を評価した。最初の被験者 5 名は本剤の止血効果を確認するためオンデマンド療法を受け、それ以降の被験者は、被験者の希望及び治験責任医師の判断に基づき、オンデマンド療法又は定期的な投与のいずれかを受けた。 **Part 3**： 適格被験者は、12～65 歳の男性で、FVIII 補充療法を受けていない時の FVIII 活性が 1%未満である重度血友病 A 患者とした。本パートでは、新規被験者を対象に本剤の継続投与の安全性及び有効性を評価し、少なくとも 13 名で PK 再評価を行った。日本の治験実施施設で登録された全被験者が PK 解析に参加した。PK 評価後、被験者は 50 投与日数（Exposure Day：ED）以上の間、オンデマンド療法又は定期的な投与を受けた。 **外科的 substudy**： 全被験者は、Part 3 が開始された後に、外科的 substudy にも適格とされた。少なくとも合計で 10 回の緊急又は待機的な大手術を受けることが予想される 5 名以上の被験者を登録することとした。本剤の用法・用量は、手術の種類及び被験者の臨床状態に基づき個別に設定した。WFH ガイドライン（WFH, 2012）が推奨する FVIII 活性レベルに到達、維持されるように、手術前、手術中、手術後の用法・用量を設定した。 Part 2 及び 3 では、治験責任医師の判断による投与量の調節を認めたが、被験

	者がレジメン及び療法群を変更することは禁じた。 有効性及び安全性評価は、治験実施施設にて、6 箇月目まで月に 1 回行い、その後試験終了まで 3 箇月に 1 回行った。
被験者数	被験者集団全体：全被験者 175 名について、同意取得後、登録した。そのうち 174 名（Part 1 で 27 名、そのうちの 26 名が Part 2 まで投与継続し、Part 3 で新たに 147 名が登録された）が本剤による治療を受けた。外科的 substudy に参加したのは 13 名であった。 日本人被験者集団：日本人被験者 10 名について、同意取得後、登録し、本剤による治療を行った（Part 3 のみ）。外科的 substudy に参加した日本人被験者はいなかった。
対象	重度血友病 A 患者
選択基準	18～65 歳（Part 1 及び 2）及び 12～65 歳（Part 3）で、重度の血友病 A（FVIII 活性が 1%未満）であることが医療記録に記載されており、FVIII 製剤の ED が 150 日を超えている男性被験者を組入れ可能とした。
除外基準	- 第 VIII 因子に対するインヒビターの既往歴のある、又は第 VIII 因子に対するインヒビターを現在有している患者 - 第 VIII 因子に対するインヒビターの家族歴（親・子・兄弟）のある患者 - 本剤の初回投与の前 30 日以内に何らかの治験薬を使用した患者 - 本剤又は対照薬の投与の前 30 日以内にクリオプレシピテート、全血、又は血漿の投与を受けた患者 - 第 VIII 因子製剤又はハムスタータンパクに対する既知の過敏症（アレルギー反応又はアナフィラキシー）を有する患者 - 先天性第 VIII 因子欠乏症以外の既知の先天性又は後天性の血液凝固障害を有する患者 - スクリーニング時に血小板数が 100,000/μL 未満の患者 - 医療記録又は入手可能なデータが測定後 1 年以上経過したものである場合にはスクリーニング時の CD4 値が 200/mm^3 未満のヒト免疫不全ウイルス（Human immunodeficiency virus：HIV）陽性患者（HIV 陽性患者は、治験責任医師の判断により本治験に参加すること及び抗ウイルス療法を受けることが認められる） - 免疫グロブリン等の免疫調節薬の IV 投与、又は慢性的に全身性コルチコステロイドの投与を受けている患者 - スクリーニング時に血清アスパラギン酸アミノトランスフェラーゼ（Aspartate aminotransferase：AST）値又は血清アラニンアミノトラン

	スフェラーゼ（Alanine aminotransferase：ALT）値が基準値上限の 5 倍を超える患者 - スクリーニング時に血清クレアチニン値が基準値上限の 2 倍を超える患者 - Day 1 の前 3 箇月以内に深部静脈血栓症、脳卒中、肺塞栓症、心筋梗塞及び動脈塞栓を含む血栓症の徴候のある患者 - Day 1 の前 3 箇月以内に生命にかかわる出血エピソードが発現した、又は大手術あるいは整形外科手術を受けた患者
被験薬	本剤は、バイアル中に凍結乾燥粉末として供給された（力価は 250、500、1000、2000 及び 3000 IU/バイアル）。投与法は、IV 投与であった。用量は、投与直前の被験者の体重及びバイアルに記載された実際の FVIII の力価（単位）に基づき決定した。
投与方法	**Part 1**： Day 1 にルリオクトコグアルファ 50 IU/kg を IV 単回投与し、4 日間の休薬期間を経て本剤 50 IU/kg を IV 単回投与した。 **Part 2**： 定期的な投与：治験責任医師の判断により 20～40 IU/kg を隔日、20～50 IU/kg を週 2～3 回、又は他の用量及び投与間隔で本剤を投与した。 オンデマンド療法:治験責任医師の判断により本治験登録前に同種の出血イベントに対し使用していた FVIII 製剤と同様の用量の本剤を投与した。 **Part 3**： 初回 PK 評価及び PK 再評価（被験者の部分集団）：初回 PK 評価時に、本剤 50 IU/kg を単回投与し、それから 3～6 箇月後の PK 再評価時に、本剤 50 IU/kg を単回投与した。 オンデマンド療法又は定期的な投与:Part 2 に上述した用量で本剤を投与した。 **手術時の投与**： 手術期間の本剤の用法・用量は、WFH が推奨するように、手術の種類及び被験者の臨床状態を考慮して決定した。
試験期間	主要試験のデザインには、28 日間のスクリーニング期間、Part 1 の PK 評価期間及びインヒビター産生率の解析に必要とされる 104 名以上を対象としたオンデマンド療法又は定期的な投与での 50 ED 以上が含まれた。Part 2 及び 3 に登録された被験者は、本剤の投与を継続投与試験が開始されるまで継続可能であり、必要であれば 24 箇月まで投与を延長することができた。試験が主要安全性評価項目の基準（104 名で 50 ED）を満たした後、被験者は ED に関係なく継続投与試験に参加可能であった。

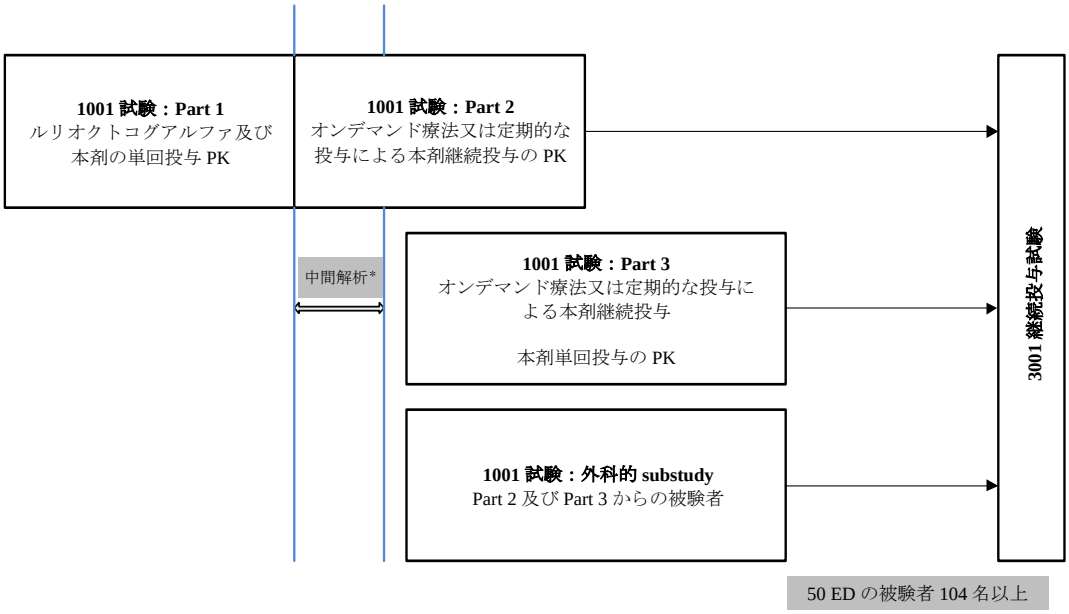
	外科的 substudy での実薬投与期間は 1～14 日であった（外科手術の種類及び治験実施施設での標準治療による）。
対照薬 （Part 1 のみ）	遺伝子組換え血液凝固第 VIII 因子（Recombinant coagulation factor VIII : rFVIII）製剤であるルリオクトコグアルファを IV 投与した。用量は、投与前の被験者の体重及び米国の添付文書（実際の力価）に従い 50 IU/kg とした。
有効性評価	主要評価項目： オンデマンド療法：止血に関する有効性について、4 点スケールによる評価で治験責任医師の総合的臨床評価が「優」又は「良」である場合に治療が成功したと定義したときの、出血エピソードの治療成功率。 定期的な投与：年換算の自然出血回数（Annualized spontaneous bleeding rate：AsBR）。 外科的 substudy：手術時の治療に関する有効性について、4 点スケールによる評価で治験責任医師の総合的臨床評価が「優」又は「良」である場合に治療が成功したと定義したときの、周術期外科的 substudy 中の治療成功率。 副次評価項目： 止血を達成するために 1、2、3、又は 4 回以上の投与を要する出血エピソードのそれぞれの割合並びに総出血エピソード､外傷性出血エピソード及び関節出血エピソードの年間出血回数（Annualized bleeding rate：ABR）。
安全性評価	主要評価項目： FVIII に対するインヒビターの産生率。初回投与時から試験終了来院まで評価した。インヒビター産生は、中央測定機関での再検査により同定、確認されたすべてのインヒビターの産生［0.6 ベセスダ単位（Bethesda Units：BU）/mL 以上］と定義した。 副次評価項目： 有害事象、チャイニーズハムスター卵巣（Chinese hamster ovary：CHO）細胞由来タンパク質に対する抗体、非阻害抗薬物抗体（Anti-drug antibody：ADA）、臨床検査値、バイタルサイン、血栓症の臨床徴候、及び局所忍容性。
臨床薬理学的評価	副次評価項目： 検証済みの発色合成基質法（Chromogenic substrate assay：ChS 法）及び凝固一段法（One-stage clotting assay：OS 法）により定量した各被験者の血漿中 FVIII 濃度並びに Part 1 で収集した本剤及びルリオクトコグアルファの以下のパラメーター - 回収率（Incremental recovery：IR） - 定量化可能な最終検体採取時刻までの活性／濃度曲線下面積［Area under the activity / concentration curve (AUC) to the last sample with

	quantifiable drug concentration：AUC_{0-t}］ - 無限大時間まで外挿した活性／濃度曲線下面積（AUC extrapolated to infinity：$AUC_{0-\infty}$） - 最高血漿中濃度（Observed maximum plasma concentration：C_{max}）、 - C_{max} までの時間（Time to C_{max}：t_{max}） - 消失速度定数 - 半減期（Half-life：$t_{1/2}$） - 終末相消失速度定数（Terminal first-order rate constant：λz） - 0 時間から無限時間までの血中濃度時間曲線の 1 次モーメント下面積（Area under the first moment versus time curve (AUMC) extrapolated to infinity：$AUMC_{0-\infty}$） - 平均滞留時間（Mean residence time：MRT） - クリアランス（Clearance：CL） - 定常状態での分布容積（Volume of distribution at steady-state：V_{ss}）
統計手法	有効性の解析： <u>出血エピソードのコントロールと抑制</u> 出血エピソード治療の止血効果について､治験責任医師による総合的臨床評価を全体及び治療群別に要約した。治療が成功した出血エピソード（4 点スケールによる評価で治験責任医師の総合的臨床評価が「優」又は「良」）の割合を 95%信頼区間（Confidence interval：CI）とともに報告した［有効性解析集団及び治験実施計画書に適合した（Per protocol：PP）解析集団］。被験者内相関を説明するために､一般化推定方程式及び無相関構造を用いて測定を繰り返した一般化線形モデル（切片項のみを含む）を用い（PROC GENMOD）､成功率の 95% CI を算出した。一般化線形モデルでは、二項分布を想定し、ロジットリンク関数を用いた。95% CI の下限が 70%を超えた場合、治療成功とした。臨床的関連性の面から、一般的に、出血治療の成功率は約 86%になると予想された。 欠損データに関する推定結果の頑健性を評価するために､止血効果について 2 つの条件、a）欠損した治験責任医師による評価を分母から除外する条件、b）欠損した治験責任医師による評価を治療成功としてカウントする条件で感度分析を行った。 止血を達成するために本剤の投与を 1､2､3 又は 4 回以上必要とした出血エピソードの数及び割合を頻度数及びパーセンテージで要約した｡これらのデータについて、統計的推測は行わなかった。 <u>定期的な投与</u>

	主要有効性評価項目は各被験者の AsBR とし、AsBR の算出には次の式を用いた。 365.25×自然出血エピソード / 治療日数 AsBR は治療群（オンデマンド療法群、定期的投与群）別に記述統計量で要約した。本治験では、主に定期的投与群とオンデマンド療法群を比較した。AsBR について 2 群間差がないということを帰無仮説とし、Poisson 回帰を基に検定を行った。2 群の AsBR の比（定期的投与群 / オンデマンド療法群）は 95% CI とともに示した。ここでは、SAS の GENMOD 手法を用いた一般化線形モデルを利用した。Poisson 分布には対数リンク関数を用い、log time offset を指定した。 治療した総出血エピソード（自然、外傷性、又は原因不明の）を基にした ABR について、主要解析と同じ解析を行った。 また、1001 試験（青年／成人ピボタル試験）の定期的投与群の AsBR 及び ABR を、Biostate（CSL ベーリング社が海外で販売している FVIII 製剤）の CSLCT-BIO-07-47 試験（clinicaltrials.gov identifier: NCT00879541；試験結果は Skotnicki et al., 2016 として公表されている）のオンデマンド療法/補充療法群のヒストリカルコントロールと比較した。 定期的な投与期間中の ABR 及び本剤の投与量は、記述統計量で（全体又はレジメンごと）要約した。 <u>外科的 substudy</u> 外科的 substudy の有効性の要約及び解析の対象は、手術時の有効性解析集団（簡単なあるいは大きな外科手術で本剤を 1 回以上投与された全被験者）であった。止血効果の 4 点スケール評価（優、良、可、不可/反応なし）による治験責任医師の総合的臨床評価を外科手術時の出血抑制評価の主要解析とした。「優」又は「良」を成功とした場合の成功率を表示した。外科手術時の主要有効性評価項目での成功の定義は、「優」又は「良」で評価された成功率が 70%以上であることとした。 他の評価項目（予想及び推定失血量、予想及び実際の輸血量、並びにヘモグロビンレベルの変化）は、記述統計量で要約した。 PK 解析： Part 1 及び 3 の PK 解析集団（PK 評価のために本剤を 1 回以上投与された被験者で PK プロファイルを評価するのに十分な分析可能 PK サンプル数を得た被験者）は、本剤（Part 1 及び 3）及びルリオクトコグアルファ（Part 1 のみ）を PK 評価の対象とした。

	FVIII 活性と PK パラメーター（ベースライン補正あり及び補正なし）について、記述統計量［n、平均値、標準偏差（Standard deviation：SD）、変動係数（Coefficient of variation：CV）%、中央値、最小値、及び最大値］及び幾何平均を治療群別、アッセイ法別、時点別（t_{max} は n、中央値、最小値及び最大値のみ）に示した。 グラフは FVIII 活性レベルを示した。平均値（SD）及び各被験者の活性プロファイルの経時的変化をプロット表示した。初回投与後及び反復投与後の各被験者の本剤 PK プロファイルは、プロファイルの違いを視覚的に評価するために、プロットを重ねて表示した。 安全性解析： FVIII に対するインヒビター産生率評価にあたり、分子を「本剤の ED に関わらずインヒビターを発現した全被験者」とし、分母を「50 ED 以上の被験者 + ED が 50 未満だがインヒビターを発現している被験者」とした。インヒビター産生率の正確な両側 95% CI を算出した。インヒビターが検出されない場合は、片側 97.5% CI 上限を算出した。SAS の FREQ procedure を用いて Clopper-Pearson CI を求めた。CI 上限が許容上限の 6.8%未満であれば成功とした。追加解析として、安全性解析集団［試験期間中、本剤を 1 用量（又は一部用量）以上投与された全被験者］でのインヒビター産生率及び 95% CI も示した。表示の際、分子を「インヒビターが発現した全被験者」、分母を「安全性解析集団の全被験者」とした。 1 件以上の AE が発現した被験者数及び被験者の割合、並びに AE 数は、器官別大分類（System Organ Class：SOC）及び基本語（Preferred Term：PT）別に示した。また、治験治療下で発現した AE（Treatment-emergent adverse event：TEAE）の概要には、治験薬と関連がある AE、最大重症度別 AE、死亡に至った AE、重篤な AE（Serious adverse event：SAE）、治験薬と関連がある SAE 及び試験中止に至った AE を示した。 被験者による局所忍容性の評価及び治験責任医師による紅斑の評価は、本剤の全投与回数を基にした頻度数及びパーセンテージで要約した。 臨床検査値、非阻害 ADA 及び CHO 細胞由来タンパク質、並びにバイタルサインの結果を要約した。治験治療下での臨床検査値異常又は臨床的に問題がある可能性のあるバイタルサイン値が認められた被験者の数と割合を表記した。 外科的 substudy での安全性について、主要試験と同様に要約した。

図 2.7.6.1-1　1001 試験：試験デザインの概要



略語：ED、投与日数；PK、薬物動態；WFH、世界血友病連盟
*中間解析は、Part 1 で PK 評価可能な最終被験者から最後のサンプルを採取した後に行った。Part 1 の PK データから（WFH ガイドラインに基づく）Part 3 の用量選択及び投与スケジュールを決定した。
引用：1001 試験 CSR 図 9-1

（2） 試験成績

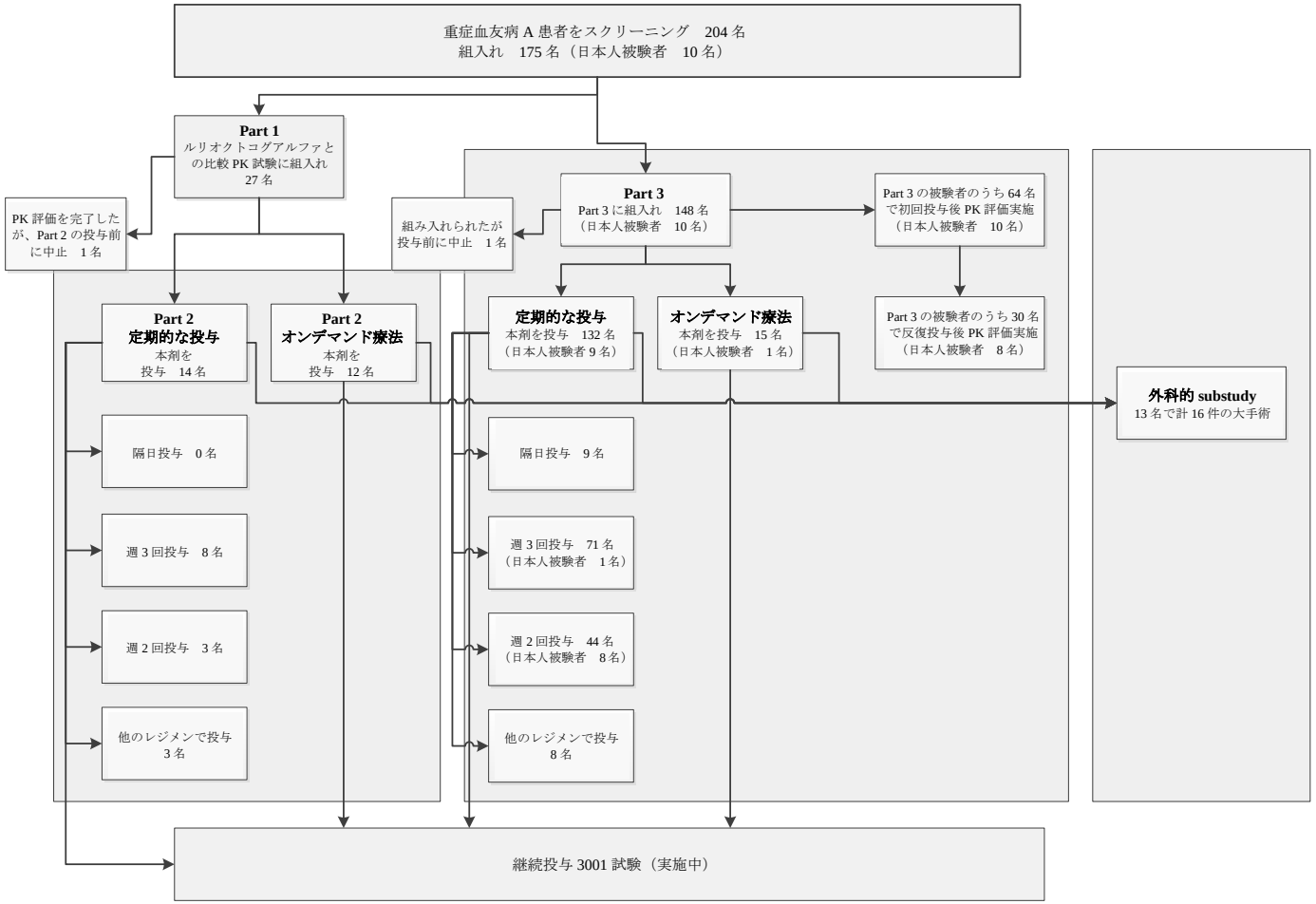
1） 被験者の内訳

合計 175 名を登録し、そのうち治療を受けた 174 名を安全性解析集団とした。有効性解析集団は 173 名であった（146 名を定期的投与群に、27 名をオンデマンド療法群に割り付けた）。有効性解析集団 173 名中 12 名（各群 6 名）が試験を中止したため、試験を完了したのは 161 名であった。

日本人被験者 10 名が Part 3 に参加し、全員試験を完了した。

被験者の内訳を図 2.7.6.1-2 及び表 2.7.6.1-1 に示す。

図 2.7.6.1-2　1001 試験：被験者の内訳



略語：PK、薬物動態；本剤、遺伝子組換え単鎖血液凝固第 VIII 因子
注：
括弧内は日本人被験者数を示す。
引用：1001 試験 CSR 図 10-1、表 14.2.16.22.1、5.3.5.1 項 表 14.1.1.2J、表 14.1.10J

表 2.7.6.1-1　1001 試験：被験者の内訳（有効性解析集団）

	オンデマンド療法 (N = 27)	定期的な投与 (N = 146)	全体 (N = 173)
有効性解析集団	27	146	173
治験完了	21 (77.8)	140 (95.9)	161 (93.1)
治験中止	6 (22.2)	6 (4.1)	12 (6.9)
中止理由			
同意撤回	1 (3.7)	6 (4.1)	7 (4.0)
その他	4 (14.8)	0	4 (2.3)
医師の判断	1 (3.7)	0	1 (0.6)

略語：N、総被験者数
注：
[1] 被験者の数及びパーセント[n (%)]を表す。
[2] パーセントは有効性解析集団の被験者数を基に算出した。
引用：1001 試験 CSR 表 14.1.2.2

治験実施計画書からの重大な逸脱：

17 名（日本人 1 名を含む）は、規定用量又は規定の定期的な投与の不遵守が認められたため、PP 解析集団から除外した。定期的な投与の遵守とは、定期的な投与スケジュールの 80～120%で実施された場合とした。規定用量の遵守率とは、投与量が処方量の±10%（定期的な投与及びオンデマンド療法）であった投与の割合とした。規定用量の遵守率が 80～100%であれば、用量について遵守したとみなした（表 2.7.6.1-2）。

表 2.7.6.1-2　1001 試験：PP 解析集団からの除外（有効性解析集団）

	被験者数（%）	
	全体 (N = 173)	日本人 (N = 10)
PP 解析集団からの除外	17 (9.8)	1 (10%)
PP 解析集団からの除外理由		
規定用量の不遵守	9 (5.2)	1 (10%)
規定の定期的な投与の不遵守	8 (4.6)	0

略語：N、総被験者数；PP、治験実施計画書に適合した
注：被験者の数及びパーセント[n (%)]を表す。
引用：1001 試験 CSR 表 14.1.3.4、一覧表 16.2.3

2）解析対象集団の内訳

安全性解析集団は 174 名で、そのうちの 173 名が有効性解析集団（定期的投与群 146 名、オンデマンド療法群 27 名）、156 名が PP 解析集団、27 名が Part 1 の PK 解析集団、64 名が Part 3 の PK 解析集団、13 名が外科手術時補充療法解析集団であった。

10 名の日本人被験者は全員が有効性、安全性、及び Part 3 の PK 解析集団に含まれた。Part 1 の PK 解析集団又は外科手術時補充療法解析集団に日本人被験者は含まれなかった（表 2.7.6.1-3）。

表 2.7.6.1-3　1001 試験：解析対象集団（全被験者）

	被験者数	
	全体	日本人
安全性解析集団	174	10
有効性解析集団	173	10
定期的な投与	146	9
オンデマンド療法	27	1
PP 解析集団	156	9
PK 解析集団		
PK Part 1	27	0
PK Part 3	64	10
外科手術時補充療法解析集団（(外科的 substudy）	13	0

略語：PK、薬物動態；PP、治験実施計画書に適合した
引用：1001 試験 CSR 表 14.1.1.2、5.3.5.1 項 表 14.1.1.2J

3）人口統計学的及び他の基準値の特性

全被験者が男性であった。有効性解析集団全体で、被験者の大部分は白人（72.4%）で、非ヒスパニック系又は非ラテン系（92.5%）であった。被験者の平均年齢は 31.3 歳（範囲：12～64 歳）であった。12 歳以上 18 歳未満の被験者は 14 名であり、その全員が定期的な投与に登録された。

日本人の安全性解析集団（10 名）では、被験者の平均年齢は 28.3 歳（範囲：12～46 歳）であった。12 歳以上 18 歳未満の被験者は 2 名であり、2 名とも定期的な投与に登録された。

病歴と手術歴に関し、日本人被験者集団と被験者集団全体に重要な違いは認められなかった（2.7.3 項 表 2.7.3.4）。

表 2.7.6.1-4　1001 試験：人口統計学的及び患者背景の特性（安全性解析集団）

	全体 (N = 174)	日本人 (N = 10)
年齢 (歳)		
被験者数	174	10
平均値 (SD)	31.3 (11.77)	28.3 (11.62)
中央値	29.5	31.5
最小値、最大値	12, 64	12, 46
年齢群 [n (%)]		
12 歳以上 18 歳未満	14 (8.0)	2 (20.0)
18 歳以上 65 歳以下	160 (92.0)	8 (80.0)
体重 (kg)		
平均値 (SD)	74.6 (16.99)	57.7 (10.83)
中央値	75.0	59.3
最小値、最大値	27, 120	38, 74
BMI (kg/m^2)		
平均値 (SD)	24.3 (4.70)	20.9 (3.22)
中央値	24.5	20.4
最小値、最大値	13, 39	15, 25
BMI 分類 [n (%)]		
30 kg/m^2 未満	156 (89.7)	10 (100.0)
30 kg/m^2 以上	18 (10.3)	0
人種 [n (%)]		
アジア人	31 (17.8)	10 (100.0)
黒人又はアフリカ系アメリカ人	14 (8.0)	0
白人	126 (72.4)	0
その他	3 (1.7)	0
民族 [n (%)]		
ヒスパニック系又はラテン系	12 (6.9)	0
非ヒスパニック系又は非ラテン系	161 (92.5)	10 (100.0)
報告なし	1 (0.6)	0
地域 [n (%)]		
米国	22 (12.6)	0
日本	10 (5.7)	10 (100.0)
欧州	86 (49.4)	0
その他の地域	56 (32.2)	0

略語：BMI、体格指数；N、総被験者数（全体又は日本人）；n、当該カテゴリーの被験者数；SD、標準偏差

注：

[1] BMI は次式により求めた。スクリーニング時の BMI = スクリーニング時の体重（kg） / [スクリーニング時の身長 (m)]^2

[2] パーセントは各解析対象集団の被験者数を基に算出した。

引用：1001 試験 CSR 表 14.1.5.2、5.3.5.1 項、表 14.1.5.1J

4） 治験薬の投与状況

安全性解析集団全体の ED の平均値（SD）は 82.2（61.35）ED であった。50 ED 以上であった被験者は 120 名（69.0%）であり、そのうちの 52 名（29.9%）は 100 ED 以上であった。

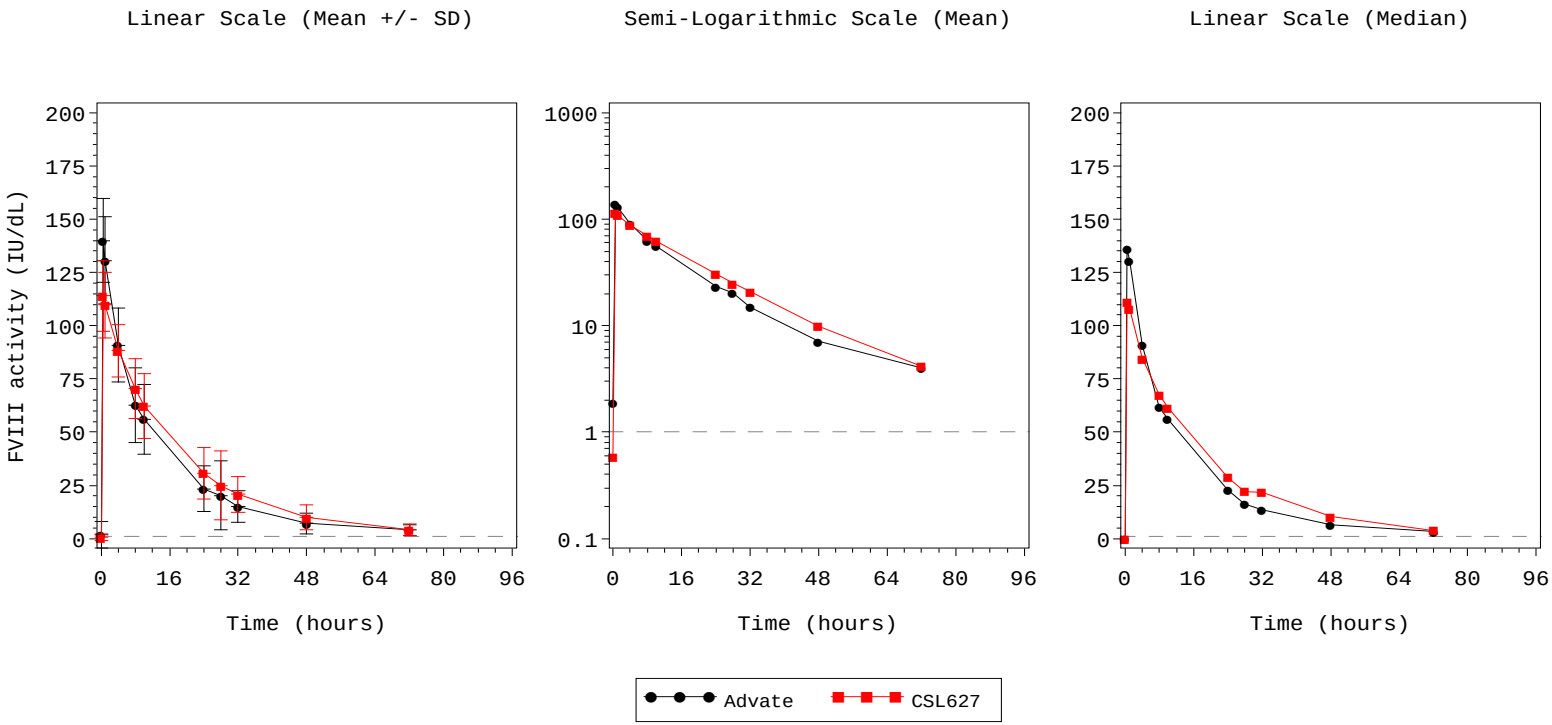
日本人の安全性解析集団の ED の平均値（SD）は 83.2（31.89）ED であった。50 ED 以上であった被験者は 8 名（80.0%）であり、そのうちの 3 名（30.0%）は 100 ED 以上であった。

5） 臨床薬理学的評価の結果

Part 1（本剤及びルリオクトコグアルファの 50 IU/kg 単回投与の PK 比較）：

ChS 法で測定した場合、本剤及びルリオクトコグアルファ投与後のベースライン補正なしでの FVIII 活性は同様であると考えられる（図 2.7.6.1-3）。

図 2.7.6.1-3　1001 試験：本剤及びルリオクトコグアルファ単回投与後（50 IU/kg ± 10%）の FVIII 活性［平均値（SD）及び中央値、ベースライン補正なし］ー時間プロファイル – Part 1（ChS 法、PK 解析集団全体）



略語：ChS、発色合成基質法；FVIII、血液凝固第 VIII 因子；IU、国際単位；OS、凝固一段法；PK、薬物動態；SD、標準偏差
注：
[1] Advate = ルリオクトコグアルファ；CSL627 = rVIII-SingleChain
[2] 定量下限（LLOQ）：ChS 法 = 1.00 IU/dL；OS 法 = 0.1 IU/dL.
[3] 全測定値を記述統計の計算に用い、LLOQ 未満の測定値は 0 とした。したがって、平均値が LLOQ 未満となる可能性があった。
引用：1001 試験 CSR 図 14.2.1.1.2

ともに 50 IU/kg を投与した場合、本剤投与群はルリオクトコグアルファ投与群よりも高い AUC、低い CL、及び長い平均 $t_{1/2}$ を示したことから、PK プロファイルはルリオクトコグアルファ投与群よりも良好であることが示された。IR 及び C_{max} は、両群で同様であった（表 2.7.6.1-5）。OS 法により得られた FVIII 活性レベルは、ChS 法により得られたものより約 45%低く、この差は PK パラメーターで一貫して認められた。

表 2.7.6.1-5　1001 試験：本剤及びルリオクトコグアルファ投与後（50 IU/kg）の FVIII の PK パラメーター平均値（CV%）－Part 1（ChS 法、PK 解析集団全体）

パラメーター、単位	ルリオクトコグアルファ 50 IU/kg (n = 26)	本剤 50 IU/kg (n = 26)
Cmax (IU/dL)	118 (14.8)	114 (14.7)
IR (IU/dL)/(IU/kg)	2.35 (15.0)	2.27 (14.7)
AUC_{0-t} (IU*h/dL)	1510 (32.9)	2030 (27.8)
$AUC_{0-\infty}$ (IU*h/dL)	1580 (34.6)	2130 (29.8)
$t_{1/2}$ (h)	13.4 (33.0)	14.7 (25.4)
CL (mL/h/kg)	3.58 (37.1)	2.55 (28.9)
V_{ss} (mL/kg)	56.2 (18.8)	49.3 (13.5)

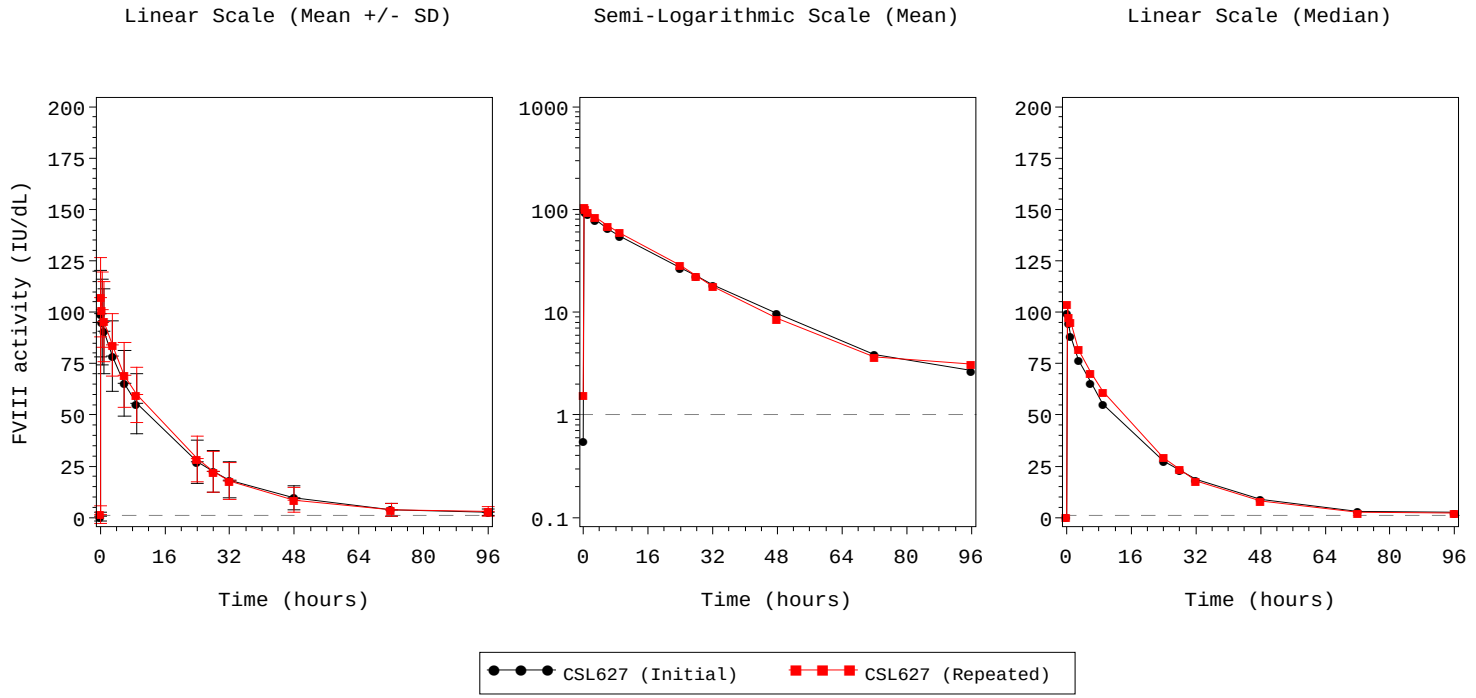
略語：AUC_{0-t}、定量化可能な最終検体採取時刻までの活性／濃度曲線下面積；$AUC_{0-\infty}$、無限大時間まで外挿した活性／濃度曲線下面積；ChS、発色合成基質法；CL、クリアランス；C_{max}、最高血漿中濃度；CV%、変動係数%；FVIII、血液凝固第 VIII 因子；IR、回収率；IU、国際単位；n、当該製剤群内総被験者数；PK、薬物動態；$t_{1/2}$、半減期；　V_{ss}、定常状態での分布容積
注：IR 及び C_{max} は、各被験者の投与前 FVIII 活性レベルを投与後の各時点で得られた活性レベルから減算して、ベースライン補正を行った。その他のパラメーターではベースライン補正を行わなかった。
引用：1001 試験 CSR 表 14.2.13.1.2（rVIII-SingleChain）、表 14.2.13.3.2（ルリオクトコグアルファ）

Part 3（50 IU/kg の初回投与後及び反復投与後での本剤の PK）：

ChS 法の結果では、初回 PK 評価時の本剤（50 IU/kg）投与後での、青年及び成人の平均 IR は 1.85 (IU/dL)/(IU/kg)、平均 $AUC_{0-\infty}$は 1830 IU*h/dL、平均 CL は 3.15 mL/h/kg、平均 $t_{1/2}$ は 14.1 h、及び平均 V_{ss} は 59.5 mL/kg であった（表 2.7.6.1-6）。

初回 PK 評価から 3～6 箇月後に行った反復投与後の PK 評価は、初回 PK と同様であった。このことは、本剤の PK プロファイルは少なくとも 3～6 箇月の間、安定していた（時間非依存性）ということを示唆している。また、50 IU/kg の初回投与後に再評価した本剤の PK プロファイルは、比較バイオアベイラビリティー評価で得られた PK プロファイルと同様であった（Part 1）（図 2.7.6.1-4）。PK パラメーターは、a）12 歳以上 18 歳未満の被験者と 18 歳以上の被験者で同様であり、b）本剤 250 IU/mL を投与された被験者と 3000 IU/mL を投与された被験者で同様であった。

図 2.7.6.1-4　1001 試験：本剤（50 IU/kg ±10%）単回投与後の FVIII 活性［平均値（SD）及び中央値、ベースライン補正なし］ー時間プロファイルーPart 3（ChS 法、PK 解析集団全体）



略語：ChS、発色合成基質法；FVIII、血液凝固第 VIII 因子；IU、国際単位；OS、凝固一段法；PK、薬物動態；SD、標準偏差
注：
[1] CSL627 = 本剤
[2] 定量下限（LLOQ）：ChS 法=1.00 IU/dL；OS 法=0.1 IU/dL
[3] 全測定値を記述統計の計算に用い、LLOQ 未満の測定値は 0 とした。したがって、平均値が LLOQ 未満となる可能性があった。
引用：1001 試験 CSR 図 14.2.4.1.1

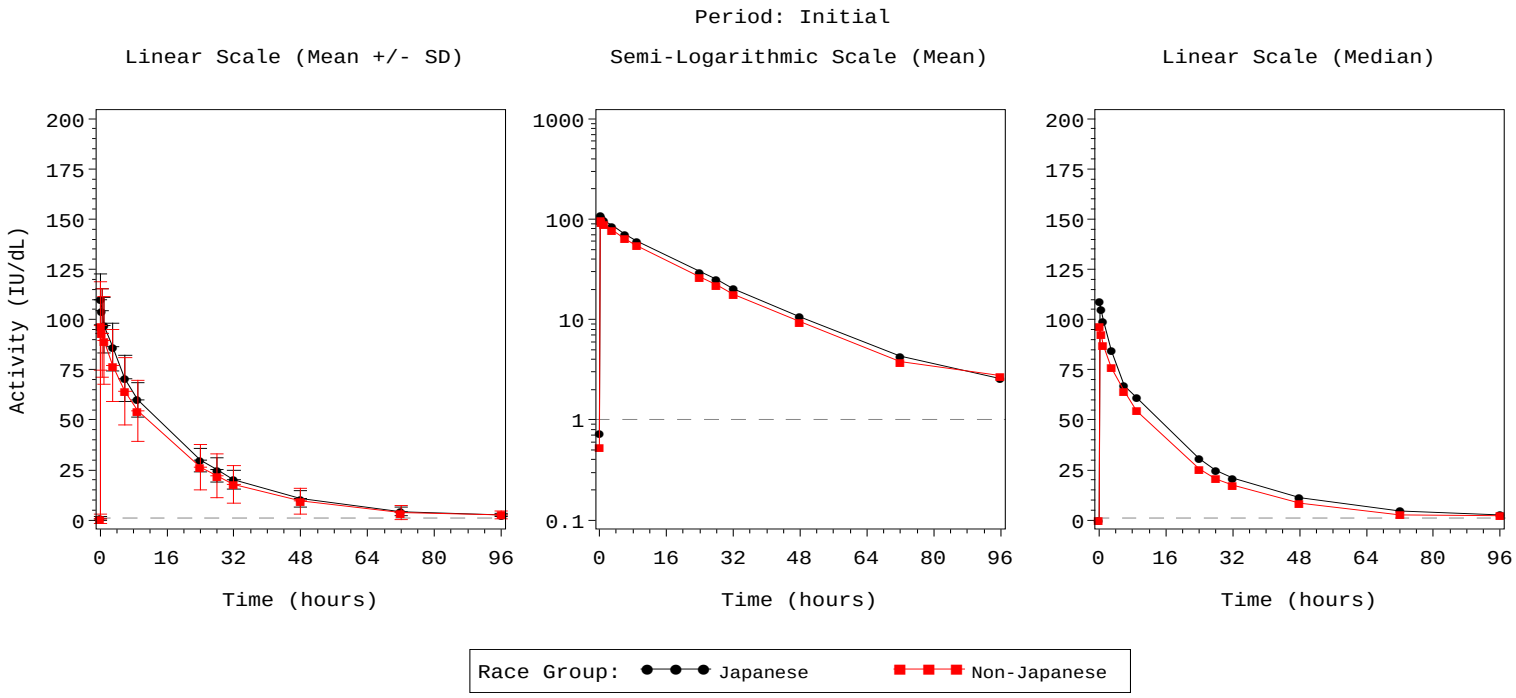
表 2.7.6.1-6　1001 試験：本剤（50 IU/kg）投与後の FVIII の PK パラメーター平均値（CV%）の要約　–Part 3（ChS 法、PK 解析集団全体）

パラメーター、単位	初回投与後の PK (n = 64)	反復投与後の PK (n = 30)
C_{max} (IU/dL)	99.9 (19.9)	108 (17.2)
IR (IU/dL)/(IU/kg)	1.85 (21.8)	1.99 (17.7)
AUC_{0-t} (IU*h/dL)	1780 (34.5)	1850 (33.0)
$AUC_{0-\infty}$ (IU*h/dL)	1830 (34.9)	1880 (34.5)
$t_{1/2}$ (h)	14.1 (27.1)	12.9 (29.4)
CL (mL/h/kg)	3.15 (38.2)	3.05 (36.0)
V_{ss} (mL/kg)	59.5 (23.9)	53.1 (16.4)
MRT (h)	20.3 (26.4)	18.9 (28.5)

略語：AUC_{0-t}、定量化可能な最終検体採取時刻までの活性／濃度曲線下面積；$AUC_{0-\infty}$、無限大時間まで外挿した活性／濃度曲線下面積；ChS、発色合成基質法；CL、クリアランス；C_{max}、最高血漿中濃度；CV%、変動係数%；FVIII、血液凝固第 VIII 因子；IR、回収率；IU、国際単位；MRT、平均滞留時間；n、当該製剤群内総被験者数；PK、薬物動態；$t_{1/2}$、半減期；　V_{ss}、定常状態での分布容積
注：IR 及び C_{max} は、各被験者の投与前 FVIII 活性レベルを投与後の各時点で得られた活性レベルから減算して、ベースライン補正を行った。その他のパラメーターではベースライン補正を行わなかった。
引用：1001 試験 CSR　表 14.2.16.1.1、表 14.2.16.2.1、表 14.2.16.9.1 及び表 14.2.16.10.1

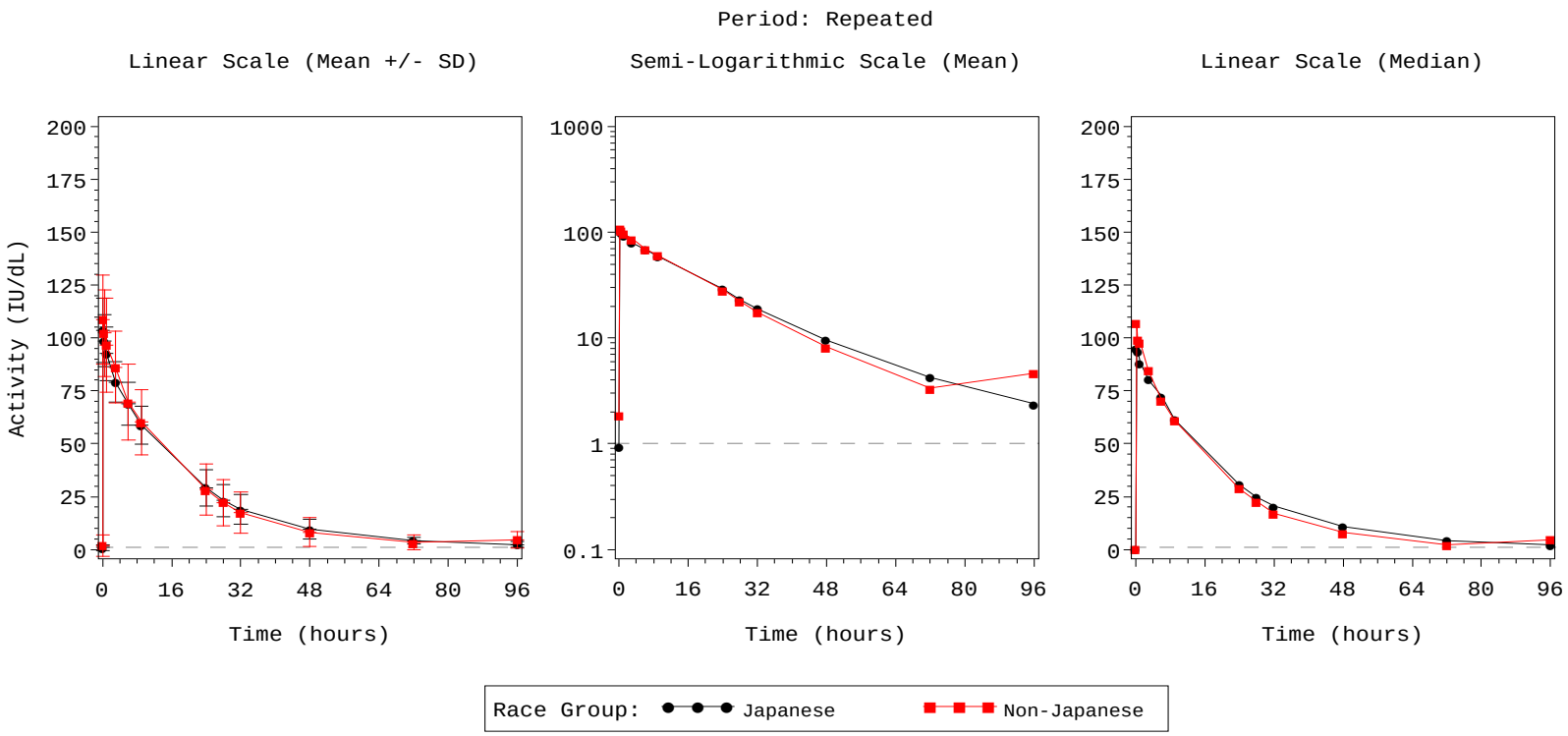
本剤（50 IU/kg）の初回投与後（図 2.7.6.1-5）及び反復投与後（図 2.7.6.1-6）での FVIII 活性及び PK パラメーターは、日本人被験者と非日本人被験者で同様であった（表 2.7.6.1-7）。

図 2.7.6.1-5　1001 試験：日本人及び非日本人被験者での本剤（50 IU/kg）初回投与後の FVIII 活性［平均値（SD）及び中央値、ベースライン補正なし］ー時間プロファイルー Part 3（ChS 法）



略語：ChS、発色合成基質法；FVIII、血液凝固第 VIII 因子；IU、国際単位；OS、凝固一段法；SD、標準偏差
注：
[1] 定量下限（LLOQ）：ChS 法=1.00 IU/dL；OS 法=0.1 IU/dL
[2] 全測定値を記述統計の計算に用い、LLOQ 未満の測定値は 0 とした。そのため、平均値が LLOQ 未満となる可能性があった。
引用：1001 試験 CSR 図 14.2.7.1.2

図 2.7.6.1-6　1001 試験：日本人及び非日本人被験者での本剤（50 IU/kg）反復投与後の FVIII 活性［平均値（SD）及び中央値、ベースライン補正なし］ー時間プロファイルー Part 3（ChS 法）



略語：ChS、発色合成基質法；FVIII、血液凝固第 VIII 因子；IU、国際単位；OS、凝固一段法；SD、標準偏差
注：
[1] 定量下限（LLOQ）：ChS 法=1.00 IU/dL；OS 法=0.1 IU/dL
[2] 全測定値を記述統計の計算に用い、LLOQ 未満の測定値は 0 とした。したがって、平均値が LLOQ 未満となる可能性があった。
引用：1001 試験 CSR 図 14.2.7.1.2

表 2.7.6.1-7　1001 試験：本剤（50 IU/kg）初回投与後及び反復投与後の FVIII の PK パラメーターに関する日本人被験者と非日本人被験者の比較（ノンコンパートメント解析）－Part 3（ChS 法、日本人及び非日本人 PK 解析集団）

パラメーター (単位)	平均値 (CV%) 初回投与後の PK 非日本人 (n = 54)	初回投与後の PK 日本人 (n = 10)	反復投与後の PK 非日本人 (n = 22)	反復投与後の PK 日本人 (n = 8)
ベースライン補正なし				
IR (IU/dL)/(IU/kg) [a,b]	1.81 (23.1)	2.07 (11.2)	2.0 (19.4)	1.97 (13.1)
C_{max} (IU/dL) [a,b]	98.2 (20.9)	109 (11.9)	109 (17.9)	103 (15.3)
AUC_{0-t} (IU*h/dL)	1740 (37.3)	2000 (15.7)	1840 (36.9)	1900 (22.0)
$AUC_{0-\infty}$ (IU*h/dL)	1790 (37.7)	2060 (15.9)	1860 (38.6)	1940 (22.9)
$t_{1/2}$ (h)	13.7 (25.7)	16.4 (29.0)	12.2 (28.6)	14.8 (27.9)
CL (mL/h/kg)	3.28 (38.6)	2.49 (17.1)	3.16 (37.1)	2.73 (30.9)
V_{ss} (mL/kg)	60.2 (24.4)	55.7 (20.5)	52.6 (17.1)	54.7 (15.4)
MRT (h)	19.9 (26.1)	23.0 (25.4)	18.0 (27.7)	21.3 (28.3)

略語：AUC_{0-t}、定量化可能な最終検体採取時刻までの活性／濃度曲線下面積；$AUC_{0-\infty}$、無限大時間まで外挿した活性／濃度曲線下面積；ChS、発色合成基質法；CL、クリアランス；C_{max}、最高血漿中濃度；CV%、変動係数%；IR、回収率；IU、国際単位；MRT、平均滞留時間；n、当該投与群の被験者数；PK、薬物動態；$t_{1/2}$、半減期；V_{ss}、定常状態での分布容積

[a] IR 及び C_{max} について、ベースライン補正ありの測定値が評価可能である被験者数は初回投与後 PK が 63 名、反復投与後 PK が 29 名であった。

[b] IR 及び C_{max} について、2.7.2 項 2.7.2.1.5.1 で示したように、各時点の FVIII 活性値から投与前の FVIII 活性値を差し引き、ベースライン補正を行った。他のパラメーターではベースライン補正を行わなかった。

注：Part 3 での PK 解析集団は 64 名

引用：1001 試験 CSR 表 14.2.16.21.1、表 14.2.16.22.1、表 14.2.16.23.1 及び表 14.2.16.24.1

6）有効性の結果

出血エピソードのコントロールと抑制：

被験者集団全体での出血エピソード発現率は、関節、他の組織、筋肉の順に高かった。これらの組織において出血箇所は様々で、明確なパターンは認められなかった。被験者集団全体で 848 件の出血エピソードについて本剤の投与効果を評価した。全体で 92.3%の出血エピソードが、治験責任医師による止血効果の総合的臨床評価で「優」又は「良」とされ、治療成功とされた。治療成功率はオンデマンド療法（92.4%）と定期的な投与（92.2%）で同様であった（表 2.7.6.1-8）。全体で 93.5%の出血エピソードが 1～2 回の本剤の投与によってコントロールされた。被験者集団全体で、出血エピソード 1 件に使用した本剤総投与量の中央値は 34.7 IU/kg で、出血エピソード 1 件における 1 回の投与量の中央値は 31.7 IU/kg であった。

日本人被験者集団の治療成功率は被験者集団全体と同様であった。全体で 29 件中 26 件（89.7%）の出血エピソードが、治験責任医師による止血効果の総合的臨床評価で「優」又は「良」とされ、治療成功とされた（表 2.7.6.1-9）。全体で 82.8%

の出血エピソードが 1～2 回の本剤の投与によってコントロールされた。日本人被験者で、出血エピソード 1 件に使用した本剤総投与量の中央値は 39.6 IU/kg で、出血エピソード 1 件における 1 回の投与量の中央値は 33.6 IU/kg であった。

治験責任医師による止血効果の総合的臨床評価は、他の地域間及び評価した年齢群間で同様であった。

表 2.7.6.1-8　1001 試験：治験責任医師による止血効果の総合的臨床評価
（有効性解析集団全体）

出血エピソードの評価	オンデマンド療法 (N = 27)	定期的な投与 (N = 146)	全体 (N = 173)
出血エピソード数	594	278	872
治療した出血エピソード数	590	258	848
優 [n (%)]	421 (71.4)	182 (70.5)	603 (71.1)
良 [n (%)]	124 (21.0)	56 (21.7)	180 (21.2)
可 [n (%)]	32 (5.4)	20 (7.8)	52 (6.1)
不可/反応なし	0	0	0
欠測	13 (2.2)	0	13 (1.5)
治療成功 (a)	545 (92.4)	238 (92.2)	783 (92.3)
治療成功率	92.4	92.2	92.3
95% CI	(87.8, 95.3)	(86.3, 95.8)	(88.9, 94.8)
治療成功 (b)	545 (94.5)	238 (92.2)	783 (93.8)
治療成功率	94.5	92.2	93.8
95% CI	(90.9, 96.7)	(86.3, 95.8)	(91.0, 95.7)
治療成功 (c)	558 (94.6)	238 (92.2)	796 (93.9)
治療成功率	94.6	92.2	93.9
95% CI	(91.0, 96.8)	(86.3, 95.8)	(91.1, 95.8)

略語：CI、信頼区間；N、総被験者数（全体又は当該療法群内）
注：
[1] 治療成功は「優」又は「良」と定義した。(a) 主要解析：欠測値は治療不成功、(b) 感度解析：欠測値はすべて除外、(c) 感度解析：欠測値を治療成功として扱った。
[2] 95% CI は被験者内相関を考慮した一般化線形モデルを基に算出した。
[3] 表中、出血エピソードの数及びパーセント[n (%)]を表す。
[4] パーセントは治療された出血エピソード数を基に算出した。
引用：1001 試験 CSR 表 14.2.1.1

表 2.7.6.1-9　1001 試験：治験責任医師による止血効果の総合的臨床評価
（日本人被験者の有効性解析集団）

出血エピソードの評価	オンデマンド療法 (N = 1)	定期的な投与 (N = 9)	日本人全体 (N =10)
出血エピソード数	8	27	35
治療した出血エピソード数	7	22	29
優 [n (%)]	4 (57.1)	17 (77.3)	21 (72.4)
良 [n (%)]	2 (28.6)	3 (13.6)	5 (17.2)
可 [n (%)]	1 (14.3)	2 (9.1)	3 (10.3)
不可/反応なし	0	0	0
欠測	0	0	0
治療成功 (a)	6 (85.7)	20 (90.9)	26 (89.7)
治療成功率	85.7	90.9	89.7
95% CI	(85.7, 85.7)	(69.6, 97.8)	(74.7, 96.2)
治療成功 (b)	6 (85.7)	20 (90.9)	26 (89.7)
治療成功率	85.7	90.9	89.7
95% CI	(85.7, 85.7)	(69.6, 97.8)	(74.7, 96.2)
治療成功 (c)	6 (85.7)	20 (90.9)	26 (89.7)
治療成功率	85.7	90.9	89.7
95% CI	(85.7, 85.7)	(69.6, 97.8)	(74.7, 96.2)

略語：CI、信頼区間；N、総被験者数（全体又は当該療法群内）
注：
[1] 治療成功は「優」又は「良」と定義した。(a) 主要解析：欠測値は治療不成功、(b) 感度解析：欠測値はすべて除外、(c) 感度解析：欠測値を治療成功として扱った。
[2] 95% CI は被験者内相関を考慮した一般化線形モデルを基に算出した。
[3] 表中、出血エピソードの数及びパーセント[n (%)]を表す。
[4] パーセントは治療された出血エピソード数を基に算出した。
引用：5.3.5.1 項 表 14.2.1.1J

定期的な投与：

被験者集団全体では、本剤を用いた定期的な投与により、オンデマンド療法と比較して AsBR で 92%、ABR で 90%の有意な低下が認められた（有効性解析集団、Poisson モデルによる検定で P < 0.0001）。定期的な投与全体の AsBR の中央値（Q1, Q3）は 0.0 件（0.0, 2.4）で、ABR の中央値（Q1, Q3）は 1.14 件（0.0, 4.2）であるのに対し、オンデマンド療法の AsBR の中央値（Q1, Q3）は 11.73 件（2.8, 36.5）で、ABR の中央値（Q1, Q3）は 19.64 件（6.2, 46.5）であった（表 2.7.6.1-10）。

日本人被験者集団では、定期的な投与すべてを合わせた場合の AsBR の中央値（Q1, Q3）は 0.00 件（0.0, 1.1）で、ABR の中央値（Q1, Q3）は 0.00 件（0.0, 1.4）であるのに対し、オンデマンド療法の AsBR の中央値（Q1, Q3）は 3.55 件（3.6, 3.6）で、ABR の中央値（Q1, Q3）は 6.22 件（6.2, 6.2）であった。

表 2.7.6.1-10　1001 試験：ABR 及び A_SBR –本剤の定期的な投与とオンデマンド療法の比較（有効性解析集団）

	全体		日本人	
	オンデマンド療法 (N = 27)	**定期的な投与 (N = 146)**	**オンデマンド療法 (N = 1)**	**定期的な投与 (N = 9)**
自然出血エピソード（AsBR)				
平均値 (SD)	24.84 (33.843)	2.10 (4.764)	3.55	1.83 (4.268)
中央値	11.73	0.00	3.55	0.00
Q1, Q3	2.8, 36.5	0.0, 2.4	3.6, 3.6	0.0, 1.1
最小値, 最大値	0.0, 151.0	0.0, 40.6	3.6, 3.6	0.0, 13.0
年間出血エピソード数 (95% CI)	19.5 (17.8, 21.3)	1.6 (1.3, 1.8)	3.6 (1.3, 9.5)	2.0 (1.2, 3.3)
P 値	< 0.0001		0.3093	
定期的な投与/オンデマンド療法比 (95% CI)	0.08 (0.07, 0.10)		0.56 (0.19, 1.70)	
総出血エピソード（ABR)				
平均値 (SD)	31.14 (35.560)	3.11 (5.045)	6.22	2.51 (4.556)
中央値	19.64	1.14	6.22	0.00
Q1, Q3	6.2, 46.5	0.0, 4.2	6.2, 6.2	0.0, 1.4
最小値, 最大値	0.0, 163.3	0.0, 40.6	6.2, 6.2	0.0, 13.0
年間出血エピソード数 (95% CI)	24.9 (23.0, 27.0)	2.6 (2.3, 2.9)	6.2 (3.0, 13.0)	2.9 (1.9, 4.5)
P 値	< 0.0001		0.0845	
定期的な投与/オンデマンド療法比 (95% CI)	0.10 (0.09, 0.12)		0.47 (0.20, 1.11)	

略語：CI、信頼区間；N、当該療法群内被験者数；Q1、第 1 四分位；Q3、第 3 四分位；SD、標準偏差
注：
[1] 年間出血エピソード回数（95% CI)、p 値、及び療法比は Poisson 分布を基に算出した。
引用：1001 試験 CSR 表 14.2.2.2.1（被験者集団全体のデータ)、表 14.2.2.3（日本人被験者集団の p 値及び定期的な投与/オンデマンド療法比)、5.3.5.1 項 表 14.2.2.2.1.J

表 2.7.6.1-11　1001 試験：定期的な投与での投与量及び投与量調整の要約（有効性解析集団）

	隔日 (N = 9)	週 3 回 (N = 79)	週 2 回 (N = 47)	他の療法 (N = 11)
投与量 (IU/kg)				
被験者数	9	79	47	11
平均値 (SD)	31.0 (7.55)	31.9 (8.45)	35.5 (8.52)	33.3 (10.79)
中央値	30.0	30.0	35.0	30.0
最小値、最大値	20, 42	12, 50	17, 50	17, 46
被験者あたりの投与量調整回数 [n (%)]				
0 回	7 (77.8)	52 (65.8)	34 (72.3)	7 (63.6)
1 回	2 (22.2)	15 (19.0)	9 (19.1)	2 (18.2)
2 回	0	8 (10.1)	3 (6.4)	1 (9.1)
3 回以上	0	4 (5.1)	1 (2.1)	1 (9.1)
投与量 20 IU/kg 未満の被験者数 **[n (%)]**	0	2 (2.5)	1 (2.1)	2 (18.2)
投与量 50 IU/kg 超の被験者数 **[n (%)]**	0	1 (1.3)	0	0
投与量調整の理由 [n (%)]				
出血	0	5 (6.3)	0	0
医師の判断	2 (22.2)	14 (17.7)	9 (19.1)	2 (27.3)
その他	0	15 (19.0)	3 (6.4)	2 (18.2)

略語：IU、国際単位；N、当該療法群内被験者数；SD、標準偏差
注：
[1] 表中、被験者の数及びパーセント[n (%)]を表す。
[2] パーセントは当該集団の被験者数を基に算出した。
[3] 開始用量及び調整後用量を基に 20 IU/kg 未満又は 50 IU/kg 超の被験者数を表す。
引用：1001 試験 CSR 表 14.1.10

被験者の大多数は、定期的な投与として、本剤 20～50 IU/kg を週に 2～3 回投与されていた（表 2.7.6.1-11）。定期的な投与では、被験者あたりの月間投与量の平均値（SD）は、被験者集団全体で 374.5（148.18）IU/kg、日本人被験者集団で 318.9（120.58）IU/kg であった（表 2.7.6.1-12）。

表 2.7.6.1-12　1001 試験：定期的な投与期間中での本剤の投与量（有効性解析集団）

	全体	日本人
定期的投与群の被験者数	**146**	**9**
定期的な投与での総投与回数	**12343**	**731**
被験者あたりの定期的な投与の月間投与量 [1] (IU/kg)		
平均値 (SD)	374.5 (148.18)	318.9 (120.58)
中央値	356.9	292.8
最小値, 最大値	31, 1522	198, 592
被験者あたりの全体の月間投与量[1] (IU/kg)		
平均値 (SD)	417.9 (194.11)	332.5 (127.08)
中央値	388.5	292.8
最小値, 最大値	173, 1732	198, 621
被験者あたりの定期的な投与の年間投与量 [1] (IU/kg)		
平均値 (SD)	4494.4 (1778.17)	3827.3 (1447.01)
中央値	4282.9	3514.0
最小値, 最大値	372, 18263	2379, 7108
被験者あたりの全体の年間投与量[1] (IU/kg)		
平均値 (SD)	5015.0 (2329.33)	3990.2 (1524.98)
中央値	4661.5	3514.0
最小値, 最大値	2078, 20789	2379, 7454
定期的な投与中の月間 IU		
平均値 (SD)	28065.5 (14648.99)	18224.7 (6836.88)
中央値	26686.8	16997.5
最小値, 最大値	2792, 136969	7593, 29736
全体の月間 IU		
平均値 (SD)	31598.0 (19149.31)	18853.2 (6850.02)
中央値	27706.4	17423.7
最小値, 最大値	8677, 155916	8677, 31184

略語：IU、国際単位；N、当該療法群内被験者数；SD、標準偏差
注：
[1] 定期的な投与の投与量は「定期的/予防的」投与として記録された投与を含める。また、全体の投与量は、「出血イベント」、「手術」、「術後」、「活性前の抑制」及び「追加治療」のための投与記録を含む。
引用：1001 試験 CSR 表 14.2.5.1、5.3.5.1 項 表 14.2.5.1J

外科手術時の補充療法：

本治験で、16 件の外科手術があり、これらはすべて非日本人被験者で行われた待機的手術であった。外科手術時補充療法の止血効果は、16 件すべてで「優」又は「良」と評価され、外科手術時の補充療法での本剤投与の治療成功率は 100%であった（表 2.7.6.1-13）。

術中の実際の失血量及び輸血必要量の推定値は予想値に近かった。ヘモグロビン値は手術期間中、施行された手術の種類での予測範囲内のレベルで維持されていた。

表 2.7.6.1-13　1001 試験：周術期の定期的な投与での本剤の有効性
（外科手術時の補充療法解析集団）

評価	全体 (N = 13)
外科手術の件数	16
優, n (%)	15 (93.8)
良, n (%)	1 (6.3)
可, n (%)	0
不可/反応なし, n (%)	0
治療成功, n (%)[a]	16 (100.0)

略語：N、外科手術時の補充療法解析集団の被験者総数；n、各評価の手術数
[a] 治療成功は「優」又は「良」と定義した。
注：手術数を基にパーセントを算出した。
引用：2.7.3 項 表 2.7.3.19

7） 安全性の結果

全体的に、本剤の IV 投与に関する安全性プロファイル及び忍容性は、オンデマンド療法時、様々なレジメンでの定期的な投与時、及び出血の術中コントロール時で、いずれも良好であった。安全性プロファイル及び忍容性プロファイルについて、日本人被験者集団と被験者集団全体に臨床的に重要な差は認められなかった。

いずれの被験者にも本剤に対するインヒビター及び CHO 細胞由来タンパク質に対する抗体は検出されず、50 ED 以上の被験者［95% CI（0.0%～3.0%）］及び安全性解析集団［95% CI（0.0%～2.1%）］でのインヒビター産生率は、ともに 0%であり、事前に規定した成功の基準（CI の上限が許容される上限の 6.8%未満であること）を満たした。

試験期間中、4 名が非阻害 ADA 陽性を示し、そのうちの 2 名は試験終了来院時に ADA 検査で陰性となったが、残りの 2 名は陽性のままであった。非阻害 ADA の発現に関連する AE は認められなかった。試験期間中、日本人で非阻害 ADA 陽性を示した被験者はいなかった。

本治験で、死亡又は治験中止に至った TEAE は認められなかった。一部の被験者［被験者集団全体で 13 名（7.5%）、日本人被験者集団で 1 名（10%）］で、本剤の投与に関連すると考えられる TEAE が認められたが、非日本人 1 名で認められた重度の過敏症を除き、重症度は軽度又は中等度であった（表 2.7.6.1-14）。

本剤の投与に関する TEAE プロファイルは、血友病 A 患者の病状及び同じ薬物クラスに属する他の製剤で予想可能なものであった（表 2.7.6.1-15）。血栓塞栓イベントの報告はなく、過敏症を発現した被験者の全体での割合は 1.1%（2 名）と低かった。

表 2.7.6.1-14 1001 試験：AE の要約（安全性解析集団）

	全体 (N=174)		日本人(N=10)	
	被験者数 (%)	発現件数	被験者数 (%)	発現件数
AE	121 (69.5)	325	8 (80.0)	20
TEAE	113 (64.9)	292	8 (80.0)	20
治験中止に至った TEAE	0	0	0	0
TEAE の重症度				
軽度	94 (54.0)	225	8 (80.0)	18
中等度	43 (24.7)	61	2 (20.0)	2
重度	5 (2.9)	6	0	0
治験薬に関連する TEAE	13 (7.5)	19	1 (10.0)	1
TEAE の転帰				
AE に関連する死亡	0	0	0	0
未回復/未消失	22 (12.6)	25	3 (30.0)	3
回復/消失	104 (59.8)	256	8 (80.0)	17
回復/消失したが後遺症あり	1 (0.6)	1	0	0
軽快	9 (5.2)	10	0	0
SAE	8 (4.6)	10	0	0
TESAE	7 (4.0)	9	0	0
治験薬に関連する TESAE	1 (0.6)	1	0	0

略語：AE、有害事象；N、総被験者数（全体又は日本人集団）；SAE、重篤な有害事象；TEAE、治験治療下で発現した有害事象；TESAE、治験治療下で発現した重篤な有害事象

注：

[1] 当該事象が認められた被験者の数及びパーセント、並びに当該事象の発現件数を表す。

[2] パーセントは当該集団の被験者数を基に算出した。

引用：1001 試験 CSR 表 14.3.2.1、5.3.5.1 項 表 14.3.2.1J

表 2.7.6.1-15 1001 試験：器官別大分類及び基本語別 TEAE（安全性解析集団）

	全体 (N = 174)		日本人 (N =10)	
	被験者数 (%)	発現件数	被験者数 (%)	発現件数
TEAE	113 (64.9)	292	8 (80.0)	20
感染症および寄生虫症	**45 (25.9)**	**61**	**6 (60.0)**	**9**
鼻咽頭炎	18 (10.3)	22	4 (40.0)	4
上気道感染	6 (3.4)	6	0	0
インフルエンザ	4 (2.3)	4	2 (20.0)	2
ウイルス感染	3 (1.7)	4	0	0
副鼻腔炎	3 (1.7)	3	1 (10.0)	1
胃腸炎	2 (1.1)	2	0	0
ウイルス性胃腸炎	2 (1.1)	2	0	0
咽頭炎	2 (1.1)	2	0	0
ウイルス性上気道感染	2 (1.1)	2	0	0
気管支炎	1 (0.6)	1	0	0
耳感染	1 (0.6)	1	0	0
皮膚真菌感染	1 (0.6)	1	0	0
骨折	1 (0.6)	1	0	0
下気道感染	1 (0.6)	1	0	0
口腔真菌感染	1 (0.6)	1	0	0
口腔ヘルペス	1 (0.6)	1	1 (10.0)	1
中耳炎	1 (0.6)	1	1 (10.0)	1
直腸周囲膿瘍	1 (0.6)	1	0	0
気道感染	1 (0.6)	1	0	0
鼻炎	1 (0.6)	1	0	0
扁桃炎	1 (0.6)	1	0	0

表 2.7.6.1-15　1001 試験：器官別大分類及び基本語別 TEAE（安全性解析集団）（続き）

	全体 (N = 174)		日本人 (N =10)	
	被験者数 (%)	発現件数	被験者数 (%)	発現件数
歯膿瘍	1 (0.6)	1	0	0
尿路感染	1 (0.6)	1	0	0
筋骨格系および結合組織障害	**26 (14.9)**	**46**	**0**	**0**
関節痛	17 (9.8)	19	0	0
背部痛	5 (2.9)	6	0	0
血友病性関節症	3 (1.7)	11	0	0
四肢痛	2 (1.1)	3	0	0
鼡径部痛	1 (0.6)	1	0	0
関節可動域低下	1 (0.6)	1	0	0
関節腫脹	1 (0.6)	1	0	0
腰部脊柱管狭窄症	1 (0.6)	1	0	0
筋痙縮	1 (0.6)	1	0	0
頚部痛	1 (0.6)	1	0	0
滑液嚢腫	1 (0.6)	1	0	0
傷害、中毒および処置合併症	**26 (14.9)**	**34**	**3 (30.0)**	**4**
関節損傷	3 (1.7)	4	0	0
転倒	3 (1.7)	3	0	0
四肢損傷	2 (1.1)	3	0	0
挫傷	2 (1.1)	2	0	0
裂傷	2 (1.1)	2	0	0
靭帯捻挫	2 (1.1)	2	0	0
外傷後疼痛	2 (1.1)	2	0	0
熱傷	2 (1.1)	2	0	0
創傷	2 (1.1)	2	0	0
足関節部骨折	1 (0.6)	1	0	0
節足動物咬傷	1 (0.6)	1	0	0
凍瘡	1 (0.6)	1	1 (10.0)	1
結膜擦過傷	1 (0.6)	1	1 (10.0)	1
手骨折	1 (0.6)	1	0	0
肉離れ	1 (0.6)	1	0	0
交通事故	1 (0.6)	1	0	0
サンバーン	1 (0.6)	1	1 (10.0)	1
腱断裂	1 (0.6)	1	0	0
舌損傷	1 (0.6)	1	1 (10.0)	1
外傷性血腫	1 (0.6)	1	0	0
創傷出血	1 (0.6)	1	0	0
神経系障害	**19 (10.9)**	**25**	**2 (20.0)**	**2**
頭痛	12 (6.9)	13	1 (10.0)	1
浮動性めまい	4 (2.3)	5	1 (10.0)	1
錯感覚	2 (1.1)	2	0	0
傾眠	1 (0.6)	3	0	0
感覚鈍麻	1 (0.6)	1	0	0
片頭痛	1 (0.6)	1	0	0
胃腸障害	**17 (9.8)**	**23**	**0**	**0**
歯痛	6 (3.4)	8	0	0
齲歯	3 (1.7)	3	0	0
腹痛	2 (1.1)	3	0	0
便秘	1 (0.6)	1	0	0
下痢	1 (0.6)	1	0	0
胃炎	1 (0.6)	1	0	0
血便排泄	1 (0.6)	1	0	0

表 2.7.6.1-15　1001 試験：器官別大分類及び基本語別 TEAE（安全性解析集団）（続き）

	全体 (N = 174)		日本人 (N =10)	
	被験者数 (%)	発現件数	被験者数 (%)	発現件数
痔出血	1 (0.6)	1	0	0
弛緩歯	1 (0.6)	1	0	0
食道炎	1 (0.6)	1	0	0
臍ヘルニア	1 (0.6)	1	0	0
食道静脈瘤	1 (0.6)	1	0	0
皮膚および皮下組織障害	**17 (9.8)**	**21**	**3 (30.0)**	**4**
発疹	7 (4.0)	8	1 (10.0)	1
ざ瘡	2 (1.1)	2	1 (10.0)	1
日光性角化症	1 (0.6)	1	0	0
皮膚炎	1 (0.6)	1	0	0
アレルギー性皮膚炎	1 (0.6)	1	0	0
アトピー性皮膚炎	1 (0.6)	1	0	0
接触性皮膚炎	1 (0.6)	1	0	0
発汗障害	1 (0.6)	1	1 (10.0)	1
斑状出血	1 (0.6)	1	0	0
紅斑	1 (0.6)	1	0	0
紅色汗疹	1 (0.6)	1	1 (10.0)	1
点状出血	1 (0.6)	1	0	0
そう痒症	1 (0.6)	1	0	0
一般・全身障害および投与部位の状態	**17 (9.8)**	**20**	**0**	**0**
発熱	4 (2.3)	5	0	0
無力症	2 (1.1)	2	0	0
胸痛	2 (1.1)	2	0	0
注射部位疼痛	2 (1.1)	2	0	0
悪寒	1 (0.6)	2	0	0
医薬品副作用	1 (0.6)	1	0	0
熱感	1 (0.6)	1	0	0
局所腫脹	1 (0.6)	1	0	0
限局性浮腫	1 (0.6)	1	0	0
倦怠感	1 (0.6)	1	0	0
末梢性浮腫	1 (0.6)	1	0	0
疼痛	1 (0.6)	1	0	0
呼吸器、胸郭および縦隔障害	**9 (5.2)**	**17**	**0**	**0**
咳嗽	5 (2.9)	6	0	0
口腔咽頭痛	3 (1.7)	3	0	0
鼻閉	2 (1.1)	2	0	0
鼻漏	2 (1.1)	2	0	0
鼻粘膜障害	1 (0.6)	1	0	0
咽頭紅斑	1 (0.6)	1	0	0
くしゃみ	1 (0.6)	1	0	0
扁桃出血	1 (0.6)	1	0	0
臨床検査	**9 (5.2)**	**13**	**0**	**0**
肝機能検査異常	2 (1.1)	2	0	0
血中尿酸増加	1 (0.6)	3	0	0
血中ブドウ糖増加	1 (0.6)	2	0	0
血中乳酸脱水素酵素増加	1 (0.6)	1	0	0
血中トリグリセリド増加	1 (0.6)	1	0	0
血中尿素増加	1 (0.6)	1	0	0
C-反応性蛋白増加	1 (0.6)	1	0	0
薬物特異性抗体陽性	1 (0.6)	1	0	0
γ-グルタルトランスフェラーゼ増加	1 (0.6)	1	0	0

表 2.7.6.1-15　1001 試験：器官別大分類及び基本語別 TEAE（安全性解析集団）（続き）

	全体 (N = 174)		日本人 (N =10)	
	被験者数 (%)	発現件数	被験者数 (%)	発現件数
血管障害	**7 (4.0)**	**7**	**0**	**0**
高血圧	5 (2.9)	5	0	0
毛細血管脆弱	1 (0.6)	1	0	0
血腫	1 (0.6)	1	0	0
血液およびリンパ系障害	**6 (3.4)**	**7**	**0**	**0**
貧血	2 (1.1)	2	0	0
白血球増加症	2 (1.1)	2	0	0
好酸球増加症	1 (0.6)	1	0	0
鉄欠乏性貧血	1 (0.6)	1	0	0
血小板減少症	1 (0.6)	1	0	0
免疫系障害	**3 (1.7)**	**4**	**0**	**0**
過敏症	2 (1.1)	3	0	0
季節性アレルギー	1 (0.6)	1	0	0
腎および尿路障害	**3 (1.7)**	**3**	**0**	**0**
血尿	1 (0.6)	1	0	0
頻尿	1 (0.6)	1	0	0
腎仙痛	1 (0.6)	1	0	0
眼障害	**2 (1.1)**	**2**	**0**	**0**
結膜炎	2 (1.1)	2	0	0
代謝および栄養障害	**2 (1.1)**	**2**	**1 (10.0)**	**1**
高尿酸血症	1 (0.6)	1	1 (10.0)	1
鉄欠乏	1 (0.6)	1	0	0
外科および内科処置	**1 (0.6)**	**2**	**0**	**0**
抜歯	1 (0.6)	2	0	0
心臓障害	**1 (0.6)**	**1**	**0**	**0**
不整脈	1 (0.6)	1	0	0
耳および迷路障害	**1 (0.6)**	**1**	**0**	**0**
耳痛	1 (0.6)	1	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）	**1 (0.6)**	**1**	**0**	**0**
胃腸管腺腫	1 (0.6)	1	0	0
精神障害	**1 (0.6)**	**1**	**0**	**0**
自殺念慮	1 (0.6)	1	0	0
生殖系および乳房障害	**1 (0.6)**	**1**	**0**	**0**
陰茎分泌物	1 (0.6)	1	0	0

略語：MedDRA、ICH 国際医薬用語集；N、総被験者数（全体又は日本人集団）；TEAE、治験治療下で発現した有害事象
注：
[1] 当該事象が認められた被験者の数及びパーセント、並びに当該事象の発現件数を表す。
[2] パーセントは当該集団の被験者数を基に算出した。
[3] 手術期間中に発現した事象は TEAE から除外した。
[4] 有害事象の読替えには MedDRA Version 14.1 を用いた。
引用：1001 試験 CSR 表 14.3.2.4、5.3.5.1 項 表 14.3.2.4J

治験治療下で発現した SAE（Treatment-emergent serious adverse event：TESAE）の一覧表を表 2.7.6.1-16 に示す。

被験者の一部（7 名、4.0%）で TESAE が認められたが、関連ありとされた過敏症 1 件を除き、治験責任医師により本剤との関連はないと判断された。投与との

関連ありと判断された過敏症の SAE を発現した被験者は、後遺症なく回復し、前投薬をしながら治験を継続した（その他の AE は報告されず）（表 2.7.6.1-16 の下に示した叙述を参照)。

日本人被験者で TESAE は認められなかった。

表 2.7.6.1-16　1001 試験：TESAE が認められた被験者一覧（安全性解析集団）

被験者番号	人種	年齢（歳）	割り付けられた本剤投与法及び用量 (IU/kg)	AE（PT）	発現日/消失日 発現日の試験開始からの日数 TESAE 持続期間	因果関係/重症度	処置[a]	転帰
2760066-1003	白人	3[redacted]	定期的な投与、週 3 回、50 IU/kg	扁桃出血	[redacted] 年 3 月 19 日/ #同 年 3 月 22 日 Day 148 4 日間	関連なし/ 中等度	投与量変更せず	回復/消失
3800022-1002	白人	4[redacted]	オンデマンド療法、35 IU/kg	貧血	[redacted] 年 12 月 24 日/ #翌 年 3 月 4 日 Day 428 71 日間	関連なし/ 重度	投与量変更せず	回復/消失
				血小板減少症	[redacted] 年 12 月 24 日/ #翌 年 1 月 29 日 Day 428 37 日間	関連なし/ 重度	投与量変更せず	回復/消失
6080002-1001	アジア人	1[redacted]	定期的な投与、週 2 回、43 IU/kg	過敏症	[redacted] 年 2 月 11 日 /#同 年 2 月 11 日 Day 22 1 日間	関連あり/ 重度	投与量減量	回復/消失
6160014-1009	白人	5[redacted]	定期的な投与、週 3 回、35 IU/kg	血中尿酸増加	[redacted] 年 3 月 25 日 /#同 年 3 月 28 日 Day 104 4 日間	関連なし/ 軽度	投与量変更せず	回復/消失
				食道静脈瘤	[redacted] 年 10 月 13 日 /#同 年 10 月 16 日 Day 306 4 日間	関連なし/ 軽度	投与量変更せず	回復/消失
6420030-1002	白人	5[redacted]	定期的な投与、週 3 回、28 IU/kg	ウイルス感染	[redacted] 年 11 月 20 日 /#同 年 11 月 28 日 Day 120 9 日間	関連なし/ 中等度	投与量変更せず	回復/消失
7240008-1001	白人	4[redacted]	定期的な投与、週 2 回、42 IU/kg	術後創感染 b	[redacted] 年 1 月 28 日 /#同 年 2 月 27 日 Day 72 31 日間	関連なし/ 重度	投与量変更せず	回復/消失

#新薬承認情報提供時に置き換え

表 2.7.6.1-16　1001 試験：TESAE が認められた被験者一覧（安全性解析集団）（続き）

被験者番号	人種	年齢（歳）	割り付けられた本剤投与法及び用量 (IU/kg)	AE（PT）	発現日/消失日 発現日の試験開始からの日数 TESAE 持続期間	因果関係/重症度	処置[a]	転帰
8400204-1001	白人	2[redacted]	オンデマンド療法、42 IU/kg	足関節部骨折	[redacted] 年 1 月 19 日 /#同 年 5 月 12 日 Day 404 114 日間	関連なし/重度	投与量変更せず	回復/消失
8400184-1006	白人	1[redacted]	定期的な投与、週 2 回、35 IU/kg	自殺念慮	[redacted] 年 1 月 13 日 /#同 年 1 月 15 日 Day 113 3 日間	関連なし/重度	投与量変更せず	回復/消失

略語：AE、有害事象；IU、国際単位；PT、基本語；TESAE、治験治療下で発現した重篤な有害事象
[a] 本剤に対する処置
[b] 外科的 substudy 中に発現した事象
引用：5.3.5.1 項 一覧表 16.2.7.2J

#新薬承認情報提供時に置き換え

被験者番号 6080002-1001（治験薬投与と関連のある SAE：過敏症）：

[redacted]年2月11日、1[redacted]歳のフィリピン系アジア人男性(被験者番号6080002-1001)で過敏症反応の SAE が報告された。重篤な過敏症反応の症例報告には、そう痒症、発熱、紅斑、頭痛、呼吸困難、胸部不快感、及び発疹の症状が含まれていた。被験者は定期的な投与に割り付けられており、投与量は 43 IU/kg であった。

被験者の病歴には、クリオプレシピテートに対する過敏症、「leucoplast」の絆創膏に対する局所過敏症、及び外因性喘息があった。また、被験者は急性扁桃咽頭炎、喉頭炎を伴う上気道感染、咽頭炎及び扁桃炎の既往歴も報告していた。

#同 年 2 月 11 日午前 1:00、治験薬の最終投与後約 2.5 時間の時点で、重度の過敏症反応（重度のそう痒症）が発現した。午前 9:30 に被験者は呼吸困難（胸部圧迫感）、両手・上腕の皮膚の発赤、及び重度の頭痛を報告した。#同 年 2 月 11 日に来院し、入院した。入院時にバイタルサインはすべて正常で、胸部は清明で喘鳴はなく、両側の空気流入は良好であった。上肢に紅斑が認められたが、下肢に発疹はなかった。救急室にて治療され、ステロイド及び抗ヒスタミン薬が投与された。約 17.5 時間後、午後 12:30 に過敏症反応は消失したと判断され、被験者は退院した。退院時には 5 日分のステロイドが漸減用量で処方された。次回の治験薬投与は、治験実施施設にて観察下で行われ、低用量を抗ヒスタミン薬と併せて投与した。観察下で投与した後、治験薬に対する反応は発現せず、その後の治験薬投与を続け、後遺症は認められなかった。

被験者は後遺症なく回復し、当該事象は治験薬と関連ありと判断された。被験者は前投薬を受けて試験を継続し、他の AE は報告されなかった。

年齢群別［青年（12 歳以上 18 歳未満）及び成人（18 歳以上 65 歳以下）］の TEAE 解析での安全性プロファイルは被験者全体のプロファイルと同様であった。

評価した投与の大多数では、被験者（被験者集団全体：投与の 99.3%、日本人被験者集団：投与の 99.8%）及び治験責任医師（被験者集団全体：投与の 99.8%、日本人被験者集団：投与の 100.0%）からの局所反応についての報告はなかった。

臨床検査値又はバイタルサインのパラメーターに関して、注目すべき所見は認められなかった。

(3)　まとめ

本剤は出血エピソードの治療に極めて有効であり、周術期において止血をコントロールした。本剤を用いた定期的な投与では、オンデマンド療法に比べ AsBR 及び ABR が有意に低かったことから、定期的な投与の有意性が示された。本剤の PK プロファイルは、ルリオクトコグアルファより改善されており、投与開始 3～6 箇月後において時間非依存性であることが明らかになった。インヒビターは産生されず、本剤の安全

性及び忍容性プロファイルは良好であることが示された。

本剤の PK、有効性、及び安全性プロファイルにおいて、日本人被験者と非日本人被験者／全被験者に重要な差は認められなかった。

以上より、本剤の投与は、安全かつ忍容性が良好であり、出血エピソードのコントロール及び抑制、投与間隔が週 2～3 回の定期的な投与での使用、並びに成人及び青年の血友病 A 患者の周術期出血コントロールに適した有効な FVIII 補充療法である。

2.7.6.2　第 III 相試験（試験番号　CSL627_3002　評価資料：5.3.5.2）

標題：重度血友病 A の患児を対象とし、遺伝子組換え単鎖血液凝固第 VIII 因子の薬物動態、有効性及び安全性を検討する非盲検第 III 相試験

（1）　試験方法

試験方法の概要を以下に示す。

項目	内容
治験調整医師	Prof. Dr. med. Ingrid Pabinger, Division of Hematology and Hemostaseology, Department of Internal Medicine I, Medical University Vienna
実施国及び実施施設数	北米、欧州、その他の地域の 37 施設
公表文献	なし
実施期間	20[redacted] 年[redacted] 月[redacted] 日～20[redacted] 年[redacted] 月[redacted] 日
開発のフェーズ	第 III 相
試験の目的	主要目的：治験責任医師による 4 点評価尺度に基づき、大出血及び小出血の治療における本剤の有効性を評価する 副次的目的： - 定期的な投与での ABR を評価する - オンデマンド療法での ABR を評価する - 止血を達成するために本剤投与を 1、2、3、又は 4 回以上必要とする出血エピソードの発現割合を評価する - 本剤の使用量を評価する - 本剤の PK プロファイルを評価する - 本剤に対するインヒビター産生率を評価する - 本剤の安全性として、AE、臨床検査パラメーター、身体検査及びバイタルサイン（血圧、心拍数、体温、呼吸数）を評価する
試験デザイン	本治験は、重度血友病 A の小児患者を対象とした、本剤の有効性、安全性、

	及び PK を評価する多施設、国際共同、非盲検試験であった。北米、欧州、その他の地域の約 60 施設が参加予定であった。50 名の評価可能な被験者（6 歳以上 12 歳未満：25 名、0 歳以上 6 歳未満：25 名）を得るために、約 75 名を登録する予定であった。本治験実施の設定根拠は、重度血友病 A の小児患者集団での定期的な投与、出血エピソードの抑制及び治療における有効性、安全性、PK、及び本剤使用量のデータ収集であった。 PK 期間：被験者は、本剤の PK 評価期間へ参加することにより治験開始とされた。本治験の PK パートへの参加は 24 名以上（0 歳以上 6 歳未満：12 名、6 歳以上 12 歳未満：12 名）とした。当該被験者に本剤 50 IU/kg を投与し、PK 評価のための検体は、投与前及び投与後 1 時間（±5 分）、5 時間（± 60 分）、10 時間（±120 分）、24 時間（± 120 分）及び 48 時間（± 120 分）の時点で採取した。FVIII 活性を、ChS 法及び OS 法で測定した。ChS 法は、PK 解析の主要測定法とした。FVIII 活性のノンコンパートメント PK 解析を、各被験者の投与前の血漿中 FVIII 活性に対して、ベースライン補正あり及びなしで行った。FVIII 活性のベースライン補正は、被験者の投与前活性レベルを、投与後の各時点で得られた活性レベルから減算して行った。 PK 検体の最終採取後、定期的投与群の被験者は、治験実施施設にて本剤の最初の投与を受け、オンデマンド療法群の被験者は、在宅投与用の本剤を処方された。本時点を有効性評価のための治療期間の開始とした。 治療期間：治療期間中、投与日数が 50 ED に達するまで被験者に本剤を投与した。被験者は 6 箇月目まで 1 箇月（28 ± 7 日）に 1 回、評価のために治験実施施設に来院することとした。6 箇月目の評価後、被験者は少なくとも投与日数が 50 ED に達するまで 3 箇月（± 7 日）に 1 回、評価のために治験実施施設に来院した。50 ED 以降、被験者は次の予定来院日（1 箇月又は 3 箇月ごと）又は治験終了時来院日に、治験実施施設に来院した。したがって、50 名以上（各年齢群 25 名以上）の被験者で投与日数が 50 ED に達するまで、被験者は 1～6 箇月目は毎月 1 回、その後は 3 箇月に 1 回、及び治験終了時来院日に治験実施施設に来院した。50 名（各年齢群 25 名）で投与日数が 50 ED となった後、残りの被験者は、投与日数に関わらず実施中の継続投与試験である 3001 試験に直接移行できることとした。 - 定期的な投与：投与日数が 50 ED 以上に達するまで（又は 50 ED に達した被験者が各年齢群で 25 名以上となるまで）、被験者に本剤を投与することとし、その期間は、治療期間開始後約 6 箇月間と予測され

	た。 - オンデマンド療法：投与日数が 50 ED 以上に達するまで（又は 50 ED に達した被験者が各年齢群で 25 名以上となるまで）、被験者に本剤を投与することとし、最長で治療期間開始後 2 年までかかると考えられた。 本治験では大手術実施時の本剤投与は禁止とし、大手術を避けられない場合、被験者は治験を中止した。 安全性評価及び AE の記録は継続して実施した。
被験者数	84 名を本治験に登録した（0 歳以上 6 歳未満：35 名、6 歳以上 12 歳未満：49 名）。
対象	重度血友病 A 患者
選択基準	本治験の主要選択基準は、重度血友病 A（FVIII 活性が 1%未満）であることが医療記録に記載されており、FVIII に対するインヒビターの既往歴又は家族歴（親・子・兄弟）がなく、FVIII 製剤の過去の投与日数が 50 ED を超える年齢 0 歳以上 12 歳未満の男性患者とした。
除外基準	- 第 VIII 因子に対するインヒビターの既往歴のある、又は FVIII に対するインヒビターを現在有している患者 - 第 VIII 因子に対するインヒビターの家族歴（親・子・兄弟）のある患者 - 本剤の初回投与の前 30 日以内に何らかの治験薬を使用した患者 - 本剤又は対照薬の投与の前 30 日以内にクリオプレシピテート、全血又は血漿の投与を受けた患者 - 第 VIII 因子製剤又はハムスタータンパクに対する既知の過敏症（アレルギー反応又はアナフィラキシー）を有する患者 - 免疫グロブリン等の免疫調節薬の IV 投与、又は慢性的に全身性コルチコステロイドの投与を受けている患者 - スクリーニング時に AST 値又は ALT 値が基準値上限の 5 倍を超える患者 - スクリーニング時に血清クレアチニン値が基準値上限の 2 倍を超える患者 - Day 1 の前 3 箇月以内に深部静脈血栓症、脳卒中、肺塞栓症、心筋梗塞及び動脈塞栓を含む血栓症の徴候のある患者 - Day 1 の前 3 箇月以内に生命にかかわる出血エピソードが発現した、又は大手術あるいは整形外科手術を受けた患者

被験薬	本剤は、単回使用バイアル入りの凍結乾燥粉末（力価：250 IU/バイアル、500 IU/バイアル、1000 IU/バイアル、2000 IU/バイアル、及び 3000 IU/バイアル）として供給された。
投与方法	バイアルのラベルに表示された実際の力価を基に算出した用量を、治験責任医師の判断で小児患者に適切かつ被験者が忍容できる速度で IV 投与した。 PK 評価：Day 1 に本剤 50 IU/kg を単回投与した。 定期的な投与：本剤を、隔日若しくは週 2～3 回 15～50 IU/kg で、又は過去の FVIII 用量及び PK データに基づき治験責任医師が決定した用量及び頻度で投与した。より高い強度のレジメンへの用量漸増は、治験責任医師の判断により可能とした。 オンデマンド療法：本剤を治験責任医師が処方した用量で投与した。
対照薬	なし
試験期間	各被験者の試験期間は、定期的投与群の被験者で約 6 箇月間、オンデマンド療法群の被験者で最長 2 年間と予測され、投与日数が 50 ED 以上に達するまで（又は 50 ED に達した被験者が各年齢群で 25 名以上となるまで）の期間とした。
有効性評価	主要評価項目： 治療された全出血エピソードについて、治験責任医師の総合的臨床評価が「優」又は「良」の場合を治療成功と定義したときの治療成功率 副次評価項目： - 定期的な投与及びオンデマンド療法中の ABR（外傷性出血及び非外傷性／自然出血） - 止血を達成するために、本剤投与を 1、2、3、又は 4 回以上必要とする出血（外傷性及び非外傷性／自然）エピソードの発現 - 本剤の使用量（1 箇月あたり及び 1 年あたりの投与回数及び IU/kg で表す）、及びイベントあたりの IU/kg（定期的な投与、及びオンデマンド療法）
安全性評価	副次評価項目： - 初回投与から治験終了までに評価された FVIII に対するインヒビター産生の発現 - 治療期間の AE、臨床検査値、身体検査所見、及びバイタルサイン（血圧、心拍数、体温、呼吸数）
臨床薬理学的評価	副次評価項目： 本剤の PK パラメーター［IR、$t_{1/2}$、AUC_{0-t}、$AUC_{0-\infty}$、C_{max}、t_{max}、λ_z、$AUMC_{0-}$

	$_{\infty}$、MRT、CL、V_z（終末期の分布容積）、V_{ss}］
統計手法	PK 解析： 正式な PK 解析集団は、PK 評価に参加し、本剤の投与を 1 回以上受け、本剤の PK プロファイルを評価できる十分な数の測定可能な PK 評価用の検体が得られたすべての被験者で構成された。 ベースライン補正あり及びなしの FVIII 活性及び PK パラメーターについて、投与群、測定法（ChS 法、OS 法）、及び年齢群（0 歳以上 6 歳未満、6 歳以上 12 歳未満）ごとに、記述統計量（n、平均、SD、CV%（変動係数%）、中央値、最小値、最大値）及び幾何平均値を示した。 FVIII 活性レベルについて、平均値（SD）及び各被験者の値の経時的推移を図示した。 有効性解析： 有効性解析は有効性解析集団及び PP 解析集団で実施した。有効性解析集団は、治験中に定期的な投与又はオンデマンド療法として本剤の投与を 1 回以上受けたすべての被験者で構成された。PP 解析集団は、有効性解析集団の被験者で、治験実施計画書からの重大な逸脱、又は主要有効性評価項目の評価に影響を及ぼすような治験実施計画書からの逸脱がなく本治験を完了したすべての被験者で構成された。 主要有効性評価項目： 出血エピソード数及び治療された出血エピソード数を要約した。治療が成功（止血効果の評価が「優」又は「良」）であった出血エピソードの割合である治療成功率及び 95% CI を算出した。治療成功率は、分子を本剤で治療され、「優」又は「良」と評価された出血エピソード、分母を治療された全出血エピソードとする割合として算出した。主要解析では、治験責任医師の評価のない治療された出血エピソードは治療不良とみなした。感度分析では、治験責任医師の評価のない治療された出血エピソードは解析対象外、又は治療成功とみなした。被験者内の相関関係を説明するために、SAS の GENMOD 手法による一般化線形モデルを用いた。 止血効果に関する治験責任医師の総合的臨床評価を、有効性解析集団及び PP 解析集団で要約し、有効性解析集団での解析を主要解析とした。止血効果に関する治験責任医師の総合的臨床評価について、有効性解析集団での年齢、BMI、人種及び地域別サブグループ解析も実施した。 副次的有効性評価項目： ABR は、365.25×（治療を要した出血エピソード回数/有効性評価日数）と定義した。総出血、自然出血、外傷性出血、及び関節出血の ABR を算出し、記

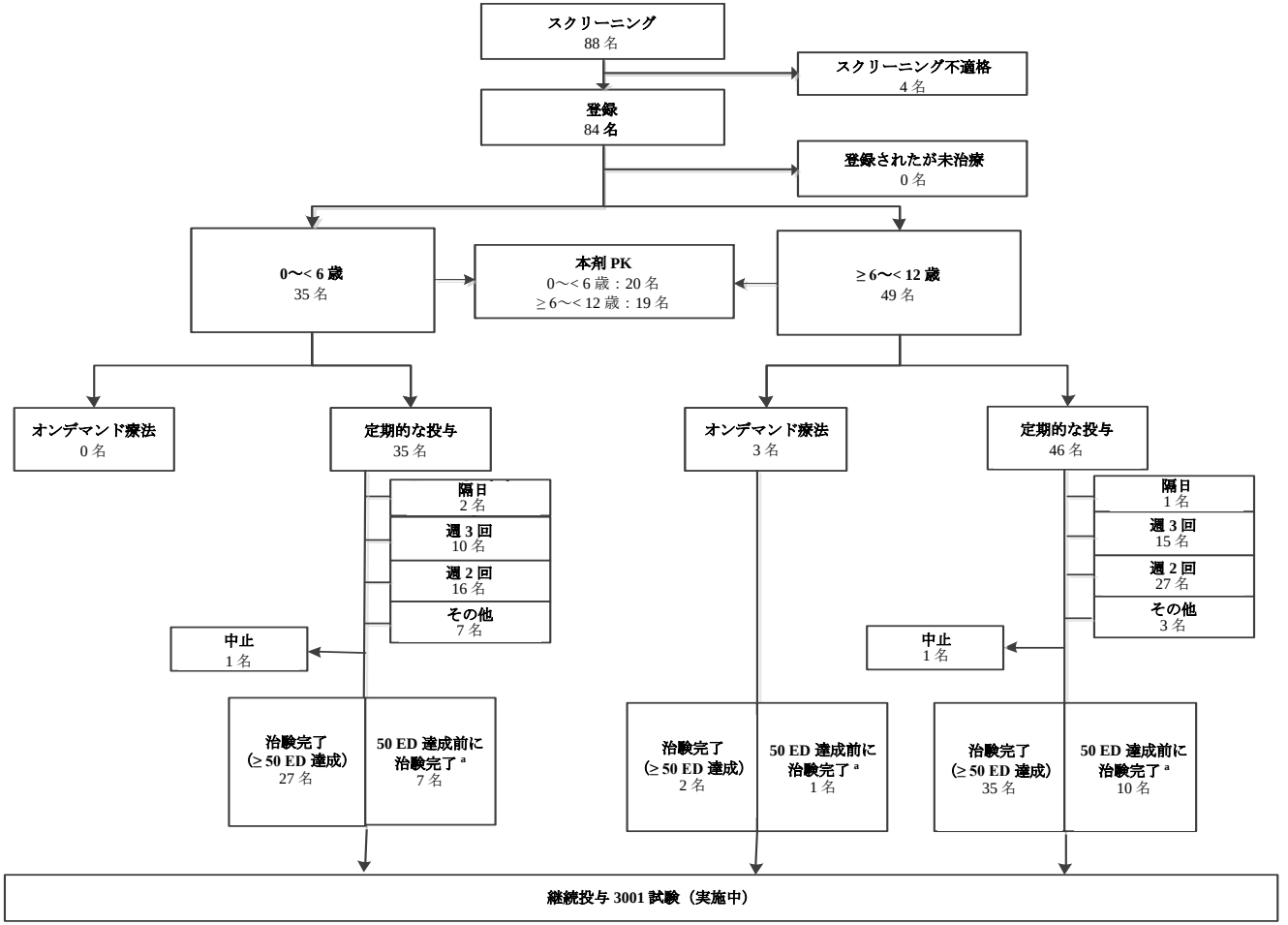
	述統計量を用いて要約した。また、Poisson モデルに基づき、出血エピソード（総出血、自然出血、外傷性出血、及び関節出血）の年間発現回数及び 95% CI を算出した。 ABR は、治療法（オンデマンド療法又は定期的な投与）別に示し、有効性解析集団及び PP 解析集団で要約した。年齢、BMI、人種及び地域別サブグループ解析も有効性解析集団で実施した。 止血を達成するために、本剤投与を 1、2、3、又は 4 回以上必要とする出血エピソードの発現回数及び割合を、オンデマンド療法群、定期的投与群、及び全体で表に示し、有効性解析集団（全体及び年齢群別）及び PP 解析集団で要約した。 本剤の使用量を、治療法（オンデマンド療法又は定期的な投与）別に、投与回数又は記述統計量を用いて要約した。定期的投与群の使用量は、有効性解析集団（全体及び年齢群別）及び PP 解析集団で要約し、オンデマンド療法群の使用量は、有効性解析集団（全体及び年齢群別）でのみ要約した。 安全性解析： 安全性解析集団は、本治験で本剤の投与を 1 回以上受けたすべての被験者で構成された。FVIII に対するインヒビターが発現した被験者数及び被験者の割合を表に示し、インヒビター産生の正確な二項分布の 95% CI を示した。治験薬投与開始後に臨床検査値異常が発現した被験者数及び被験者の割合、並びに臨床的に重要なバイタルサインを示した被験者数及び被験者の割合を表に示した。AE が発現した被験者数及び被験者の割合を、MedDRA に基づき SOC 及び PT 別に全体で要約し、最大重症度及び治験薬との因果関係に基づき要約した。 インヒビター、非阻害 ADA、及び CHO 細胞由来タンパク質に対する抗体の検査が陽性であった被験者数及び被験者の割合を表に示した。

（2） 試験成績

1） 被験者の内訳

84 名が本治験に登録され、そのうち、0 歳以上 6 歳未満が 35 名、6 歳以上 12 歳未満が 49 名であった。被験者の内訳を図 2.7.6.2-1 に示し、表 2.7.6.2-1 に要約した。

図 2.7.6.2-1　3002 試験：被験者の内訳



略語：ED、投与日数；PK、薬物動態；本剤、遺伝子組換え単鎖血液凝固第 VIII 因子

[a]　主要目的（各年齢群で 50 ED に達した被験者が 25 名以上）を達成したため被験者は治験を完了した。被験者は、被験者募集中の継続投与 3001 試験に移行可能であった。

引用：3002 試験 CSR 表 14.1.2.1、表 14.1.2.2、表 14.1.10.2.1、表 14.1.10.3.1、一覧表 16.2.1.4、一覧表 16.2.3、一覧表 16.2.5.3

表 2.7.6.2-1　3002 試験：被験者の内訳（全被験者）

	被験者数(%)		
	0 歳以上 6 歳未満 (N = 35)	**6 歳以上 12 歳未満 (N = 49)**	**合計 (N = 84)**
治験完了	27 (77.1)	38 (77.6)	65 (77.4)
治験中止	8 (22.9)	11 (22.4)	19 (22.6)
中止理由			
AE	0	1 (2.0)	1 (1.2)
医師の判断	1 (2.9)	0	1 (1.2)
治験依頼者による中止 a	7 (20.0)	10 (20.4)	17 (20.2)

略語：AE、有害事象；ED、投与日数；N、総被験者数（当該年齢群内又は合計）
[a]　各年齢群で 50 ED に達した被験者が 25 名以上となったことによる中止。中止時点で治験中であった被験者は、本治験での ED 数によらず 3001 試験に移行した。
引用：3002 試験 CSR 表 14.1.2.1

治験実施計画書からの重大な逸脱

全体で、治験実施計画書からの重大な逸脱が 9 名に認められ、PP 解析集団から除外された。

- 1 名は、臨床検査実施時のエラーにより、FVIII に対するインヒビター陰性と当初報告されていたが、FVIII に対するインヒビターを既に有していたことが明らかとなった。当該被験者は治験を継続したが、有効性解析集団及び PP 解析集団から除外された。
- 8 名（各年齢群 4 名）は、用量及び／又は療法不遵守であることが明らかとなり、PP 対象解析集団から除外された。

治験実施計画書から逸脱し PP 解析集団から除外された被験者を表 2.7.6.2-2 に要約する。

表 2.7.6.2-2　3002 試験：治験実施計画書から逸脱し PP 解析集団から除外された被験者

	オンデマンド療法 (N = 3) n (%)	**定期的な投与 (N = 80) n (%)**	**合計 (N = 83) n (%)**
PP 解析集団からの除外	0	8 (10.0)	8 (9.6)
PP 解析集団からの除外理由			
規定用量の不遵守	0	5 (6.3)	5 (6.0)
規定の定期的な投与の不遵守	0	4 (5.0)	4 (4.8)

略語：N、総被験者数（当該療法群内又は合計）；n、当該カテゴリーの被験者数；PP、治験実施計画書に適合した
注：
[1] 被験者の数及びパーセント[n (%)]を表す。
[2] パーセントは有効性解析集団の被験者数を基に算出した。
引用：3002 試験 CSR 表 14.1.3.2.1

2）　解析対象集団の内訳

本剤を投与された全 84 名を安全性解析集団とした。

安全性解析集団から、スクリーニング時に FVIII に対するインヒビターを既に有していたことが明らかとなった 1 名を除外した 83 名を有効性解析集団とした。有効性解析集団から、用量又は定期的な投与の不遵守により治験実施計画書からの重大な逸脱となった 8 名を除外した 75 名を PP 解析集団とした。84 名中、十分な PK 評価用データが得られた 39 名（0 歳以上 6 歳未満：20 名、6 歳以上 12 歳未満：19 名）を PK 解析集団とした（表 2.7.6.2-3）。

表 2.7.6.2-3　3002 試験：解析対象集団

	被験者数		
	0 歳以上 6 歳未満	**6 歳以上 12 歳未満**	**合計**
登録例	35	49	84
安全性解析集団	35	49	84
有効性解析集団	35	48	83
PP 解析集団	31	44	75
PK 解析集団	20	19	39

略語：PP、治験実施計画書に適合した；PK、薬物動態
引用：3002 試験 CSR 表 14.1.1.2

3）人口統計学的及び他の基準値の特性

全 84 名が男性であった。84 名中 61 名（72.6%）が白人、22 名（26.2%）がアジア人、1 名（1.2%）がその他であった。また、2 名（2.4%）がヒスパニック系又はラテン系であった。被験者の平均年齢は 6.6 歳（範囲：1～11 歳）であった（表 2.7.6.2-4）。

表 2.7.6.2-4　3002 試験：人口統計学的及び患者背景の特性（安全性解析集団）

	0 歳以上 6 歳未満 (N = 35)	6 歳以上 12 歳未満 (N = 49)	合計 (N = 84)
年齢（歳）			
平均値（SD）	3.5 (1.34)	8.8 (1.77)	6.6 (3.11)
中央値	4.0	9.0	7.0
最小値、最大値	1, 5	6, 11	1, 11
体重（kg）			
平均値（SD）	16.62 (3.566)	35.45 (12.361)	27.60 (13.447)
中央値	16.00	32.00	25.00
最小値、最大値	10.0, 26.2	18.7, 87.5	10.0, 87.5
BMI（kg/m^2）			
平均値（SD）	15.81 (1.660)	18.50 (4.018)	17.38 (3.500)
中央値	15.63	17.60	16.80
最小値、最大値	13.4, 20.0	11.9, 29.6	11.9, 29.6
人種, n (%)			
アジア人	9 (25.7)	13 (26.5)	22 (26.2)
白人	25 (71.4)	36 (73.5)	61 (72.6)
その他	1 (2.9)	0	1 (1.2)
民族, n (%)			
ヒスパニック系又はラテン系	1 (2.9)	1 (2.0)	2 (2.4)
非ヒスパニック系又は非ラテン系	33 (94.3)	48 (98.0)	81 (96.4)
報告なし	1 (2.9)	0	1 (1.2)

略語：BMI、体格指数；N、総被験者数（当該年齢群内又は合計）；n、各カテゴリーの被験者数；SD、標準偏差
注：
[1] BMI は次式により求めた：スクリーニング時の BMI = スクリーニング時の体重（kg） / [スクリーニング時の身長 (m)]^2
[2] パーセントは安全性解析集団の被験者数を基に算出した。
引用：3002 試験 CSR 表 14.1.4.1

4） 治験薬の投与状況

安全性解析集団（84 名）で、全体での投与日数の平均値（SD）は、62.4（24.73）ED であった。6 歳以上 12 歳未満群で、0 歳以上 6 歳未満群と比べて投与日数が多かった［それぞれの平均値（SD）：66.4（27.64）ED、56.7（18.90）ED］。投与日数が 50 ED 以上であった被験者は 65 名（77.4%）で、そのうち 8 名（9.5%）で投与日数が 100 ED 以上であった（表 2.7.6.2-5）。

表 2.7.6.2-5　3002 試験：本剤の曝露状況（安全性解析集団）

	0 歳以上 6 歳未満 (N = 35)	**6 歳以上 12 歳未満 (N = 49)**	**合計 (N = 84)**
投与日数（ED）			
平均値（SD）	56.7 (18.90)	66.4 (27.64)	62.4 (24.73)
中央値	52.0	59.0	58.5
最小値、最大値	4, 98	9, 142	4, 142
< 50 ED, n (%)	8 (22.9)	11 (22.4)	19 (22.6)
≥ 50 ED, n (%)	27 (77.1)	38 (77.6)	65 (77.4)
≥ 100 ED, n (%)	0	8 (16.3)	8 (9.5)
投与回数			
平均値（SD）	56.9 (19.20)	67.8 (28.93)	63.3 (25.77)
中央値	52.0	60.0	59.0
最小値、最大値	4, 100	9, 145	4, 145
総投与回数	1991	3322	5313
1 投与あたりの総投与量（IU/kg）			
平均値（SD）	38.3 (11.21)	35.0 (12.11)	36.3 (11.89)
中央値	37.7	30.8	33.0
最小値、最大値	16, 76	11, 93	11, 93
総投与量（IU）			
平均値（SD）	2263.5 (1011.13)	2471.8 (1371.59)	2385.0 (1231.84)
中央値	2079.1	2124.2	2079.2
最小値、最大値	176, 5918	222, 7831	176, 7831

略語：ED、投与日数；IU、国際単位；N、総被験者数（当該年齢群内又は合計）；n、当該カテゴリーの被験者数
注：パーセントは当該集団の被験者数を基に算出した。
引用：3002 試験 CSR 表 14.1.8.5.1

5）臨床薬理学的評価の結果

ChS 法で測定した主要な PK パラメーターの平均値は、0 歳以上 6 歳未満群及び 6 歳以上 12 歳未満群で、それぞれ、C_{max} が 80.2 及び 83.5 IU/dL、IR が 1.60 及び 1.66 (IU/dL)/(IU/kg)、$AUC_{0-\infty}$が 1080 及び 1170 IU*h/dL、$t_{1/2}$ が 10.4 及び 10.2 h、CL が 5.07 及び 4.63 mL/h/kg、MRT が 12.4 及び 12.3 h であった（表 2.7.6.2-6）。

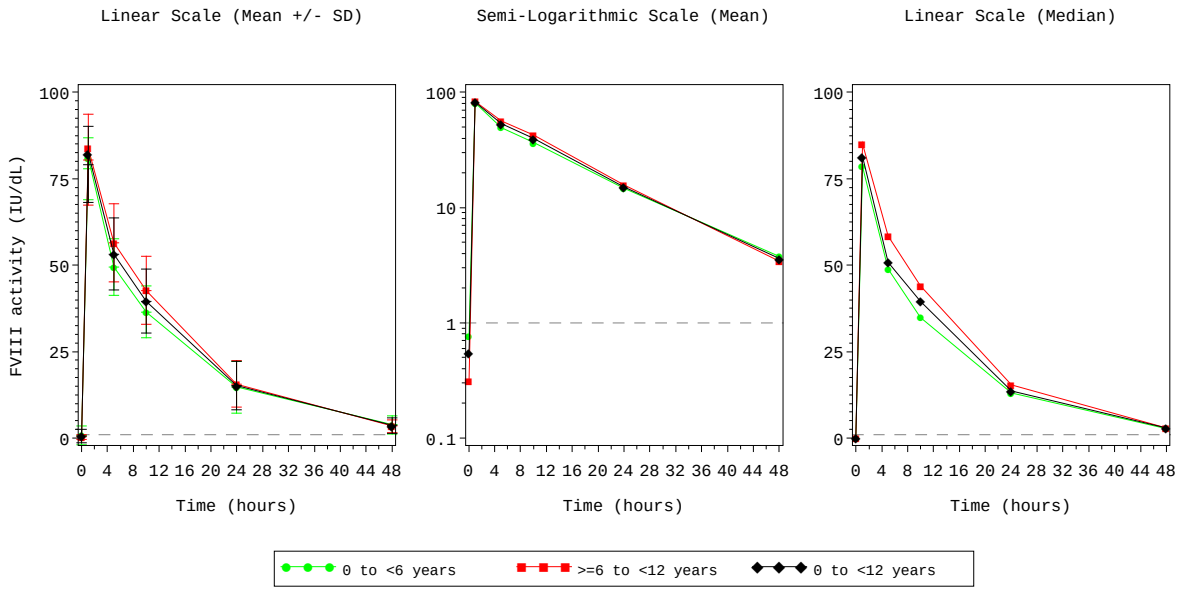
表 2.7.6.2-6　3002 試験：年齢別 FVIII PK パラメーターの平均値（CV%）
（PK 解析集団の全被験者）－ChS 法

パラメーター、単位	平均値 (CV%)	
	0 歳以上 6 歳未満 (N = 20)	**6 歳以上 12 歳未満 (N = 19)**
Cmaxa, IU/dL	80.2 (20.6)	83.5 (19.5)
IRa, (IU/dL)/(IU/kg)	1.60 (21.1)	1.66 (19.7)
AUC0-t, IU*h/dL	1010 (28.4)	1090 (26.4)
AUC0-∞, IU*h/dL	1080 (31.0)	1170 (26.3)
t1/2, h	10.4 (28.7)	10.2 (19.4)
CL, mL/h/kg	5.07 (29.6)	4.63 (29.5)
Vss, mL/kg	71.0 (11.8)	67.1 (22.3)
MRT, h	12.4 (25.0)	12.3 (16.8)

略語：AUC_{0-t}、定量化可能な最終検体採取時刻までの活性/濃度曲線下面積；$AUC_{0-\infty}$、無限大時間まで外挿した活性/濃度曲線下面積；ChS、発色合成基質法；CL、クリアランス；Cmax、最高血漿中濃度；CV%、変動係数%；FVIII、血液凝固第 VIII 因子；IR、回収率、IU、国際単位；MRT、平均滞留時間；N、総被験者数；PK、薬物動態；$t_{1/2}$、半減期；Vss、定常状態での分布容積
[a] C_{max} 及び IR は、投与後の各時点で得られた活性レベルから各被験者の投与前 FVIII 活性レベルを減算して、ベースライン補正を行った。その他のパラメーターではベースライン補正を行わなかった。
引用：3002 試験 CSR 表 14.2.12.2

ChS 法で測定した FVIII 活性プロファイル及び PK パラメーターの平均値は、0 歳以上 6 歳未満の被験者と 6 歳以上 12 歳未満の被験者で類似していた（図 2.7.6.2-2）。最終検体採取時間（48 時間）に、0 歳以上 6 歳未満の被験者 20 名中 16 名、及び 6 歳以上 12 歳未満の被験者 19 名中 16 名で、FVIII 活性レベルが 1%を超えており、平均レベルはそれぞれ 3.78 及び 3.43 IU/dL であった。

図 2.7.6.2-2　3002 試験：年齢別の投与前 FVIII 活性（ベースライン補正なし）（PK 解析集団の全被験者）－ChS 法



略語：ChS、発色合成基質法；FVIII、血液凝固第 VIII 因子；IU、国際単位；PK、薬物動態
注：
[1] 定量下限値（LLOQ）：ChS 法=1.00 IU/dL
[2] 全測定値を記述統計量の算出に用い、LLOQ 未満の測定値は 0 とした。したがって、平均値が LLOQ 未満となる可能性があった。
引用：3002 試験 CSR 図 14.2.1.1.1

OS 法で測定した FVIII 活性レベルは ChS 法を用いた場合と比較して約 45%低かった。これは、OS 法と ChS 法の 2 種類のアッセイ間で知られている差異と合致しており、また、青年及び成人を対象とした 1001 試験で得られた結果と同様であった。この差異は他の PK パラメーターでも同様に認められた。

本治験では、成人及び青年を対象とした 1001 試験と比較して PK 検体数が少なかったが、本治験の対象集団である小児での血漿中 FVIII 活性の時間推移により、FVIII 活性のプロファイルが明らかとなった。さらに、本剤の ChS 法による FVIII の PK パラメーターの精度は妥当であり、CV%は約 30%であった。

また、主要な PK パラメーター、AUC、CL、V_{ss} 及び MRT は比較的頑健であり、分布相で結果が低く見積もられることによる影響はわずかであった。IV 投与では、血漿中 FVIII 活性は、投与終了時が最も高くその後減少する。本治験での PK 検体採取スケジュールでは、最初の PK 検体採取時間は注入 1 時間後であり、C_{max} と IR の測定値は実際より低くなると予測され、さらに分布相は実際より低く見積もられる可能性があった。しかし、本剤の IV 投与後の分布は非常に速く、全体の

PK プロファイルに及ぼす分布相の影響はわずかであった。

全体として、本剤 50 IU/kg の単回投与後の PK 特性が明らかとなった。予想されたとおり、小児集団では、1001 試験での青年／成人と比較して、CL は高く $t_{1/2}$ は短かった。しかし、2 つの年齢群間での差は認められなかった。

6）有効性の結果

出血エピソードの治療及び定期的な投与での本剤の有効性を、12 歳未満の血友病 A 患者 83 名で評価した。全体的に、本剤の出血エピソードの止血効果は高く、ABR は低かった。大多数の被験者で投与量は 20～50 IU/kg であり、被験者の約 50%が週 2 回の投与を継続した。

全体で、投与量又は投与頻度が増加する傾向は認められなかった。投与量又は投与スケジュールを調整しなかった被験者は、有効性解析集団 83 名中 51 名（61.4%）であった（表 2.7.6.2-7）。

表 2.7.6.2-7　3002 試験：割付用量及び調整用量の要約（有効性解析集団）

	オンデマンド療法 (N = 3)	定期的な投与				合計 (N = 83)
		隔日 (N = 3)	週 3 回 (N = 24)	週 2 回 (N = 43)	他の療法 (N = 10)	
初回割付用量、IU/kg						
N	3	3	24	43	10	83
平均値（SD）	26.0 (2.65)	39.0 (11.53)	33.8 (9.64)	34.7 (10.12)	43.0 (12.73)	35.3 (10.56)
中央値	25.0	40.0	32.0	35.0	50.0	34.0
最小値、最大値	24, 29	27, 50	19, 50	20, 57	23, 55	19, 57
割付用量が< 15 IU/kg であった被験者数、n (%)	0	0	0	0	0	0
割付用量が> 50 IU/kg であった被験者数、n (%)	0	0	0	4 (9.3)	3 (30.0)	7 (8.4)
最終割付用量、IU/kg						
N	3	3	32	38	7	83
平均値（SD）	25.0 (4.00)	44.3 (5.13)	34.9 (10.02)	36.2 (10.37)	43.1 (13.75)	36.2 (10.64)
中央値	25.0	43.0	32.0	35.5	50.0	35.0
最小値、最大値	21, 29	40, 50	20, 50	20, 57	23, 55	20, 57
被験者あたりの用量調整回数、n (%)						
0	2 (66.7)	2 (66.7)	14 (58.3)	26 (60.5)	7 (70.0)	51 (61.4)
1	1 (33.3)	1 (33.3)	7 (29.2)	10 (23.3)	2 (20.0)	21 (25.3)
2	0	0	3 (12.5)	2 (4.7)	0	5 (6.0)
> 2	0	0	0	5 (11.6)	1 (10.0)	6 (7.2)
用量調整理由、n (%)[a]						
医師の判断	1 (33.3)	1 (33.3)	8 (33.3)	13 (30.2)	3 (30.0)	26 (31.3)
有効性欠如	0	0	0	1 (2.3)	0	1 (1.2)
その他	0	0	4 (16.7)	4 (9.3)	0	8 (9.6)

略語：IU、国際単位；N、総被験者数（全体又は当該療法群内）；n、当該カテゴリーの被験者数；SD、標準偏差

[a] 異なる理由で 2 回以上用量調整を行った被験者では、それぞれの用量調整理由を含めた。

注：

[1] 被験者の数及びパーセント[n (%)]を表す。パーセントは当該集団の被験者数を基に算出した。

[2] 割付用量が< 15 IU/kg、又は> 50 IU/kg であった被験者には、初回割付用量及び調整用量が含まれる。

引用：3002 試験 CSR 表 14.1.10.1.1、表 14.1.10.4.1

出血エピソードの治療における本剤投与で得られた主な有効性の結果を以下に示す。

- 全体で、最も出血頻度が高かった部位は関節（61.7%）であり、次いで、その他の部位（23.1%）、筋肉（14.4%）であった。出血エピソードは、各関節、筋肉、及びその他の部位内の広い範囲で発現しており、明らかな傾向は認められなかった。
- 全体で、評価可能であった治療された出血エピソードのうち、96.3%（334/347 件）が、治験責任医師により治療成功と評価され、止血効果に関する治験責任医師の総合的臨床評価が「優」又は「良」であった。
- 全体で、出血エピソードの 95.7%が、本剤の 1～2 回投与でコントロールされた。
- 全体で、1 出血エピソードあたりの投与量の中央値は 27.6 IU/kg、1 出血エピソードでの 1 投与回数あたりの投与量の中央値は 27.3 IU/kg であった。
- 以下に示すように、全体で、2 つの年齢群間で、出血エピソードの治療に明らかな違いは認められなかった。
  - 治療成功率は、0 歳以上 6 歳未満群 94.0%、6 歳以上 12 歳未満群 96.6%で、同様であった（表 2.7.6.2-9）。
  - 本剤の 1～2 回投与でコントロールされた出血エピソードの割合は、0 歳以上 6 歳未満群 94.0%、6 歳以上 12 歳未満群 96.0%で、同様であった（表 2.7.6.2-10）。

出血エピソードの治療の要約を表 2.7.6.2-8、表 2.7.6.2-9 及び表 2.7.6.2-10 に示す。

表 2.7.6.2-8　3002 試験：治療成功－止血効果に関する治験責任医師の総合的臨床評価
（有効性解析集団）

出血エピソード評価	オンデマンド療法 (N = 3)	定期的な投与 (N = 80)	全体 (N = 83)
出血エピソード数	133	256	389
治療された出血エピソード数	132	215	347
優、n (%)	132 (100.0)	164 (76.3)	296 (85.3)
良、n (%)	0	38 (17.7)	38 (11.0)
可、n (%)	0	12 (5.6)	12 (3.5)
不可／反応なし、n (%)	0	1 (0.5)	1 (0.3)
治療成功(a)	132	202	334
治療成功率	100.0	94.0	96.3
95% CI	N/A	[87.8, 97.1]	[91.3, 98.4]
治療成功(b)	132	202	334
治療成功率	100.0	94.0	96.3
95% CI	N/A	[87.8, 97.1]	[91.3, 98.4]
治療成功(c)	132	202	334
治療成功率	100.0	94.0	96.3
95% CI	N/A	[87.8, 97.1]	[91.3, 98.4]

略語：CI、信頼区間；N、総被験者数（全体又は当該療法群内）；n、当該カテゴリーの被験者数；N/A、該当せず

注：

[1] 治療成功は「優」又は「良」と定義した。(a)主要解析：欠測値は治療不成功、(b)感度分析：欠測値はすべて除外、(c)感度分析：欠測値は治療成功として扱った。

[2] 95% CI は被験者内相関を考慮した一般化線形モデルを基に算出した。

[3] 表中、出血エピソードの数及びパーセント[n (%)]を表す。

[4] パーセントは治療された出血エピソード数を基に算出した。

引用：3002 試験 CSR 表 14.2.1.1.1

表 2.7.6.2-9　3002 試験：年齢群別治療成功－止血効果に関する治験責任医師の総合的臨床評価（有効性解析集団）

年齢群 出血エピソード評価	オンデマンド療法	定期的な投与	全体
年齢群：0 歳以上 6 歳未満	(N = 0)	(N = 35)	(N = 35)
出血エピソード数	0	79	79
治療された出血エピソード数	0	50	50
優、n (%)	0	37 (74.0)	37 (74.0)
良、n (%)	0	10 (20.0)	10 (20.0)
可、n (%)	0	3 (6.0)	3 (6.0)
不可／反応なし、n (%)	0	0	0
治療成功(a)	0	47	47
治療成功率	N/A	94.0	94.0
95% CI	N/A	[83.7, 97.9]	[83.7, 97.9]
治療成功(b)	0	47	47
治療成功率	N/A	94.0	94.0
95% CI	N/A	[83.7, 97.9]	[83.7, 97.9]
治療成功(c)	0	47	47
治療成功率	N/A	94.0	94.0
95% CI	N/A	[83.7, 97.9]	[83.7, 97.9]
年齢群：6 歳以上 12 歳未満	(N = 3)	(N = 45)	(N = 48)
出血エピソード数	133	177	310
治療された出血エピソード	132	165	297
優、n (%)	132 (100.0)	127 (77.0)	259 (87.2)
良、n (%)	0	28 (17.0)	28 (9.4)
可、n (%)	0	9 (5.5)	9 (3.0)
不可／反応なし、n (%)	0	1 (0.6)	1 (0.3)
治療成功(a)	132	155	287
治療成功率	100.0	93.9	96.6
95% CI	N/A	[85.8, 97.5]	[90.6, 98.8]
治療成功(b)	132	155	287
治療成功率	100.0	93.9	96.6
95% CI	N/A	[85.8, 97.5]	[90.6, 98.8]
治療成功(c)	132	155	287
治療成功率	100.0	93.9	96.6
95% CI	N/A	[85.8, 97.5]	[90.6, 98.8]

略語：CI、信頼区間；N、総被験者数（全体又は当該療法／年齢群内）；n、当該カテゴリーの被験者数；N/A、該当せず

注：

[1] 治療成功は「優」又は「良」と定義した。(a)主要解析：欠測値は治療不成功、(b)感度分析：欠測値はすべて除外、(c)感度分析：欠測値は治療成功として扱った。

[2] 95% CI は被験者内相関を考慮した一般化線形モデルを基に算出した。

[3] 表中、出血エピソードの数及びパーセント[n (%)]を表す。

[4] パーセントは治療された出血エピソード数を基に算出した。

引用：3002 試験 CSR 表 14.2.1.3、表 14.2.1.4

表 2.7.6.2-10　3002 試験 : 止血を達成するために必要とした本剤の投与回数及び本剤の投与量（有効性解析集団）

	オンデマンド療法 (N = 3)	定期的な投与 (N = 80)	全体 (N = 83)
出血エピソード数	133	256	389
治療された出血エピソード数	132	215	347
出血エピソードが 1 回以上の被験者数	3	63	66
治療された出血エピソードが 1 回以上の被験者数	3	59	62
止血達成に要した投与回数（治療された出血エピソードに対するパーセント）			
1 回	131 (99.2)	167 (77.7)	298 (85.9)
2 回	0	34 (15.8)	34 (9.8)
3 回	1 (0.8)	7 (3.3)	8 (2.3)
> 3 回	0	7 (3.3)	7 (2.0)
1 出血エピソードあたりの総投与量（IU/kg）			
平均値（SD）	27.8 (7.70)	47.2 (36.88)	39.8 (30.86)
中央値 (最小値、最大値)	25.9 (21, 78)	37.0 (16, 282)	27.6 (16, 282)
1 出血エピソードの 1 投与あたりの総投与量（IU/kg）			
平均値（SD）	27.4 (6.33)	34.1 (11.41)	31.5 (10.30)
中央値 (最小値、最大値)	25.9 (21, 57)	30.0 (16, 76)	27.3 (16, 76)

略語：IU、国際単位；N、総被験者数（全体又は当該療法群内）；SD、標準偏差
引用：3002 試験 CSR 表 14.2.3.1

定期的な投与における本剤投与で得られた主な有効性の結果を以下に示す。

- 本剤の定期的な投与での ABR は低く、中央値は、総出血エピソードが被験者一人あたり 3.69 件、自然出血エピソードが 0.00 件であった（表 2.7.6.2-11）。

表 2.7.6.2-11　3002 試験：ABR 及び AsBR（有効性解析集団）

	オンデマンド療法 (N = 3)	定期的な投与 (N = 80)
総出血エピソード		
平均値（SD）	66.77 (27.702)	5.22 (5.557)
中央値	78.56	3.69
Q1、Q3	35.12, 86.62	0.00, 7.20
最小値、最大値	35.1, 86.6	0.0, 23.7
年間出血エピソード回数[95% CI]	71.5 [60.3, 84.8]	5.5 [4.8, 6.3]
自然出血エピソード		
平均値（SD）	24.83 (22.191)	1.70 (2.972)
中央値	31.76	0.00
Q1、Q3	0.00, 42.73	0.00, 2.20
最小値、最大値	0.0, 42.7	0.0, 14.0
年間出血エピソード回数[95% CI]	28.7 [21.9, 37.6]	1.9 [1.5, 2.4]
外傷性出血エピソード		
平均値（SD）	28.95 (11.320)	2.28 (2.583)
中央値	35.12	1.97
Q1、Q3	15.88, 35.84	0.00, 3.81
最小値、最大値	15.9, 35.8	0.0, 10.0
年間出血エピソード回数[95% CI]	28.2 [21.5, 37.0]	2.5 [2.0, 3.0]
関節出血エピソード		
平均値（SD）	43.51 (22.544)	2.91 (4.103)
中央値	43.31	1.62
Q1、Q3	21.07, 66.16	0.00, 4.87
最小値、最大値	21.1, 66.2	0.0, 20.5
年間出血エピソード回数[95% CI]	47.1 [38.2, 58.2]	3.3 [2.7, 3.9]
治療された出血エピソードの発現がなかった被験者数(%)	0	21 (26.3)

略語：CI、信頼区間；N、当該療法群内総被験者数；Q1、第 1 四分位；Q3、第 3 四分位；SD、標準偏差
注：年間出血エピソード回数[95% CI]は Poisson 分布を基に算出した。
引用：3002 試験 CSR 表 14.2.2.1

- ABR のサブグループ解析で、以下の重要な差異が認められた。

  - 定期的投与群の ABR の中央値は、0 歳以上 6 歳未満群（2.12 件）で、6 歳以上 12 歳未満群（5.11 件）と比較して低かったが、AsBR の中央値は、いずれの年齢群でも 0.00 件であった（表 2.7.6.2-12）。

表 2.7.6.2-12　3002 試験：年齢群別の ABR 及び AsBR（有効性解析集団）

	オンデマンド療法	定期的な投与
年齢群：0 歳以上 6 歳未満	**(N = 0)**	**(N = 35)**
総出血エピソード		
平均値（SD）	N/A	3.00 (3.932)
中央値	N/A	2.12
Q1、Q3	N/A	0.00, 4.54
最小値、最大値	N/A	0.0, 17.0
年間出血エピソード回数[95% CI]	N/A	3.0 [2.3, 4.0]
自然出血エピソード		
平均値（SD）	N/A	0.81 (1.499)
中央値	N/A	0.00
Q1、Q3	N/A	0.00, 1.46
最小値、最大値	N/A	0.0, 5.4
年間出血エピソード回数[95% CI]	N/A	0.9 [0.5, 1.5]
治療された出血エピソードの発現がなかった被験者数(%)	0	14 (40.0)
年齢群：6 歳以上 12 歳未満	**(N = 3)**	**(N = 45)**
総出血エピソード		
平均値（SD）	66.77 (27.702)	6.94 (6.047)
中央値	78.56	5.11
Q1、Q3	35.12, 86.62	2.52, 10.50
最小値、最大値	35.1, 86.6	0.0, 23.7
年間出血エピソード回数[95% CI]	71.5 [60.3, 84.8]	7.4 [6.3, 8.6]
自然出血エピソード		
平均値（SD）	24.83 (22.191)	2.39 (3.607)
中央値	31.76	0.00
Q1、Q3	0.00, 42.73	0.00, 3.20
最小値、最大値	0.0, 42.7	0.0, 14.0
年間出血エピソード回数[95% CI]	28.7 [21.9, 37.6]	2.6 [2.0, 3.3]
治療された出血エピソードの発現がなかった被験者数(%)	0	7 (15.6)

略語：ABR、年間出血回数；AsBR、年換算の自然出血回数；CI、信頼区間；N、当該療法／年齢群内総被験者数；N/A、該当せず；Q1、第 1 四分位；Q3、第 3 四分位；SD、標準偏差
注：年間出血エピソード回数[95% CI]は Poisson 布を基に算出した。
引用：3002 試験 CSR 表 14.2.2.3 及び表 14.2.2.4

- 定期的な投与で週 3 回投与された被験者での ABR の中央値（2.30 件）は、週 2 回投与された被験者（4.37 件）と比較して低かったが、AsBR の中央値は、いずれの療法でも 0.00 件であった（表 2.7.6.2-13）。

表 2.7.6.2-13　3002 試験：定期的な投与別の ABR 及び AsBR（有効性解析集団、開始用量 15～50 IU/kg の被験者）

	隔日 (N = 3)	週 3 回 (N = 24)	週 2 回 (N = 40)	他の療法 (N = 7)
総出血エピソード				
平均値（SD）	3.22 (2.848)	5.80 (6.743)	5.62 (5.461)	4.01 (3.755)
中央値	4.27	2.30	4.37	3.71
Q1、Q3	0.00, 5.40	0.00, 11.58	2.31, 7.24	0.00, 6.16
最小値、最大値	0.0, 5.4	0.0, 18.0	0.0, 23.7	0.0, 10.5
年間出血エピソード回数 [95% CI]	4.5 [1.9, 10.7]	5.8 [4.5, 7.4]	6.2 [5.2, 7.4]	3.7 [2.2, 6.1]
自然出血エピソード				
平均値（SD）	2.51 (2.718)	1.82 (2.808)	1.62 (3.285)	2.63 (3.101)
中央値	2.14	0.00	0.00	2.17
Q1、Q3	0.00, 5.40	0.00, 3.03	0.00, 2.08	0.00, 4.15
最小値、最大値	0.0, 5.4	0.0, 10.3	0.0, 14.0	0.0, 8.4
年間出血エピソード回数 [95% CI]	3.6 [1.3, 9.5]	1.8 [1.2, 2.9]	1.9 [1.4, 2.6]	2.5 [1.3, 4.6]
外傷性出血エピソード				
平均値（SD）	0.71 (1.233)	1.91 (2.882)	2.86 (2.435)	1.08 (2.298)
中央値	0.00	0.00	2.63	0.00
Q1、Q3	0.00, 2.14	0.00, 2.55	0.77, 4.06	0.00, 1.38
最小値、最大値	0.0, 2.1	0.0, 10.0	0.0, 8.7	0.0, 6.2
年間出血エピソード回数 [95% CI]	0.9 [0.1, 6.3]	2.1 [1.4, 3.2]	3.1 [2.5, 4.0]	1.0 [0.4, 2.6]
関節出血エピソード				
平均値（SD）	2.51 (2.718)	3.03 (4.203)	3.14 (4.445)	2.69 (4.126)
中央値	2.14	0.82	1.93	0.00
Q1、Q3	0.00, 5.40	0.00, 5.32	0.00, 4.61	0.00, 6.16
最小値、最大値	0.0, 5.4	0.0, 12.5	0.0, 20.5	0.0, 10.5
年間出血エピソード回数 [95% CI]	3.6 [1.3, 9.5]	3.1 [2.2, 4.4]	3.8 [3.1, 4.8]	2.2 [1.2, 4.3]
治療された出血エピソードの発現がなかった被験者数(%)	1 (33.3)	9 (37.5)	6 (15.0)	2 (28.6)

略語：ABR、年間出血回数；AsBR、年換算の自然出血回数；CI、信頼区間；IU、国際単位；N、当該療法群内総被験者数； Q1、第 1 四分位；Q3、第 3 四分位；SD、標準偏差
注：年間出血エピソード回数[95% CI]、p 値及び割合は Poisson 分布を基に算出した。
引用：3002 試験 CSR 表 14.2.2.15

- 投与量又は投与スケジュールを調整しなかった被験者での ABR の中央値（2.73 件）は、投与量を調整した被験者（5.53 件）又は 2 週間隔の間に自然出血エピソードが 2 回以上認められたが投与量を調整しなかった被験者（6.94 件）と比較して低かった（3002 試験 CSR 表 14.2.2.21、表 14.2.2.24、表 14.2.2.30）。

- 試験中の ADA 検査結果が陽性であった被験者での ABR は、有効性解析集団全体と比較して高くはなかった（3002 試験 CSR 表 14.2.2.18、表 11-20）。

- 定期的投与群全体で、被験者一人あたりの定期的な投与での投与量の中央値は342 IU/kg/月、4109 IU/kg/年であり、週 2 回投与と週 3 回投与とでは、明らかな差は認められなかった（表 2.7.6.2-14）。

表 2.7.6.2-14　3002 試験：定期的な投与時の本剤使用量（有効性解析集団）

	週 2 回 (N = 43)	週 3 回 (N = 24)	全頻度 (N = 80)
定期的な投与の総投与回数	2354	1519	4524
被験者あたりの定期的な投与の月間投与量（IU/kg）			
平均値（SD）	325 (100.9)	439 (122.0)	359 (124.2)
中央値	320	409	342
最小値、最大値	179, 547	280, 717	71, 717
被験者あたりの定期的な投与の年間投与量[1]（IU/kg）			
平均値（SD）	3902 (1210.6)	5266 (1464.0)	4312 (1490.9)
中央値	3836	4913	4109
最小値、最大値	2142, 6560	3356, 8601	848, 8601
定期的な投与の月間投与量[1]（IU）			
平均値（SD）	8967 (4920.1)	11808 (5929.0)	9728 (5778.6)
中央値	7822	9688	7810
最小値、最大値	3853, 28791	3560, 23165	870, 28955
総投与回数	2590	1704	5088
被験者あたりの月間総投与量[2]（IU/kg）			
平均値（SD）	361 (109.3)	502 (148.3)	414 (180.2)
中央値	343	456	378
最小値、最大値	185, 580	307, 873	153, 1394
被験者あたりの年間総投与量[2]（IU/kg）			
平均値（SD）	4338 (1311.9)	6022 (1779.6)	4974 (2163.0)
中央値	4117	5469	4541
最小値、最大値	2223, 6965	3687, 10473	1839, 16727
月間総投与量[2]（IU）			
平均値（SD）	9997 (5378.7)	13964 (8302.9)	11460 (8287.8)
中央値	9080	11217	9028
最小値、最大値	4303, 30373	3689, 34395	1885, 51575

略語：IU、国際単位；N、総被験者数（全体又は当該療法群内）；SD、標準偏差
注：
[1] 定期的な投与の投与量には「定期的／予防的」投与として記録された投与を含める。
[2] 総投与量には、「出血イベント処置」、「術中」、「術後」、「術前」及び「追加的」投与として記録された投与も含める。
[3] 残りの 13 名は他の定期的な投与レジメン（隔日又はその他の頻度）であった。
引用：3002 試験 CSR 表 14.2.5.1

- 定期的投与群で、週 2 回投与又は週 3 回投与に割り付けられた被験者は 84%で、治験終了時に週 2 回投与又は週 3 回投与を受けていた被験者は 88%であった。

- 定期的投与群全体での投与量は治験期間を通して増加しなかった。週 2 回投与、隔日投与、又は週 1 回投与から、週 3 回投与に変更した被験者は少数であった（それぞれ 6 名、1 名、及び 1 名）（3002 試験 CSR 一覧表 16.2.5.3）。

- 追加投与（止血達成のための必要量を超えた投与）された出血の割合は、347 件中 17 件とわずかであった（3002 試験 CSR 表 14.1.8.7.1）。

7）安全性の結果

本治験で治療歴のある 84 名から得られた安全性の結果から、12 歳未満の重度血友病 A の患者に本剤を定期的な投与、予防療法、及び出血エピソードに対する治療法として投与した時、本剤は優れた安全性プロファイルを示した。本治験で得られた主な安全性の結果を以下に示す。

本剤投与で、FVIII に対するインヒビターを産生した被験者はいなかった。インヒビターを既に有しておりインヒビター力価が低値であった被験者で、本剤は良好な忍容性を示した。このインヒビターは、スクリーニング時に存在しており、本剤投与により発現した新規のインヒビターではなかった。本剤の集中的な定期的な投与下、インヒビター力価は経時的に減少し、当該被験者は 4 箇月目の来院までにインヒビター陰性となり、それ以降、治験終了時まで陰性のままであった。当該被験者の叙述を 2.7.4.2.1.3.2 項に示す。治験開始時に 10 名が非阻害 ADA 陽性であった。治験中に合計 10 名が非阻害 ADA 陽性を示した。これら 10 名のうち 3 名が治験終了時来院時に陰性、7 名が陽性であった。陽性であった 7 名のうち、メディカルレビューで報告されている非阻害 ADA に関連すると考えられる TEAE を発現した被験者はいなかった。

CHO 細胞由来タンパク質に対する抗体の発現は認められなかった。

本治験で死亡は認められなかった。1 件の TEAE（股関節痛）が中止に至った。本事象は、非重篤で、本剤との因果関係は否定された。1 件の TEAE が治験責任医師により本剤と関連ありと判断された（過敏症、軽度、非重篤、治験薬の変更なし）。ほとんどの TEAE は軽度又は中等度で、重度の TEAE は 4 件認められた［3 件の TESAE（肺炎、全身性炎症反応症候群、脾破裂）及び 1 件の非重篤 TEAE（齲歯）］。重度の TEAE はいずれも、治験責任医師により本剤との因果関係は否定された（表 2.7.6.2-15）。

TEAE は、概して、本治験対象集団で予測される事象と一致しており、感染症が高頻度に認められ、最も発現頻度の高かった TEAE は鼻咽頭炎（16.7%）であった。他に感染症では、上気道感染（4.8%）や鼻炎（4.8%）が高頻度に認められた。その他、高頻度に認められた TEAE は、関節痛（9.5%）、咳嗽（8.3%）、頭痛（8.3%）であった（表 2.7.6.1-16）。感染病原体の伝播を示唆する TEAE 又は ALT 異常若し

くは AST 異常を示す TEAE は認められず、アナフィラキシー反応又は血栓塞栓性事象も認められなかった。1 名で TESAE の医療機器塞栓が認められたが、本事象は MedDRA 標準検索式の検索用語「塞栓及び血栓」で特定された、投与機器に限定された合併症を表す事象であり、血管内血栓形成と関連するものではなかった。当該被験者の叙述を 2.7.4.2.1.3.2 項に示す。注目すべき医学的事象が 4 名（4.8%）に 4 件認められたが、安全性上の懸念は認められなかった。すべての注目すべき医学的事象は治験終了までに消失した。

表 2.7.6.2-15　3002 試験：AE の要約（安全性解析集団）

	0 歳以上 6 歳未満 (N = 35)		**6 歳以上 12 歳未満 (N = 49)**		**合計 (N = 84)**	
	被験者数 (%)	**発現件数**	**被験者数 (%)**	**発現件数**	**被験者数 (%)**	**発現件数**
AE	28 (80.0)	85	36 (73.5)	108	64 (76.2)	193
TEAE	28 (80.0)	79	36 (73.5)	104	64 (76.2)	183
治験中止に至った TEAE	0	0	1 (2.0)	1	1 (1.2)	1
TEAE 重症度						
軽度	22 (62.9)	57	30 (61.2)	80	52 (61.9)	137
中等度	11 (31.4)	19	14 (28.6)	23	25 (29.8)	42
重度	3 (8.6)	3	1 (2.0)	1	4 (4.8)	4
治験薬に関連する TEAE	0	0	1 (2.0)	1	1 (1.2)	1
TEAE 転帰						
AE に関連する死亡	0	0	0	0	0	0
未回復/未消失	3 (8.6)	3	3 (6.1)	6	6 (7.1)	9
回復/消失	26 (74.3)	74	35 (71.4)	94	61 (72.6)	168
回復/消失したが後遺症あり	0	0	0	0	0	0
軽快	1 (2.9)	1	3 (6.1)	3	4 (4.8)	4
不明	1 (2.9)	1	1 (2.0)	1	2 (2.4)	2
SAE	4 (11.4)	6	5 (10.2)	6	9 (10.7)	12
TESAE	4 (11.4)	6	5 (10.2)	5	9 (10.7)	11
治験薬に関連する TESAE	0	0	0	0	0	0

略語：AE、有害事象；N、総被験者数（当該年齢群内又は合計）；SAE、重篤な有害事象；TEAE、治験治療下で発現した有害事象；TESAE、治験治療下で発現した重篤な有害事象
注：
[1] 当該事象が認められた被験者数及びパーセントを表す。
[2] パーセントは当該集団の被験者数を基に算出した。
[3] 1 被験者に複数の事象が認められた場合、各カテゴリーの被験者数では 1 回のみカウントした。
引用：3002 試験 CSR 表 14.3.1.1

表 2.7.6.2-16 3002 試験：器官別大分類及び基本語別 TEAE（安全性解析集団）

	0 歳以上 6 歳未満 (N = 35)		6 歳以上 12 歳未満 (N = 49)		合計 (N = 84)	
	被験者数 (%)	発現件数	被験者数 (%)	発現件数	被験者数 (%)	発現件数
TEAE	**28 (80.0)**	**79**	**36 (73.5)**	**104**	**64 (76.2)**	**183**
感染症および寄生虫症	**18 (51.4)**	**29**	**20 (40.8)**	**31**	**38 (45.2)**	**60**
鼻咽頭炎	6 (17.1)	7	8 (16.3)	8	14 (16.7)	15
上気道感染	2 (5.7)	3	2 (4.1)	2	4 (4.8)	5
鼻炎	0	0	4 (8.2)	4	4 (4.8)	4
耳感染	1 (2.9)	1	2 (4.1)	2	3 (3.6)	3
下気道感染	1 (2.9)	2	1 (2.0)	1	2 (2.4)	3
医療機器関連感染	2 (5.7)	2	0	0	2 (2.4)	2
胃腸炎	2 (5.7)	2	0	0	2 (2.4)	2
咽頭炎	1 (2.9)	1	1 (2.0)	1	2 (2.4)	2
皮膚感染	0	0	2 (4.1)	2	2 (2.4)	2
ウイルス感染	1 (2.9)	1	1 (2.0)	1	2 (2.4)	2
急性扁桃炎	1 (2.9)	1	0	0	1 (1.2)	1
菌血症	0	0	1 (2.0)	1	1 (1.2)	1
気管支炎	1 (2.9)	1	0	0	1 (1.2)	1
感染性クループ	1 (2.9)	1	0	0	1 (1.2)	1
ウイルス性胃腸炎	0	0	1 (2.0)	1	1 (1.2)	1
麦粒腫	0	0	1 (2.0)	1	1 (1.2)	1
寄生虫感染	0	0	1 (2.0)	1	1 (1.2)	1
喉頭炎	1 (2.9)	1	0	0	1 (1.2)	1
外耳炎	1 (2.9)	1	0	0	1 (1.2)	1
中耳炎	0	0	1 (2.0)	1	1 (1.2)	1
急性中耳炎	0	0	1 (2.0)	1	1 (1.2)	1
爪囲炎	0	0	1 (2.0)	1	1 (1.2)	1
耳下腺炎	0	0	1 (2.0)	1	1 (1.2)	1
肺炎	1 (2.9)	1	0	0	1 (1.2)	1
気道感染	0	0	1 (2.0)	1	1 (1.2)	1
扁桃炎	1 (2.9)	1	0	0	1 (1.2)	1
気管気管支炎	1 (2.9)	1	0	0	1 (1.2)	1
尿路感染	0	0	1 (2.0)	1	1 (1.2)	1
ウイルス性筋炎	1 (2.9)	1	0	0	1 (1.2)	1
ウイルス性上気道感染	1 (2.9)	1	0	0	1 (1.2)	1
傷害、中毒および処置合併症	**10 (28.6)**	**15**	**10 (20.4)**	**17**	**20 (23.8)**	**32**
頭部損傷	3 (8.6)	3	2 (4.1)	3	5 (6.0)	6
転倒	3 (8.6)	3	1 (2.0)	1	4 (4.8)	4
挫傷	0	0	3 (6.1)	6	3 (3.6)	6
裂傷	1 (2.9)	1	2 (4.1)	3	3 (3.6)	4
靭帯捻挫	1 (2.9)	1	1 (2.0)	1	2 (2.4)	2
四肢損傷	1 (2.9)	1	1 (2.0)	1	2 (2.4)	2
擦過傷	1 (2.9)	1	0	0	1 (1.2)	1
手骨折	0	0	1 (2.0)	1	1 (1.2)	1
関節損傷	1 (2.9)	1	0	0	1 (1.2)	1
口唇損傷	1 (2.9)	1	0	0	1 (1.2)	1
脾破裂	0	0	1 (2.0)	1	1 (1.2)	1
舌損傷	1 (2.9)	1	0	0	1 (1.2)	1
上肢骨折	1 (2.9)	1	0	0	1 (1.2)	1
創傷	1 (2.9)	1	0	0	1 (1.2)	1
筋骨格系および結合組織障害	**4 (11.4)**	**4**	**11 (22.4)**	**14**	**15 (17.9)**	**18**
関節痛	3 (8.6)	3	5 (10.2)	5	8 (9.5)	8
四肢痛	0	0	4 (8.2)	4	4 (4.8)	4
筋骨格痛	0	0	2 (4.1)	2	2 (2.4)	2

表 2.7.6.2-16　3002 試験：器官別大分類及び基本語別 TEAE（安全性解析集団）（続き）

	0 歳以上 6 歳未満 (N = 35)		6 歳以上 12 歳未満 (N = 49)		合計 (N = 84)	
	被験者数 (%)	発現件数	被験者数 (%)	発現件数	被験者数 (%)	発現件数
背部痛	0	0	1 (2.0)	1	1 (1.2)	1
側腹部痛	0	0	1 (2.0)	1	1 (1.2)	1
滑液嚢腫	0	0	1 (2.0)	1	1 (1.2)	1
滑膜障害	1 (2.9)	1	0	0	1 (1.2)	1
呼吸器、胸郭および縦隔障害	**3 (8.6)**	**8**	**9 (18.4)**	**11**	**12 (14.3)**	**19**
咳嗽	2 (5.7)	3	5 (10.2)	7	7 (8.3)	10
口腔咽頭痛	1 (2.9)	1	2 (4.1)	2	3 (3.6)	3
アレルギー性鼻炎	1 (2.9)	1	2 (4.1)	2	3 (3.6)	3
喘息	1 (2.9)	2	0	0	1 (1.2)	2
扁桃障害	1 (2.9)	1	0	0	1 (1.2)	1
神経系障害	**1 (2.9)**	**1**	**7 (14.3)**	**13**	**8 (9.5)**	**14**
頭痛	1 (2.9)	1	6 (12.2)	8	7 (8.3)	9
痙攣	0	0	1 (2.0)	2	1 (1.2)	2
浮動性めまい	0	0	1 (2.0)	1	1 (1.2)	1
錯感覚	0	0	1 (2.0)	1	1 (1.2)	1
外傷後頭痛	0	0	1 (2.0)	1	1 (1.2)	1
一般・全身障害および投与部位の状態	**5 (14.3)**	**5**	**3 (6.1)**	**3**	**8 (9.5)**	**8**
発熱	4 (11.4)	4	1 (2.0)	1	5 (6.0)	5
医療機器閉塞	0	0	1 (2.0)	1	1 (1.2)	1
疼痛	0	0	1 (2.0)	1	1 (1.2)	1
全身性炎症反応症候群	1 (2.9)	1	0	0	1 (1.2)	1
胃腸障害	**3 (8.6)**	**3**	**4 (8.2)**	**5**	**7 (8.3)**	**8**
齲歯	1 (2.9)	1	1 (2.0)	1	2 (2.4)	2
嘔吐	1 (2.9)	1	1 (2.0)	1	2 (2.4)	2
腹痛	0	0	1 (2.0)	1	1 (1.2)	1
消化不良	1 (2.9)	1	0	0	1 (1.2)	1
悪心	0	0	1 (2.0)	1	1 (1.2)	1
歯の脱落	0	0	1 (2.0)	1	1 (1.2)	1
血液およびリンパ系障害	**2 (5.7)**	**4**	**4 (8.2)**	**4**	**6 (7.1)**	**8**
貧血	1 (2.9)	3	2 (4.1)	2	3 (3.6)	5
鉄欠乏性貧血	0	0	2 (4.1)	2	2 (2.4)	2
低色素性貧血	1 (2.9)	1	0	0	1 (1.2)	1
皮膚および皮下組織障害	**3 (8.6)**	**3**	**1 (2.0)**	**1**	**4 (4.8)**	**4**
皮膚乾燥	1 (2.9)	1	0	0	1 (1.2)	1
斑状出血	0	0	1 (2.0)	1	1 (1.2)	1
湿疹	1 (2.9)	1	0	0	1 (1.2)	1
紅斑性皮疹	1 (2.9)	1	0	0	1 (1.2)	1
耳および迷路障害	**2 (5.7)**	**2**	**1 (2.0)**	**1**	**3 (3.6)**	**3**
耳痛	1 (2.9)	1	1 (2.0)	1	2 (2.4)	2
耳垢栓塞	1 (2.9)	1	0	0	1 (1.2)	1
眼障害	**2 (5.7)**	**2**	**1 (2.0)**	**1**	**3 (3.6)**	**3**
眼瞼炎	1 (2.9)	1	0	0	1 (1.2)	1
結膜炎	1 (2.9)	1	0	0	1 (1.2)	1
複視	0	0	1 (2.0)	1	1 (1.2)	1
臨床検査	**1 (2.9)**	**1**	**1 (2.0)**	**1**	**2 (2.4)**	**2**
心雑音	1 (2.9)	1	0	0	1 (1.2)	1
ヘモグロビン減少	0	0	1 (2.0)	1	1 (1.2)	1
心臓障害	**0**	**0**	**1 (2.0)**	**1**	**1 (1.2)**	**1**
洞性不整脈	0	0	1 (2.0)	1	1 (1.2)	1

表 2.7.6.2-16　3002 試験：器官別大分類及び基本語別 TEAE（安全性解析集団）（続き）

	0 歳以上 6 歳未満 (N = 35)		6 歳以上 12 歳未満 (N = 49)		合計 (N = 84)	
	被験者数 (%)	発現件数	被験者数 (%)	被験者数(%)	発現件数	被験者数(%)
免疫系障害	**0**	**0**	**1 (2.0)**	**1**	**1 (1.2)**	**1**
過敏症	0	0	1 (2.0)	1	1 (1.2)	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 (2.9)**	**1**	**0**	**0**	**1 (1.2)**	**1**
皮膚乳頭腫	1 (2.9)	1	0	0	1 (1.2)	1
生殖系および乳房障害	**1 (2.9)**	**1**	**0**	**0**	**1 (1.2)**	**1**
亀頭炎	1 (2.9)	1	0	0	1 (1.2)	1

略語：N、総被験者数（当該年齢群内又は合計）；TEAE、治験治療下で発現した有害事象
注：
[1] 当該事象が認められた被験者の数及びパーセント、並びに当該事象の発現件数を表す。
[2] パーセントは当該集団の被験者数を基に算出した。
引用：3002 試験 CSR 表 14.3.1.4.1

TESAE の一覧を表 2.7.6.2-17 に示す。

9 名で 11 件の TESAE が認められたが、いずれの事象も、治験責任医師により本剤との因果関係は否定された。

表 2.7.6.2-17　3002 試験：TESAE が認められた被験者一覧（安全性解析集団）

被験者番号	人種	年齢（歳）	割り付けられた本剤投与法及び用量 (IU/kg)	AE (PT)	発現日/消失日 発現日の試験開始からの日数 TESAE 持続期間	因果関係/重症度	処置[a]	転帰
0360014-2003	白人	[redacted]	定期的な投与 週 2 回、44 IU/kg	裂傷	[redacted]年 5 月 17 日/#同 年 5 月 17 日 Day 131 1 日間	関連なし/中等度	投与量変更せず	回復/消失
5280006-2001	白人	[redacted]	定期的な投与 週 2 回、20 IU/kg	医療機器閉塞	[redacted]年 1 月 29 日/#同 年 2 月 2 日 Day 42 5 日間	関連なし/軽度	投与量増量	回復/消失
5280007-2001	白人	[redacted]	定期的な投与 隔日、40 IU/kg	貧血	[redacted]年 9 月 23 日/#同 年 9 月 25 日 Day 7 3 日間	関連なし/中等度	投与量増量	回復/消失
				貧血	[redacted]年 9 月 27 日/#同 年 10 月 14 日 Day 11 18 日間	関連なし/中等度	投与量増量	回復/消失
				貧血	[redacted]年 11 月 1 日/#同 年 11 月 14 日 Day 46 14 日間	関連なし/中等度	投与量増量	回復/消失
6080001-2004	アジア人	[redacted]	定期的な投与 週 3 回、43 IU/kg	消化不良	[redacted]年 4 月 3 日/#同 年 4 月 5 日 Day 14 3 日間	関連なし/軽度	投与量変更せず	回復/消失
6080002-2004	アジア人	[redacted]	定期的な投与 週 3 回、25 IU/kg	菌血症	[redacted]年 4 月 8 日/#同 年 4 月 20 日 Day 23 13 日間	関連なし/中等度	投与中断	回復/消失

#新薬承認情報提供時に置き換え

表 2.7.6.2-17　3002 試験：TESAE が認められた被験者一覧（安全性解析集団）（続き）

被験者番号	人種	年齢（歳）	割り付けられた本剤投与法及び用量 (IU/kg)	AE (PT)	発現日/消失日 発現日の試験開始からの日数 TESAE 持続期間	因果関係/重症度	処置[a]	転帰
6420037-2001	白人	[redacted]	定期的な投与 週 2 回、38 IU/kg	肺炎	[redacted] 年 6 月 6 日/ #同 年 6 月 11 日 Day 181 6 日間	関連なし/ 重度	投与量変更せず	回復/消失
7640002-2001	アジア人	[redacted]	定期的な投与 週 3 回、34 IU/kg	全身性炎症反応症候群	[redacted] 年 8 月 18 日/ #同 年 9 月 1 日 Day 5 15 日間	関連なし/ 重度	投与量変更せず	回復/消失
7640003-2001	アジア人	[redacted]	定期的な投与 週 2 回、20 IU/kg	手骨折	[redacted] 年 2 月 27 日/ #同 年 3 月 6 日 Day 214 8 日間	関連なし/ 中等度	投与量変更せず	回復/消失
8400184-2001	白人	[redacted]	定期的な投与 週 2 回、50 IU/kg	脾破裂	[redacted] 年 3 月 2 日/ #同 年 4 月 25 日 Day 162 55 日間	関連なし/ 重度	投与量増量	回復/消失

略語：AE、有害事象；IU、国際単位；PT、基本語；TESAE、治験治療下で発現した重篤な有害事象
[a] 本剤に対する処置
引用：5.3.5.2 項、一覧表 16.2.7.2J

#新薬承認情報提供時に置き換え

治験責任医師による局所忍容性の評価で、99.4%（309 件中 307 件）の投与が「なし」（紅斑なし）と評価された。2 名（2.4%）で 2 件の軽度な紅斑が認められたが、中等度～重度、又は重度の紅斑は認められなかった。

被験者による局所忍容性の自己評価で、99.4%（4774 件中 4747 件）の投与が「なし」（反応なし）と評価された。合計 27 件（0.57%）の反応が報告されたが、いずれも重度ではなかった。

臨床検査及びバイタルサインのパラメーターに特記すべき所見は認められなかった。

(3) まとめ

本剤は、本治験で対象とした小児年齢群で優れた安全性プロファイルを示し、インヒビター産生は 1 件も認められなかった。本剤は、2 つの年齢群のいずれでも出血エピソードの治療効果が高く、定期的投与群の小児で AsBR 及び ABR は低かった。本治験での小児年齢群の CL は、1001 試験の成人及び青年と比較して高かったが、本治験での投与量は 1001 試験での投与量と同様であり、本剤の使用量は両試験で同様であった。投与量又は投与頻度を増加しなかったにもかかわらず、ABR 及び止血効果は、他の最近承認された遺伝子組換え FVIII 濃縮製剤と同様であり、0～12 歳の全被験者を対象とした定期的な投与で 20～50 IU/kg の週 2～3 回投与を開始用量とすることを支持するものであった。

2.7.6.3　Appendix

- Study 1001, Table 14.1.1.2: Subject Populations (Enrolled Population)
- Study 1001, Table 14.1.2.2: Subject Disposition (Efficacy Population)
- Study 1001, Table 14.1.3.4: Exclusions from the Per Protocol Population (Efficacy Population)
- Study 1001, Table 14.1.5.1: Demographics (Safety Population)
- Study 1001, Table 14.2.1.1: Investigator's Overall Assessment of Hemostatic Efficacy (Efficacy Population)
- Study 1001, Table 14.2.2.1: Annualized Bleeding Rates: CSL627 Prophylaxis Compared with On-Demand/Prevention Historical Control (Efficacy Population)
- Study 1001, Table 14.2.2.2.1: Annualized Bleeding Rates: CSL627 Prophylaxis Compared with CSL627 On-Demand (Efficacy Population)
- Study 1001, Table 14.2.2.3: Annualized Bleeding Rates: CSL627 Prophylaxis Compared with CSL627 On-Demand - By Region (Efficacy Population)
- Study 1001, Table 14.2.5.1: Consumption of CSL627 During Routine Prophylaxis (Efficacy Population)
- Study 1001, Table 14.2.13.1.2: Part 1 - Summary of FVIII PK Parameters - Patients whose dosing is within +/- 10% range of planned dose (PK Population)
- Study 1001, Table 14.2.13.3.2: Part 1 - Summary of FVIII PK Parameters After Dose Adjustment - Patients whose dosing is within +/- 10% range of planned dose (PK Population)
- Study 1001, Table 14.2.16.1.1: Part 3 - FVIII PK Parameters of CSL627 ChS baseline uncorrected, initial PK (PK Population)
- Study 1001, Table 14.2.16.2.1: Part 3 - FVIII PK Parameters of CSL627 ChS baseline uncorrected, repeat PK (PK Population)
- Study 1001, Table 14.2.16.9.1: Part 3 - FVIII PK Parameters of CSL627 ChS baseline corrected, initial PK (PK Population)
- Study 1001, Table 14.2.16.10.1: Part 3 - FVIII PK Parameters of CSL627 ChS baseline corrected, repeat PK (PK Population)
- Study 1001, Table 14.2.16.21.1: Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial ChS baseline uncorrected (PK Population)
- Study 1001, Table 14.2.16.22.1: Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese repeat ChS baseline uncorrected (PK Population)
- Study 1001, Table 14.2.16.23.1: Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial ChS baseline corrected (PK Population)
- Study 1001, Table 14.2.16.24.1: Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese repeat ChS baseline corrected (PK Population)
- Study 1001, Table 14.3.2.1: Summary of Adverse Events (Safety Population)

- Study 1001, Table 14.3.2.4: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
- Study 1001, Table 14.1.1.2J: Japanese Subject Populations (Japanese Enrolled Population)
- Study 1001, Table 14.1.5.1J: Japanese Demographics (Japanese Efficacy Population)
- Study 1001, Table 14.2.1.1J: Japanese Investigator's Overall Assessment of Hemostatic Efficacy (Japanese Efficacy Population)
- Study 1001, Table 14.2.2.2.1.J: Japanese Summary of Annualized Bleeding Rates (Japanese Efficacy Population)
- Study 1001, Table 14.2.5.1J: Japanese Consumption of CSL627 During Routine Prophylaxis (Japanese Efficacy Population, Assigned Modality = Prophylaxis)
- Study 1001, Table 14.3.2.1J: Summary of Adverse Events (Japanese and Global Safety Population)
- Study 1001, Table 14.3.2.4J: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Japanese and Global Safety Population)
- Study 1001, Figure 14.2.1.1.2: Part 1 - ChS Assay Baseline Uncorrected FVIII Activities by Treatment (PK Population - Patients whose dosing is within +/- 10% range of planned dose)
- Study 1001, Figure 14.2.4.1.1: Part 3 – ChS Assay Baseline Uncorrected FVIII Activities (PK Population)
- Study 1001, Figure 14.2.7.1.2: Part 3 – ChS Assay Baseline Uncorrected FVIII Activities By Race Group (PK Population - Patients whose dosing is within +/- 10% range of planned dose)
- Study 3002, Table 14.1.1.2: Subject Populations (Enrolled Population)
- Study 3002, Table 14.1.2.1: Subject Disposition (Safety Population)
- Study 3002, Table 14.1.2.2: Subject Disposition (Efficacy Population)
- Study 3002, Table 14.1.3.2.1: Exclusions from the Per Protocol Population (Efficacy Population)
- Study 3002, Table 14.1.4.1: Demographics (Safety Population)
- Study 3002, Table 14.1.8.5.1: Extent of Exposure to CSL627 (Safety Population)
- Study 3002, Table 14.1.10.2.1: Summary of Dose Assignment and Dose Adjustment (Efficacy Population, Age 0 to <6 Years)
- Study 3002, Table 14.1.10.3.1: Summary of Dose Assignment and Dose Adjustment (Efficacy Population, Age ≥6 to <12 Years)
- Study 3002, Table 14.2.1.1.1: Investigator’s Overall Assessment of Hemostatic Efficacy (Efficacy Population)
- Study 3002, Table 14.2.2.3: Summary of Annualized Bleeding Rates (Efficacy Population, Age 0 to <6 Years)

- Study 3002, Table 14.2.2.4: Summary of Annualized Bleeding Rates (Efficacy Population, Age ≥6 to <12 Years)
- Study 3002, Table 14.2.2.16: Summary of Annualized Bleeding Rates for Prophylaxis (Efficacy Population, Initial Dose Assignment 15-50 IU/kg, Age 0 to <6 Years)
- Study 3002, Table 14.2.2.17: Summary of Annualized Bleeding Rates for Prophylaxis (Efficacy Population, Initial Dose Assignment 15-50 IU/kg, Age ≥6 to <12 Years)
- Study 3002, Table 14.2.3.1: Number of CSL627 Infusions Required to Achieve Hemostasis (Efficacy Population)
- Study 3002, Table 14.2.5.2: Consumption of CSL627 for Prophylaxis Subjects (Efficacy Population, Assigned Modality = Prophylaxis, Age 0 to <6 Years)
- Study 3002, Table 14.2.5.3: Consumption of CSL627 for Prophylaxis Subjects (Efficacy Population, Assigned Modality = Prophylaxis, Age ≥6 to <12 Years)
- Study 3002, Table 14.2.12.2: Summary of FVIII PK Parameters By Age (PK Population)
- Study 3002, Table 14.3.1.1: Summary of Adverse Events (Safety Population)
- Study 3002, Table 14.3.1.4.1: Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

Table 14.1.1.2 Subject Populations
(Enrolled Population)

	Total n
Enrolled	175
Safety Population	174
Efficacy Population	173
Prophylaxis	146
On-demand	27
PP Population	156
PK Population	91
PK Part 1	27
PK Part 3	64
Surgical Population	13

Source: Listing 16.2.3
Notes: [1] Table presents number of subjects (n)

Table 14.1.2.2 Subject Disposition
(Efficacy Population)

	On-demand (N=27)	Prophylaxis (N=146)	Total (N=173)
Efficacy Population	27	146	173
Completed Study	21 (77.8)	140 (95.9)	161 (93.1)
Discontinued from Study	6 (22.2)	6 (4.1)	12 (6.9)
Reasons for Discontinuation			
Adverse Event(s)	0	0	0
Death	0	0	0
Lack of Efficacy	0	0	0
Lost to Follow-up	0	0	0
Other	4 (14.8)	0	4 (2.3)
Physician Decision	1 (3.7)	0	1 (0.6)
Protocol Violation	0	0	0
Study Terminated by Sponsor	0	0	0
Withdrawal by Subject	1 (3.7)	6 (4.1)	7 (4.0)
Unknown	0	0	0

Source: Listing 16.2.1.2
Notes: [1] Table presents number and percentage of subjects [n (%)]
[2] Percentages are based on the number of subjects in the Efficacy Population

Table 14.1.3.4 Exclusions from the Per Protocol Population
(Efficacy Population)

	On-Demand (N=27) n	(%)	Prophylaxis (N=146) n	(%)	Total (N=173) n	(%)
Any Exclusion from the Per Protocol Population	4	(14.8)	13	(8.9)	17	(9.8)
Reasons for Exclusion from the Per Protocol Population						
Non-compliant to the Prescribed Dose	4	(14.8)	5	(3.4)	9	(5.2)
Non-compliant to the Prescribed Prophylaxis Regimen	0		8	(5.5)	8	(4.6)

Source: Listing 16.2.1.4
Notes: [1] Table presents number and percentage of subjects [n (%)].
[2] Percentages are based on the number of subjects in the Efficacy Population.

Table 14.1.5.1 Demographics
(Safety Population)

	Total (N=174)
Age (years)	
n	174
Mean (SD)	31.3 (11.77)
Median	29.5
Min, Max	12, 64
Age Group [n (%)]	
12 to <18 years	14 (8.0)
>=18 to <=65 years	160 (92.0)
Race [n (%)]	
American Indian/Alaska Native	0
Asian	31 (17.8)
Black or African American	14 (8.0)
Native Hawaiian/Other Pacific Islander	0
White	126 (72.4)
Other	3 (1.7)
Ethnicity [n (%)]	
Hispanic or Latino	12 (6.9)
Not Hispanic or Latino	161 (92.5)
Not Reported	1 (0.6)
Unknown	0

Source: Listing 16.2.4.2
Notes: [1] Abbreviations - BMI = Body mass index.
[2] BMI is calculated as follows: BMI at screening = Weight at screening (kg) / (Height at screening (m))^2.
[3] Percentages are based on the number of subjects in the respective group.

Table 14.1.5.1 Demographics
(Safety Population)

	Total (N=174)
Country [n (%)]	
Australia	8 (4.6)
Austria	5 (2.9)
Canada	1 (0.6)
Czech Republic	2 (1.1)
Germany	19 (10.9)
Hungary	2 (1.1)
Italy	10 (5.7)
Japan	10 (5.7)
Lebanon	3 (1.7)
Malaysia	9 (5.2)
Netherlands	4 (2.3)
Philippines	10 (5.7)
Poland	24 (13.8)
Romania	3 (1.7)
Russian Federation	9 (5.2)
South Africa	16 (9.2)
Spain	3 (1.7)
Ukraine	11 (6.3)
United Kingdom	3 (1.7)
United States	22 (12.6)

Notes: [1] Abbreviations - BMI = Body mass index.
[2] BMI is calculated as follows: BMI at screening = Weight at screening (kg) / (Height at screening (m))^2.
[3] Percentages are based on the number of subjects in the respective group.

Table 14.1.5.1 Demographics
(Safety Population)

	Total (N=174)
Geographical Region [n (%)]	
United States	22 (12.6)
Japan	10 (5.7)
Europe	86 (49.4)
Rest Of The World	56 (32.2)
Height (cm)	
n	174
Mean (SD)	174.6 (8.97)
Median	175.0
Min, Max	145, 198
Weight (kg)	
n	174
Mean (SD)	74.6 (16.99)
Median	75.0
Min, Max	27, 120
BMI (kg/m^2)	
n	174
Mean (SD)	24.3 (4.70)
Median	24.5
Min, Max	13, 39

Source: Listing 16.2.4.2
Notes: [1] Abbreviations - BMI = Body mass index.
[2] BMI is calculated as follows: BMI at screening = Weight at screening (kg) / (Height at screening (m))².
[3] Percentages are based on the number of subjects in the respective group.

Table 14.1.5.1 Demographics
(Safety Population)

	Total (N=174)
BMI Category [n (%)]	
<30 kg/m2	156 (89.7)
>=30 kg/m2	18 (10.3)

Source: Listing 16.2.4.2
Notes: [1] Abbreviations - BMI = Body mass index.
[2] BMI is calculated as follows: BMI at screening = Weight at screening (kg) / (Height at screening (m))².
[3] Percentages are based on the number of subjects in the respective group.

Table 14.2.1.1 Investigator's Overall Assessment of Hemostatic Efficacy
(Efficacy Population)

Bleeding Type Assessment	On-Demand (N=27)	Prophylaxis (N=146)	Total (N=173)
Total			
Number of Bleeding Events	594	278	872
Number of Treated Bleeding Events	590	258	848
Excellent	421 (71.4)	182 (70.5)	603 (71.1)
Good	124 (21.0)	56 (21.7)	180 (21.2)
Moderate	32 (5.4)	20 (7.8)	52 (6.1)
Poor/No Response	0	0	0
Missing	13 (2.2)	0	13 (1.5)
Success (a)	545 (92.4)	238 (92.2)	783 (92.3)
Rate of Success	92.4	92.2	92.3
95% CI for Rate	(87.8, 95.3)	(86.3, 95.8)	(88.9, 94.8)
Success (b)	545 (94.5)	238 (92.2)	783 (93.8)
Rate of Success	94.5	92.2	93.8
95% CI for Rate	(90.9, 96.7)	(86.3, 95.8)	(91.0, 95.7)
Success (c)	558 (94.6)	238 (92.2)	796 (93.9)
Rate of Success	94.6	92.2	93.9
95% CI for Rate	(91.0, 96.8)	(86.3, 95.8)	(91.1, 95.8)

Source: Listing 16.2.6.2
Notes: [1] Success is defined as a rating of excellent or good. [a] Primary analysis: missing counted as failure;
[b] Sensitivity analysis: all missing excluded. [c] Sensitivity analysis: missing counted as success.
[2] 95% CI based on a generalized linear model to account for within-subject correlation.
[3] Table presents number and percentage of bleeding events [(n(%)].
[4] Percentages are based on the number of treated bleeding events.

Table 14.2.2.1 Annualized Bleeding Rates: CSL627 Prophylaxis Compared with On-Demand/Prevention Historical Control (Efficacy Population)

	On-Demand/Prevention Historical Control (N=52)	Prophylaxis (N=146)	p-value	Prophylaxis/ On-demand
Spontaneous Bleeds				
n	52	146	<.0001	0.10 (0.08, 0.12)
Mean (SD)	16.49 (18.672)	2.10 (4.764)		
Median	11.70	0.00		
Q1, Q3	2.93, 23.13	0.00, 2.37		
Min, Max	0.0, 92.4	0.0, 40.6		
Number of bleeds per year (95% CI)	16.3 (14.9, 17.8)	1.6 (1.3, 1.8)		
Traumatic Bleeds				
n	52	146	<.0001	0.37 (0.27, 0.52)
Mean (SD)	2.25 (4.306)	0.72 (1.554)		
Median	0.00	0.00		
Q1, Q3	0.00, 3.05	0.00, 0.85		
Min, Max	0.0, 21.2	0.0, 9.3		
Number of bleeds per year (95% CI)	2.1 (1.6, 2.7)	0.8 (0.6, 1.0)		
Total Bleeds				
n	52	146	<.0001	0.14 (0.12, 0.16)
Mean (SD)	18.84 (19.584)	3.11 (5.045)		
Median	14.49	1.14		
Q1, Q3	4.47, 24.64	0.00, 4.15		
Min, Max	0.0, 96.8	0.0, 40.6		
Number of bleeds per year (95% CI)	18.5 (17.0, 20.1)	2.6 (2.3, 2.9)		

Source: Listing 16.2.6.2
Notes: [1] Number of bleeds per year (95% CI), p-value and ratio are based on a Poisson distribution.

Table 14.2.2.2.1 Annualized Bleeding Rates: CSL627 Prophylaxis Compared with CSL627 On-Demand (Efficacy Population)

	On-Demand (N=27)	Prophylaxis (N=146)	p-value	Prophylaxis/ On-demand
Spontaneous Bleeds				
n	27	146	<.0001	0.08 (0.07, 0.10)
Mean (SD)	24.84 (33.843)	2.10 (4.764)		
Median	11.73	0.00		
Q1, Q3	2.8, 36.5	0.0, 2.4		
Min, Max	0.0, 151.0	0.0, 40.6		
Number of bleeds per year (95% CI)	19.5 (17.8, 21.3)	1.6 (1.3, 1.8)		
Traumatic Bleeds				
n	27	146	<.0001	0.16 (0.12, 0.22)
Mean (SD)	5.46 (6.274)	0.72 (1.554)		
Median	3.12	0.00		
Q1, Q3	0.0, 8.4	0.0, 0.9		
Min, Max	0.0, 21.5	0.0, 9.3		
Number of bleeds per year (95% CI)	4.7 (3.9, 5.7)	0.8 (0.6, 1.0)		
Total Bleeds				
n	27	146	<.0001	0.10 (0.09, 0.12)
Mean (SD)	31.14 (35.560)	3.11 (5.045)		
Median	19.64	1.14		
Q1, Q3	6.2, 46.5	0.0, 4.2		
Min, Max	0.0, 163.3	0.0, 40.6		
Number of bleeds per year (95% CI)	24.9 (23.0, 27.0)	2.6 (2.3, 2.9)		
Number of subjects with zero bleeds [n(%)]	1 (3.7)	63 (43.2)		

Source: Listing 16.2.6.2
Notes: [1] Number of bleeds per year (95% CI), p-value and ratio are based on a Poisson distribution

Table 14.2.2.3 Annualized Bleeding Rates: CSL627 Prophylaxis Compared with CSL627 On-Demand - By Region (Efficacy Population)

	On-Demand (N=27)	Prophylaxis (N=146)	p-value	Prophylaxis/ On-demand
Region: United States				
Spontaneous Bleeds				
n	4	18	<.0001	0.04 (0.01, 0.10)
Mean (SD)	9.70 (7.030)	0.49 (1.210)		
Median	11.67	0.00		
Q1, Q3	4.6 ,14.9	0.0 ,0.0		
Min, Max	0.0, 15.5	0.0, 4.2		
Number of bleeds per year (95% CI)	7.0 (4.9, 10.0)	0.3 (0.1, 0.7)		
Traumatic Bleeds				
n	4	18	<.0001	0.12 (0.06, 0.24)
Mean (SD)	7.04 (7.836)	0.93 (1.163)		
Median	4.98	0.68		
Q1, Q3	2.1, 12.0	0.0, 1.5		
Min, Max	0.0 ,18.2	0.0 ,4.2		
Number of bleeds per year (95% CI)	6.6 (4.6, 9.5)	0.8 (0.5, 1.4)		
Total Bleeds				
n	4	18	<.0001	0.09 (0.05, 0.15)
Mean (SD)	17.13 (10.098)	1.73 (1.770)		
Median	17.75	1.16		
Q1, Q3	9.5, 24.8	0.0, 2.8		
Min, Max	4.7, 28.3	0.0, 6.1		
Number of bleeds per year (95% CI)	14.0 (11.0, 18.0)	1.3 (0.8, 1.9)		

Source: Listing 16.2.6.2
Notes: [1] Number of bleeds per year (95% CI), p-value and ratio are based on a Poisson distribution

Table 14.2.2.3 Annualized Bleeding Rates: CSL627 Prophylaxis Compared with CSL627 On-Demand - By Region (Efficacy Population)

	On-Demand (N=27)	Prophylaxis (N=146)	p-value	Prophylaxis/ On-demand
Region: United States				
Number of subjects with zero bleeds [n(%)]	0	5 (27.8)		
Region: Japan				
Spontaneous Bleeds				
n	1	9	0.3093	0.56 (0.19, 1.70)
Mean (SD)	3.55	1.83 (4.268)		
Median	3.55	0.00		
Q1, Q3	3.6 ,3.6	0.0 ,1.1		
Min, Max	3.6, 3.6	0.0, 13.0		
Number of bleeds per year (95% CI)	3.6 (1.3, 9.5)	2.0 (1.2, 3.3)		
Traumatic Bleeds				
n	1	9	0.1294	0.35 (0.09, 1.36)
Mean (SD)	2.67	0.68 (1.590)		
Median	2.67	0.00		
Q1, Q3	2.7, 2.7	0.0, 0.0		
Min, Max	2.7 ,2.7	0.0 ,4.7		
Number of bleeds per year (95% CI)	2.7 (0.9, 8.3)	0.9 (0.4, 2.0)		

Source: Listing 16.2.6.2
Notes: [1] Number of bleeds per year (95% CI), p-value and ratio are based on a Poisson distribution

Table 14.2.2.3 Annualized Bleeding Rates: CSL627 Prophylaxis Compared with CSL627 On-Demand - By Region (Efficacy Population)

	On-Demand (N=27)	Prophylaxis (N=146)	p-value	Prophylaxis/ On-demand
Region: Japan				
Total Bleeds				
n	1	9	0.0845	0.47 (0.20, 1.11)
Mean (SD)	6.22	2.51 (4.556)		
Median	6.22	0.00		
Q1, Q3	6.2, 6.2	0.0, 1.4		
Min, Max	6.2, 6.2	0.0, 13.0		
Number of bleeds per year (95% CI)	6.2 (3.0, 13.0)	2.9 (1.9, 4.5)		
Number of subjects with zero bleeds [n(%)]	0	5 (55.6)		
Region: Europe				
Spontaneous Bleeds				
n	16	69	<.0001	0.04 (0.03, 0.05)
Mean (SD)	35.49 (40.461)	1.46 (5.071)		
Median	22.71	0.00		
Q1, Q3	5.8 ,54.7	0.0 ,1.2		
Min, Max	0.0, 151.0	0.0, 40.6		
Number of bleeds per year (95% CI)	27.5 (24.9, 30.4)	1.0 (0.8, 1.4)		

Source: Listing 16.2.6.2
Notes: [1] Number of bleeds per year (95% CI), p-value and ratio are based on a Poisson distribution

Table 14.2.2.3 Annualized Bleeding Rates: CSL627 Prophylaxis Compared with CSL627 On-Demand - By Region (Efficacy Population)

	On-Demand (N=27)	Prophylaxis (N=146)	p-value	Prophylaxis/ On-demand
Region: Europe				
Traumatic Bleeds				
n	16	69	<.0001	0.17 (0.11, 0.25)
Mean (SD)	5.48 (5.603)	0.74 (1.717)		
Median	4.82	0.00		
Q1, Q3	0.0, 8.6	0.0, 0.5		
Min, Max	0.0 ,16.4	0.0 ,9.3		
Number of bleeds per year (95% CI)	4.4 (3.4, 5.6)	0.7 (0.5, 1.0)		
Total Bleeds				
n	16	69	<.0001	0.06 (0.05, 0.08)
Mean (SD)	41.59 (42.383)	2.48 (5.374)		
Median	28.08	0.00		
Q1, Q3	12.9, 60.3	0.0, 3.5		
Min, Max	0.0, 163.3	0.0, 40.6		
Number of bleeds per year (95% CI)	32.4 (29.6, 35.5)	2.0 (1.7, 2.5)		
Number of subjects with zero bleeds [n(%)]	1 (6.3)	36 (52.2)		

Source: Listing 16.2.6.2
Notes: [1] Number of bleeds per year (95% CI), p-value and ratio are based on a Poisson distribution

Table 14.2.2.3 Annualized Bleeding Rates: CSL627 Prophylaxis Compared with CSL627 On-Demand - By Region (Efficacy Population)

	On-Demand (N=27)	Prophylaxis (N=146)	p-value	Prophylaxis/ On-demand
Region: Rest of the World				
Spontaneous Bleeds				
n	6	50	<.0001	0.37 (0.25, 0.54)
Mean (SD)	10.08 (10.803)	3.62 (4.908)		
Median	5.54	1.33		
Q1, Q3	2.8 ,19.9	0.0 ,7.4		
Min, Max	0.0, 26.7	0.0, 18.0		
Number of bleeds per year (95% CI)	9.3 (6.7, 12.8)	3.4 (2.8, 4.2)		
Traumatic Bleeds				
n	6	50	<.0001	0.18 (0.10, 0.34)
Mean (SD)	4.80 (8.343)	0.61 (1.465)		
Median	1.37	0.00		
Q1, Q3	0.0, 4.6	0.0, 0.0		
Min, Max	0.0 ,21.5	0.0 ,7.8		
Number of bleeds per year (95% CI)	4.5 (2.8, 7.2)	0.8 (0.5, 1.3)		
Total Bleeds				
n	6	50	<.0001	0.29 (0.21, 0.40)
Mean (SD)	16.76 (15.705)	4.57 (5.222)		
Median	14.33	2.57		
Q1, Q3	2.8, 26.7	0.0, 7.7		
Min, Max	2.7, 39.7	0.0, 19.3		
Number of bleeds per year (95% CI)	15.5 (12.1, 19.9)	4.5 (3.8, 5.5)		

Source: Listing 16.2.6.2
Notes: [1] Number of bleeds per year (95% CI), p-value and ratio are based on a Poisson distribution

Table 14.2.2.3 Annualized Bleeding Rates: CSL627 Prophylaxis Compared with CSL627 On-Demand - By Region (Efficacy Population)

	On-Demand (N=27)	Prophylaxis (N=146)	p-value	Prophylaxis/ On-demand
Region: Rest of the World				
Number of subjects with zero bleeds [n(%)]	0	17 (34.0)		

Source: Listing 16.2.6.2
Notes: [1] Number of bleeds per year (95% CI), p-value and ratio are based on a Poisson distribution

Table 14.2.5.1 Consumption of CSL627 During Routine Prophylaxis
(Efficacy Population)

	Prophylaxis (N=146)
Number of Subjects on Routine Prophylaxis Treatment [n (%)]	146 (100.0)
Total Number of Prophylaxis Infusions	12343
Prophylaxis Dose Administered per Subject Per Month (IU/kg)	
n	146
Mean (SD)	374.5 (148.18)
Median	356.9
Min, Max	31, 1522
Total Dose Administered per Subject Per Month (IU/kg)	
n	146
Mean (SD)	417.9 (194.11)
Median	388.5
Min, Max	173, 1732

Source: Listing 16.2.6.4
Notes: [1] Prophylaxis infusions are those recorded as administered for 'Routine/Prophylaxis'. Total infusions also include those recorded as administered for 'Bleeding Event', 'Surgery', 'Post Surgery' 'Prevention Prior to Activity', and 'Additional Treatment'

Table 14.2.5.1 Consumption of CSL627 During Routine Prophylaxis
(Efficacy Population)

	Prophylaxis (N=146)
Prophylaxis Dose Administered per Subject Per Year (IU/kg)	
n	146
Mean (SD)	4494.4 (1778.17)
Median	4282.9
Min, Max	372, 18263
Total Dose Administered per Subject Per Year (IU/kg)	
n	146
Mean (SD)	5015.0 (2329.33)
Median	4661.5
Min, Max	2078, 20789
Prophylaxis IU per Month	
n	146
Mean (SD)	28065.5 (14648.99)
Median	26686.8
Min, Max	2792, 136969
Total IU per Month	
n	146
Mean (SD)	31598.0 (19149.31)
Median	27706.4
Min, Max	8677, 155916

Source: Listing 16.2.6.4
Notes: [1] Prophylaxis infusions are those recorded as administered for 'Routine/Prophylaxis'. Total infusions also include those recorded as administered for 'Bleeding Event', 'Surgery', 'Post Surgery' 'Prevention Prior to Activity', and 'Additional Treatment'

Table 14.2.13.1.2 Part 1 - Summary of FVIII PK Parameters - Patients whose dosing is within +/- 10% range of planned dose (PK Population)

Assay / Adjustment / Treatment	IR ([IU/dL]/[IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
CS										
Baseline Uncorrected										
Advate										
n	26	26	26	26	26	26	26	26	26	26
Mean	2.80	140	NC	1770	1850	13.4	3.05	53.4	47.9	17.3
SD	0.401	19.7	NC	585	641	4.41	1.13	11.0	9.03	5.60
CV (%)	14.3	14.1	NC	32.9	34.6	33.0	37.1	20.6	18.9	32.3
Median	2.71	136	0.583	1750	1790	13.8	2.81	51.3	46.0	17.2
Min	1.64	81.8	0.450	804	827	7.19	1.59	38.5	34.9	9.83
Max	3.42	169	0.800	2990	3150	22.2	6.05	78.5	80.7	31.1
Geo. Mean	2.77	138	NC	1680	1750	12.7	2.86	52.4	47.2	16.5
CSL627										
n	26	26	26	26	26	26	26	26	26	26
Mean	2.28	115	NC	2030	2130	14.7	2.55	51.0	49.3	20.6
SD	0.331	16.6	NC	564	634	3.72	0.738	8.09	6.64	5.45
CV (%)	14.5	14.4	NC	27.8	29.8	25.4	28.9	15.9	13.5	26.5
Median	2.22	111	0.683	1970	2070	14.5	2.42	51.5	49.5	20.8
Min	1.58	78.8	0.467	1250	1280	9.13	1.40	31.8	32.4	12.8
Max	2.90	147	1.25	3390	3520	23.9	3.89	66.9	61.6	34.5
Geo. Mean	2.26	114	NC	1960	2040	14.2	2.45	50.3	48.9	20.0

Source: Listing 16.2.9.6.2
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated; Geo. Mean=Geometric Mean.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.13.1.2 Part 1 - Summary of FVIII PK Parameters
Patients whose dosing is within +/- 10% range of planned dose
(PK Population)

Assay / Adjustment / Treatment	IR ([IU/dL]/[IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
CS										
Baseline Corrected										
Advate										
n	26	26	26	26	26	26	26	26	26	26
Mean	2.76	138	NC	1660	1710	11.7	3.25	50.5	46.8	15.6
SD	0.416	20.5	NC	530	564	3.70	1.12	12.2	9.47	4.76
CV (%)	15.0	14.8	NC	32.0	32.9	31.8	34.5	24.2	20.3	30.6
Median	2.70	136	0.583	1660	1670	11.3	2.99	47.3	44.7	15.2
Min	1.64	81.8	0.450	804	827	4.77	1.59	31.8	32.5	8.11
Max	3.37	169	0.800	2990	3150	20.2	6.05	78.5	80.7	29.5
Geo. Mean	2.73	136	NC	1580	1620	11.1	3.08	49.2	46.0	15.0
CSL627										
n	26	26	26	26	26	26	26	26	26	26
Mean	2.27	114	NC	1990	2070	14.1	2.61	50.6	48.9	19.8
SD	0.334	16.8	NC	546	608	3.37	0.706	8.01	6.61	4.84
CV (%)	14.7	14.7	NC	27.5	29.4	23.9	27.0	15.8	13.5	24.5
Median	2.20	110	0.683	1940	2000	13.7	2.50	51.4	49.0	19.5
Min	1.47	73.4	0.467	1250	1280	9.13	1.40	31.8	32.4	12.8
Max	2.90	147	1.25	3390	3520	23.9	3.89	66.9	61.6	34.5
Geo. Mean	2.24	113	NC	1920	1990	13.8	2.52	49.9	48.4	19.2

Source: Listing 16.2.9.6.2
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated; Geo. Mean=Geometric Mean.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.13.1.2 Part 1 - Summary of FVIII PK Parameters
Patients whose dosing is within +/- 10% range of planned dose
(PK Population)

Assay / Adjustment / Treatment	IR ([IU/dL]/[IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
OS										
Baseline Uncorrected										
Advate										
n	26	26	26	26	26	26	26	26	26	26
Mean	2.15	108	NC	2000	2100	14.0	2.69	50.7	50.4	20.4
SD	0.380	18.9	NC	628	719	4.42	1.01	16.3	10.2	6.33
CV (%)	17.7	17.5	NC	31.3	34.3	31.5	37.4	32.1	20.3	31.0
Median	2.15	108	0.600	1960	1990	13.3	2.49	49.2	49.2	20.0
Min	1.26	63.2	0.450	886	904	8.80	1.43	31.7	33.2	11.4
Max	3.19	159	1.12	3370	3510	26.4	5.53	119	89.4	37.9
Geo. Mean	2.12	106	NC	1910	1980	13.4	2.53	49.0	49.5	19.6
CSL627										
n	26	26	26	26	26	26	26	26	26	26
Mean	1.09	56.3	NC	1260	1340	15.5	4.13	86.1	88.8	23.3
SD	0.157	7.83	NC	361	444	4.96	1.30	14.9	12.5	7.44
CV (%)	14.3	13.9	NC	28.6	33.2	31.9	31.6	17.3	14.0	31.9
Median	1.07	56.2	0.725	1140	1190	15.5	4.20	89.1	88.6	24.0
Min	0.834	41.8	0.500	668	674	9.41	2.01	56.8	58.8	13.2
Max	1.43	71.3	1.25	2010	2510	35.0	7.42	110	110	50.5
Geo. Mean	1.08	55.8	NC	1210	1270	15.0	3.93	84.8	87.9	22.4

Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated; Geo. Mean=Geometric Mean.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.13.1.2 Part 1 - Summary of FVIII PK Parameters
Patients whose dosing is within +/- 10% range of planned dose
(PK Population)

Assay / Adjustment / Treatment	IR ([IU/dL]/[IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
OS										
Baseline Corrected										
Advate										
n	26	26	26	26	26	26	26	26	26	26
Mean	2.10	105	NC	1840	1910	11.7	3.00	47.2	50.5	18.2
SD	0.425	21.2	NC	660	689	3.93	1.22	18.3	13.3	5.13
CV (%)	20.3	20.2	NC	35.9	36.2	33.6	40.8	38.7	26.3	28.2
Median	2.13	106	0.600	1790	1810	10.7	2.76	43.0	46.9	17.0
Min	1.14	56.8	0.450	370	753	6.95	1.44	31.6	33.2	11.1
Max	3.17	159	1.12	3360	3480	21.2	6.64	114	93.9	30.8
Geo. Mean	2.05	103	NC	1700	1790	11.1	2.80	44.9	49.2	17.6
CSL627										
n	26	26	26	26	26	26	26	26	26	26
Mean	1.08	55.5	NC	1200	1260	14.3	4.32	82.8	88.7	22.1
SD	0.167	7.69	NC	336	402	5.24	1.27	18.4	14.4	7.14
CV (%)	15.5	13.9	NC	28.1	31.8	36.7	29.3	22.2	16.2	32.4
Median	1.06	54.7	0.725	1090	1160	13.9	4.32	84.1	87.1	22.0
Min	0.759	41.5	0.500	668	674	7.64	2.13	57.7	58.7	12.6
Max	1.42	71.1	1.25	2000	2370	33.5	7.42	129	124	48.3
Geo. Mean	1.07	55.0	NC	1150	1210	13.5	4.14	80.9	87.6	21.1

Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated; Geo. Mean=Geometric Mean.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.13.3.2 Part 1 - Summary of FVIII PK Parameters After Dose Adjustment - Patients whose dosing is within +/- 10% range of planned dose
(PK Population)

Assay Adjustment Treatment	IR[1] ([IU/dL]/[IU/kg])	Cmax[1] (IU/dL)	Tmax (h)	AUC0-last[1] (IU*h/dL)	AUC0-∞[1] (IU*h/dL)	t1/2 (h)	CL[1] (mL/h/kg)	Vz[1] (mL/kg)	Vss[1] (mL/kg)
CS									
Baseline Uncorrected									
Advate									
n	26	26	26	26	26	26	26	26	26
Mean	2.39	119	NC	1510	1580	13.4	3.58	62.6	56.2
SD	0.342	16.8	NC	498	546	4.41	1.33	12.9	10.6
CV (%)	14.3	14.1	NC	32.9	34.6	33.0	37.1	20.5	18.8
Median	2.31	116	0.583	1490	1520	13.8	3.30	60.2	54.0
Min	1.39	69.7	0.450	685	705	7.19	1.86	45.2	41.0
Max	2.91	144	0.800	2550	2690	22.1	7.10	92.1	94.7
Geo. Mean	2.36	118	NC	1430	1490	12.7	3.36	61.5	55.4

Source: Listing 16.2.9.6.4
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; Geo. Mean=Geometric Mean; NC=Not Calculated; [1]Dose adjusted parameter.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state.

Table 14.2.13.3.2 Part 1 - Summary of FVIII PK Parameters After Dose Adjustment
Patients whose dosing is within +/- 10% range of planned dose
(PK Population)

Assay Adjustment Treatment	IR[1] ([IU/dL]/[IU/kg])	Cmax[1] (IU/dL)	Tmax (h)	AUC0-last[1] (IU*h/dL)	AUC0-∞[1] (IU*h/dL)	t1/2 (h)	CL[1] (mL/h/kg)	Vz[1] (mL/kg)	Vss[1] (mL/kg)
CS									
Baseline Corrected									
Advate									
n	26	26	26	26	26	26	26	26	26
Mean	2.35	118	NC	1410	1460	11.7	3.81	59.3	54.9
SD	0.354	17.4	NC	452	481	3.70	1.32	14.4	11.1
CV (%)	15.0	14.8	NC	32.0	32.9	31.8	34.5	24.2	20.2
Median	2.30	116	0.583	1410	1430	11.3	3.51	55.5	52.4
Min	1.39	69.7	0.450	685	705	4.77	1.86	37.4	38.1
Max	2.87	144	0.800	2550	2690	20.2	7.10	92.1	94.7
Geo. Mean	2.32	116	NC	1340	1380	11.1	3.61	57.7	54.0

Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; Geo. Mean=Geometric Mean; NC=Not Calculated; [1]Dose adjusted parameter.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state.

Table 14.2.16.1.1 Part 3 - FVIII PK Parameters of CSL627 CS baseline uncorrected, initial PK (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
0360031-1001	1.86	98.7	0.217	1530	1550	11.8	3.24	55.4	56.8	17.5
0360031-1002	2.40	117	0.500	1550	1600	10.4	3.05	45.9	44.7	14.6
0360031-1003	2.54	137	0.200	3820	4010	21.9	1.26	39.8	40.0	31.8
0400001-1004	2.33	116	0.350	1120	1200	7.54	4.16	45.2	45.0	10.8
2760034-1001	1.88	103	0.333	1180	1220	9.67	4.14	57.8	56.9	13.7
2760034-1003	1.83	99.3	0.367	1910	1970	14.7	2.58	54.8	55.2	21.4
2760034-1004	1.91	100	0.417	1380	1400	13.9	3.58	71.5	66.2	18.5
2760034-1005	2.13	108	0.800	1850	1900	13.8	2.66	52.9	52.2	19.7
2760034-1006	1.62	84.6	0.417	1850	1920	14.7	2.60	55.0	59.9	23.1
2760087-1001	2.44	131	0.467	2040	2110	15.9	2.38	54.4	45.9	19.3
3480007-1002	2.36	118	0.633	2090	2130	12.3	2.35	41.7	43.9	18.7
3800023-1003	1.99	102	0.300	1490	1510	11.6	3.31	55.6	55.7	16.8
3800023-1004	1.99	102	0.417	1560	1580	11.5	3.17	52.6	53.5	16.9
3800049-1001	1.41	87.5	0.500	1690	1710	14.8	3.43	73.5	72.2	21.1
3920025-1001	2.38	120	0.283	1530	1600	10.6	3.12	47.5	45.4	14.6
3920025-1002	1.88	99.4	0.417	2200	2260	18.0	2.22	57.6	57.3	25.9
3920027-1001	2.00	104	0.200	2010	2090	20.8	2.40	71.9	61.3	25.6
3920028-1001	2.30	132	0.250	2170	2230	13.3	2.25	43.2	43.2	19.2
3920029-1001	1.76	89.1	0.117	1790	1830	16.3	2.74	64.4	69.6	25.4
3920030-1001	2.20	114	0.533	1520	1540	11.5	3.26	53.8	52.9	16.3
3920031-1001	2.30	117	0.333	2480	2570	20.2	1.95	56.9	51.8	26.6

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.1.1 Part 3 - FVIII PK Parameters of CSL627 CS baseline uncorrected, initial PK (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
3920031-1002	2.24	118	0.333	2000	2020	10.3	2.47	36.7	40.7	16.5
3920033-1001	1.88	104	0.167	1940	2070	23.8	2.41	82.9	76.5	31.7
3920064-1001	1.91	101	0.183	2300	2380	18.9	2.10	57.4	58.5	27.8
4580001-1001	1.14	75.5	0.233	1390	1430	14.0	4.29	86.6	87.5	20.4
4580001-1002	1.84	105	0.533	1270	1320	10.1	4.33	63.2	62.4	14.4
5280007-1001	1.75	90.5	0.250	1680	1730	14.3	2.86	58.9	57.9	20.2
5280007-1004	1.89	92.8	0.283	1780	1830	13.9	2.67	53.4	54.1	20.3
6080001-1002	1.75	88.0	0.667	1560	1580	12.3	3.17	56.4	58.4	18.4
6080001-1003	1.82	107	0.367	908	932	8.93	5.39	69.5	61.6	11.4
6080001-1005	2.16	117	1.22	2360	2420	17.9	2.06	53.1	51.6	25.0
6080001-1006	2.61	131	0.700	2170	2240	15.2	2.23	48.8	49.2	22.1
6080001-1007	1.38	79.3	0.500	1350	1370	12.4	3.65	65.3	65.2	17.8
6080001-1008	0.868	62.4	0.333	991	1010	12.3	4.93	87.8	99.6	20.2
6080001-1010	0.880	45.5	0.333	642	683	11.3	7.32	119	121	16.6
6080001-1012	1.38	72.9	0.417	1510	1590	15.8	3.15	71.7	74.9	23.8
6080002-1001	1.94	97.0	0.500	1420	1440	12.8	3.47	64.0	61.1	17.6
6080002-1002	2.23	120	0.667	2170	2190	13.5	2.29	44.4	47.6	20.8
6430015-1002	1.79	118	0.500	2350	2390	16.3	2.44	57.3	57.5	23.6
7100001-1002	1.57	83.0	0.333	1620	1640	11.7	3.19	54.1	58.9	18.5
7100001-1003	1.86	118	0.200	2130	2190	14.0	2.79	56.4	56.7	20.3
7100001-1005	2.49	134	0.233	3840	4090	23.2	1.30	43.6	45.7	35.1

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.1.1 Part 3 - FVIII PK Parameters of CSL627 CS baseline uncorrected, initial PK (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
7100001-1006	1.54	94.2	0.00	954	971	8.41	5.79	70.3	67.3	11.6
7100001-1007	1.53	82.3	0.167	1470	1490	12.8	3.45	63.6	64.7	18.7
7100001-1008	2.15	124	0.683	2120	2160	12.3	2.67	47.3	48.3	18.1
7100001-1009	2.02	96.3	0.533	1750	1790	13.1	2.66	50.4	57.4	21.6
7100001-1010	2.02	96.8	0.217	2570	2640	17.8	1.80	46.3	48.7	27.0
7100001-1012	1.42	82.8	0.217	2060	2090	16.0	2.75	63.7	73.0	26.5
7100001-1013	1.53	89.8	0.217	1580	1610	16.6	3.55	85.2	74.9	21.1
7100001-1015	2.29	132	0.217	2230	2300	20.3	2.07	60.7	48.6	23.5
7100001-1016	1.65	97.6	0.200	2550	2610	18.2	1.86	48.8	50.2	27.1
7240023-1001	2.00	111	0.250	2260	2300	15.9	2.17	49.9	52.3	24.0
8040005-1001	1.72	90.5	0.250	2250	2320	18.9	2.18	59.4	59.3	27.2
8040005-1003	1.81	95.3	0.250	895	956	7.57	5.23	57.1	59.1	11.3
8040005-1004	1.48	77.7	0.250	925	962	10.4	4.94	74.1	74.2	15.0
8040005-1005	1.76	87.0	0.250	2310	2390	19.4	2.02	56.3	58.1	28.8
8040005-1009	1.58	84.6	0.250	732	757	6.32	6.61	60.3	60.5	9.17
8040007-1001	1.30	74.4	1.03	1540	1590	14.0	3.37	68.3	71.6	21.2
8040007-1002	1.20	68.4	1.03	1200	1300	12.9	4.14	77.3	78.9	19.1
8400118-1001	2.78	151	0.233	2530	2600	13.7	1.93	38.1	37.1	19.3
8400184-1006	1.84	96.5	0.333	1170	1240	11.3	4.05	66.2	62.8	15.5
8400184-1008	1.36	71.2	0.417	1530	1560	16.4	3.21	75.8	75.0	23.4
8400184-1009	1.17	72.2	1.17	1020	1040	9.15	4.81	63.5	65.5	13.6

Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.1.1 Part 3 - FVIII PK Parameters of CSL627 CS baseline uncorrected, initial PK (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
8400241-1002	2.26	125	0.467	2150	2200	12.9	2.32	43.4	43.7	18.8
n	64	64	64	64	64	64	64	64	64	64
Mean	1.86	101	NC	1780	1830	14.1	3.15	59.5	59.5	20.3
SD	0.413	20.4	NC	614	640	3.82	1.21	14.1	14.2	5.36
CV (%)	22.1	20.3	NC	34.5	34.9	27.1	38.2	23.7	23.9	26.4
Median	1.87	99.4	0.333	1720	1760	13.8	2.83	57.0	57.7	19.9
Min	0.868	45.5	0.00	642	683	6.32	1.26	36.7	37.1	9.17
Max	2.78	151	1.22	3840	4090	23.8	7.32	119	121	35.1
Geometric Mean	1.81	98.5	NC	1680	1730	13.6	2.96	58.0	58.1	19.6

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.2.1 Part 3 - FVIII PK Parameters of CSL627 CS baseline uncorrected, repeat PK (PK Population)

Subject/ Statistic	IR (IU/dL/ IU/kg)	Cmax (IU/dL)	Tmax (h)	AUC0-tau (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)	RC (r)	RAUC (r)	Time Dep. (r)
0400001-1004	2.26	108	0.300	1080	1080	8.3	4.29	51.8	50.9	11.8	0.931	0.895	0.895
2760034-1005	2.36	128	0.317	2210	2210	11.9	2.26	38.6	40.4	17.9	1.19	1.17	1.16
2760087-1001	2.16	112	0.500	1960	1970	12.7	2.47	45.3	46.9	19.0	0.853	0.943	0.932
3480007-1002	2.11	106	0.633	1870	1890	13.1	2.65	50.2	50.6	19.1	0.895	0.884	0.880
3800023-1003	1.56	82.3	0.300	1300	1300	10.5	3.84	58.3	59.4	15.5	0.809	0.864	0.861
3800049-1001	1.65	105	0.417	2110	2140	14.7	2.74	58.0	61.4	22.4	1.20	1.25	1.24
3920025-1001	2.43	125	0.200	1720	1720	10.6	2.90	44.5	45.0	15.5	1.05	1.08	1.07
3920027-1001	1.85	95.2	0.200	2080	2130	18.3	2.35	61.9	58.5	24.9	0.913	1.03	0.995
3920028-1001	2.28	129	0.267	1830	1840	13.9	2.71	54.6	49.4	18.2	0.971	0.826	0.820
3920029-1001	1.79	90.8	0.183	1740	1770	16.0	2.83	65.1	65.4	23.1	1.02	0.974	0.955
3920030-1001	1.83	93.6	0.417	1070	1070	8.0	4.65	54.1	55.2	11.9	0.819	0.701	0.700
3920031-1001	1.97	95.2	0.633	2160	2180	14.1	2.22	45.3	46.7	21.0	0.815	0.871	0.843
3920033-1001	1.73	93.3	0.117	2160	2290	21.1	2.18	66.4	67.4	30.9	0.901	1.11	1.05
3920064-1001	1.99	108	0.167	2460	2510	16.5	1.99	47.4	50.2	25.2	1.07	1.07	1.03
4580001-1001	1.67	88.3	0.233	1270	1270	9.4	3.96	53.8	58.2	14.7	1.17	0.895	0.888
4580001-1002	1.85	112	0.200	1550	1560	10.2	3.42	50.1	51.4	15.0	1.07	1.18	1.17
6080001-1002	2.48	134	0.333	2280	2290	12.9	2.19	40.7	41.7	19.1	1.52	1.44	1.44
6080001-1003	1.78	89.2	0.667	947	948	8.5	5.27	64.9	64.1	12.1	0.836	1.02	1.02
6080002-1001	1.53	99.7	0.450	1520	1530	12.0	3.25	56.1	60.2	18.5	1.03	1.06	1.05
6080002-1002	2.01	103	0.600	2180	2190	12.5	2.27	41.0	46.5	20.5	0.864	1.01	0.997

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-tau=Area under the plasma concentration time curve during a dosing interval (tau) at steady-state; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time; RC=Accumulation Ratio of Cmax (repeat/initial); RAUC=Accumulation Ratio of AUC0-tau (repeat/initial); Time Dep.=Time Dependance (repeat/initial).

Table 14.2.16.2.1 Part 3 - FVIII PK Parameters of CSL627 CS baseline uncorrected, repeat PK (PK Population)

Subject/ Statistic	IR (IU/dL/ IU/kg)	Cmax (IU/dL)	Tmax (h)	AUC0-tau (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)	RC (r)	RAUC (r)	Time Dep. (r)
7100001-1002	2.20	139	0.217	2410	2420	11.9	2.47	42.3	47.3	19.1	1.67	1.47	1.46
7100001-1003	1.82	103	0.583	1560	1560	12.0	3.60	62.3	58.4	16.2	0.866	0.717	0.711
7100001-1005	2.32	133	0.217	3860	4110	23.5	1.31	44.5	45.5	34.7	0.996	1.00	0.942
7100001-1006	1.38	84.5	0.167	928	928	7.6	5.99	65.7	69.9	11.7	0.897	0.956	0.956
7100001-1007	1.86	97.0	0.533	1570	1580	12.5	3.30	59.7	60.4	18.3	1.18	1.06	1.05
8040007-1001	1.78	112	0.267	2020	2040	14.1	2.63	53.4	53.2	20.2	1.51	1.28	1.27
8040007-1002	1.54	80.5	0.333	1010	1010	8.2	4.94	58.9	60.4	12.2	1.18	0.784	0.780
8400118-1001	3.20	162	0.200	2620	2630	11.3	1.90	31.0	31.5	16.6	1.08	1.01	1.01
8400184-1006	1.92	99.1	0.500	1850	1850	12.2	2.70	47.4	48.4	18.0	1.03	1.50	1.50
8400241-1002	2.18	119	0.367	2310	2360	18.2	2.12	55.4	50.2	23.7	0.953	1.06	1.05
n	30	30	30	30	30	30	30	30	30	30	30	30	30
Mean	1.98	108	NC	1850	1880	12.9	3.05	52.3	53.1	18.9	1.04	1.04	1.02
SD	0.367	19.1	NC	613	649	3.7	1.10	9.05	8.74	5.39	0.215	0.202	0.202
CV (%)	18.5	17.7	NC	33.0	34.5	29.4	36.0	17.3	16.4	28.5	20.7	19.5	19.8
Median	1.89	104	0.308	1860	1870	12.4	2.71	53.6	51.1	18.4	1.01	1.02	1.00
Min	1.38	80.5	0.117	928	928	7.6	1.31	31.0	31.5	11.7	0.809	0.701	0.700
Max	3.20	162	0.667	3860	4110	23.5	5.99	66.4	69.9	34.7	1.67	1.50	1.50
Geometric Mean	1.95	106	NC	1760	1780	12.4	2.88	51.5	52.4	18.2	1.02	1.02	1.01

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-tau=Area under the plasma concentration time curve during a dosing interval (tau) at steady-state; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time; RC=Accumulation Ratio of Cmax (repeat/initial); RAUC=Accumulation Ratio of AUC0-tau (repeat/initial); Time Dep.=Time Dependance (repeat/initial).

Table 14.2.16.9.1 Part 3 - FVIII PK Parameters of CSL627 CS baseline corrected, initial PK (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
0360031-1001	1.86	98.7	0.217	1530	1550	11.8	3.24	55.4	56.8	17.5
0360031-1002	2.40	117	0.500	1550	1600	10.4	3.05	45.9	44.7	14.6
0360031-1003	2.46	133	0.200	3430	3480	15.8	1.45	32.9	37.3	25.8
0400001-1004	2.33	116	0.350	1120	1200	7.54	4.16	45.2	45.0	10.8
2760034-1001	1.88	103	0.333	1180	1220	9.67	4.14	57.8	56.9	13.7
2760034-1003	1.83	99.3	0.367	1910	1970	14.7	2.58	54.8	55.2	21.4
2760034-1004	1.91	100	0.417	1380	1400	13.9	3.58	71.5	66.2	18.5
2760034-1005	2.13	108	0.800	1850	1900	13.8	2.66	52.9	52.2	19.7
2760034-1006	1.62	84.6	0.417	1850	1920	14.7	2.60	55.0	59.9	23.1
2760087-1001	2.44	131	0.467	2040	2110	15.9	2.38	54.4	45.9	19.3
3480007-1002	2.36	118	0.633	2090	2130	12.3	2.35	41.7	43.9	18.7
3800023-1003	1.99	102	0.300	1490	1510	11.6	3.31	55.6	55.7	16.8
3800023-1004	1.99	102	0.417	1560	1580	11.5	3.17	52.6	53.5	16.9
3800049-1001	1.41	87.5	0.500	1690	1710	14.8	3.43	73.5	72.2	21.1
3920025-1001	2.38	120	0.283	1530	1600	10.6	3.12	47.5	45.4	14.6
3920025-1002	1.84	97.6	0.417	2010	2020	12.7	2.48	45.5	52.7	21.3
3920027-1001	1.98	103	0.200	1870	1900	15.7	2.64	59.5	55.8	21.2
3920028-1001	2.30	132	0.250	2170	2230	13.3	2.25	43.2	43.2	19.2
3920029-1001	1.76	89.1	0.117	1790	1830	16.3	2.74	64.4	69.6	25.4
3920030-1001	2.20	114	0.533	1520	1540	11.5	3.26	53.8	52.9	16.3
3920031-1001	2.27	115	0.333	2330	2370	14.7	2.11	44.9	48.4	22.9

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.9.1 Part 3 - FVIII PK Parameters of CSL627 CS baseline corrected, initial PK (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
3920031-1002	2.24	118	0.333	2000	2020	10.3	2.47	36.7	40.7	16.5
3920033-1001	1.82	101	0.167	1670	1690	13.9	2.96	59.6	66.7	22.5
3920064-1001	1.91	101	0.183	2300	2380	18.9	2.10	57.4	58.5	27.8
4580001-1001	1.14	75.5	0.233	1390	1430	14.0	4.29	86.6	87.5	20.4
4580001-1002	1.84	105	0.533	1270	1320	10.1	4.33	63.2	62.4	14.4
5280007-1001	1.70	88.3	0.250	1500	1510	7.64	3.29	36.3	52.1	15.8
5280007-1004	1.89	92.8	0.283	1780	1830	13.9	2.67	53.4	54.1	20.3
6080001-1002	1.75	88.0	0.667	1560	1580	12.3	3.17	56.4	58.4	18.4
6080001-1003	1.82	107	0.367	908	932	8.93	5.39	69.5	61.6	11.4
6080001-1005	2.16	117	1.22	2360	2420	17.9	2.06	53.1	51.6	25.0
6080001-1006	2.61	131	0.700	2170	2240	15.2	2.23	48.8	49.2	22.1
6080001-1007	1.38	79.3	0.500	1350	1370	12.4	3.65	65.3	65.2	17.8
6080001-1008	0.868	62.4	0.333	991	1010	12.3	4.93	87.8	99.6	20.2
6080001-1010	0.880	45.5	0.333	642	683	11.3	7.32	119	121	16.6
6080001-1012	1.38	72.9	0.417	1510	1590	15.8	3.15	71.7	74.9	23.8
6080002-1001	1.94	97.0	0.500	1420	1440	12.8	3.47	64.0	61.1	17.6
6080002-1002	2.23	120	0.667	2170	2190	13.5	2.29	44.4	47.6	20.8
6430015-1002	1.79	118	0.500	2350	2390	16.3	2.44	57.3	57.5	23.6
7100001-1002	1.57	83.0	0.333	1620	1640	11.7	3.19	54.1	58.9	18.5
7100001-1003	1.86	118	0.200	2130	2190	14.0	2.79	56.4	56.7	20.3
7100001-1005	2.20	118	0.233	2400	2430	12.8	2.19	40.5	43.3	19.7

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.9.1 Part 3 - FVIII PK Parameters of CSL627 CS baseline corrected, initial PK (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
7100001-1007	1.53	82.3	0.167	1470	1490	12.8	3.45	63.6	64.7	18.7
7100001-1008	1.81	105	0.683	1140	1150	2.36	5.03	17.2	47.3	9.39
7100001-1009	2.02	96.3	0.533	1750	1790	13.1	2.66	50.4	57.4	21.6
7100001-1010	2.02	96.8	0.217	2570	2640	17.8	1.80	46.3	48.7	27.0
7100001-1012	1.42	82.8	0.217	2060	2090	16.0	2.75	63.7	73.0	26.5
7100001-1013	1.53	89.8	0.217	1580	1610	16.6	3.55	85.2	74.9	21.1
7100001-1015	2.27	130	0.217	2100	2130	15.1	2.24	48.7	44.2	19.8
7100001-1016	1.65	97.6	0.200	2550	2610	18.2	1.86	48.8	50.2	27.1
7240023-1001	2.00	111	0.250	2260	2300	15.9	2.17	49.9	52.3	24.0
8040005-1001	1.72	90.5	0.250	2250	2320	18.9	2.18	59.4	59.3	27.2
8040005-1003	1.81	95.3	0.250	895	956	7.57	5.23	57.1	59.1	11.3
8040005-1004	1.48	77.7	0.250	925	962	10.4	4.94	74.1	74.2	15.0
8040005-1005	1.76	87.0	0.250	2310	2390	19.4	2.02	56.3	58.1	28.8
8040005-1009	1.58	84.6	0.250	732	757	6.32	6.61	60.3	60.5	9.17
8040007-1001	1.30	74.4	1.03	1540	1590	14.0	3.37	68.3	71.6	21.2
8040007-1002	1.20	68.4	1.03	1200	1300	13.4	4.13	79.7	79.4	19.3
8400118-1001	2.78	151	0.233	2530	2600	13.7	1.93	38.1	37.1	19.3
8400184-1006	1.84	96.5	0.333	1170	1240	11.3	4.05	66.2	62.8	15.5
8400184-1008	1.36	71.2	0.417	1530	1560	16.4	3.21	75.8	75.0	23.4
8400184-1009	1.17	72.2	1.17	1020	1040	9.15	4.81	63.5	65.5	13.6
8400241-1002	2.23	123	0.467	2050	2060	10.1	2.47	36.0	41.5	16.8

Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.9.1 Part 3 - FVIII PK Parameters of CSL627 CS baseline corrected, initial PK (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
n	63	63	63	63	63	63	63	63	63	63
Mean	1.85	99.9	NC	1730	1770	13.1	3.20	57.1	58.7	19.5
SD	0.404	19.9	NC	530	535	3.25	1.15	15.5	14.5	4.57
CV (%)	21.8	19.9	NC	30.6	30.2	24.7	36.1	27.1	24.6	23.4
Median	1.84	99.3	0.333	1670	1690	13.4	3.05	55.6	56.9	19.7
Min	0.868	45.5	0.117	642	683	2.36	1.45	17.2	37.1	9.17
Max	2.78	151	1.22	3430	3480	19.4	7.32	119	121	28.8
Geometric Mean	1.81	97.8	NC	1650	1690	12.6	3.02	55.1	57.2	18.9

CSL Behring GmbH: CSL627_1001/CIL-GM/FINAL/PKP301P.SAS
Produced: [redacted] 20[redacted], 12:44
Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.10.1 Part 3 - FVIII PK Parameters of CSL627 CS baseline corrected, repeat PK (PK Population)

Subject/ Statistic	IR (IU/dL/ IU/kg)	Cmax (IU/dL)	Tmax (h)	AUC0-tau (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)	RC (r)	RAUC (r)	Time Dep. (r)
0400001-1004	2.26	108	0.300	1080	1080	8.3	4.29	51.8	50.9	11.8	0.931	0.895	0.895
2760034-1005	2.36	128	0.317	2210	2210	11.9	2.26	38.6	40.4	17.9	1.19	1.17	1.16
2760087-1001	2.16	112	0.500	1960	1970	12.7	2.47	45.3	46.9	19.0	0.853	0.943	0.932
3480007-1002	2.11	106	0.633	1870	1890	13.1	2.65	50.2	50.6	19.1	0.895	0.884	0.880
3800023-1003	1.56	82.3	0.300	1300	1300	10.5	3.84	58.3	59.4	15.5	0.809	0.864	0.861
3800049-1001	1.65	105	0.417	2110	2140	14.7	2.74	58.0	61.4	22.4	1.20	1.25	1.24
3920025-1001	2.43	125	0.200	1720	1720	10.6	2.90	44.5	45.0	15.5	1.05	1.08	1.07
3920027-1001	1.82	93.8	0.200	1930	1950	13.9	2.57	51.6	54.1	21.1	0.912	1.03	1.02
3920028-1001	2.28	129	0.267	1830	1840	13.9	2.71	54.6	49.4	18.2	0.971	0.826	0.820
3920029-1001	1.79	90.8	0.183	1740	1770	16.0	2.83	65.1	65.4	23.1	1.02	0.974	0.955
3920030-1001	1.83	93.6	0.417	1070	1070	8.0	4.65	54.1	55.2	11.9	0.819	0.701	0.700
3920031-1001	1.94	93.8	0.633	2020	2030	10.9	2.39	37.6	44.8	18.8	0.813	0.867	0.856
3920033-1001	1.67	90.5	0.117	1890	1930	16.5	2.60	61.6	61.5	23.7	0.899	1.13	1.12
3920064-1001	1.99	108	0.167	2460	2510	16.5	1.99	47.4	50.2	25.2	1.07	1.07	1.03
4580001-1001	1.67	88.3	0.233	1270	1270	9.4	3.96	53.8	58.2	14.7	1.17	0.895	0.888
4580001-1002	1.85	112	0.200	1550	1560	10.2	3.42	50.1	51.4	15.0	1.07	1.18	1.17
6080001-1002	2.48	134	0.333	2280	2290	12.9	2.19	40.7	41.7	19.1	1.52	1.44	1.44
6080001-1003	1.78	89.2	0.667	947	948	8.5	5.27	64.9	64.1	12.1	0.836	1.02	1.02
6080002-1001	1.53	99.7	0.450	1520	1530	12.0	3.25	56.1	60.2	18.5	1.03	1.06	1.05
6080002-1002	2.01	103	0.600	2180	2190	12.5	2.27	41.0	46.5	20.5	0.864	1.01	0.997

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-tau=Area under the plasma concentration time curve during a dosing interval (tau) at steady-state; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time; RC=Accumulation Ratio of Cmax (repeat/initial); RAUC=Accumulation Ratio of AUC0-tau (repeat/initial); Time Dep.=Time Dependance (repeat/initial).

Table 14.2.16.10.1 Part 3 - FVIII PK Parameters of CSL627 CS baseline corrected, repeat PK (PK Population)

Subject/ Statistic	IR (IU/dL/ IU/kg)	Cmax (IU/dL)	Tmax (h)	AUC0-tau (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)	RC (r)	RAUC (r)	Time Dep. (r)
7100001-1002	2.20	139	0.217	2410	2420	11.9	2.47	42.3	47.3	19.1	1.67	1.47	1.46
7100001-1003	1.82	103	0.583	1560	1560	12.0	3.60	62.3	58.4	16.2	0.866	0.717	0.711
7100001-1005	2.03	118	0.217	2700	2760	18.2	1.95	51.3	50.7	26.0	0.995	1.11	1.11
7100001-1007	1.86	97.0	0.533	1570	1580	12.5	3.30	59.7	60.4	18.3	1.18	1.06	1.05
8040007-1001	1.78	112	0.267	2020	2040	14.1	2.63	53.4	53.2	20.2	1.51	1.28	1.27
8040007-1002	1.54	80.5	0.333	1010	1010	8.2	4.94	58.9	60.4	12.2	1.18	0.782	0.778
8400118-1001	3.20	162	0.200	2620	2630	11.3	1.90	31.0	31.5	16.6	1.08	1.01	1.01
8400184-1006	1.92	99.1	0.500	1850	1850	12.2	2.70	47.4	48.4	18.0	1.03	1.50	1.50
8400241-1002	2.15	117	0.367	2170	2180	13.4	2.29	44.3	46.4	20.3	0.953	1.05	1.05
n	29	29	29	29	29	29	29	29	29	29	29	29	29
Mean	1.99	108	NC	1820	1840	12.3	3.00	50.9	52.2	18.3	1.05	1.04	1.04
SD	0.352	18.5	NC	478	487	2.5	0.907	8.65	7.93	3.80	0.217	0.206	0.206
CV (%)	17.7	17.2	NC	26.2	26.5	20.9	30.2	17.0	15.2	20.8	20.8	19.7	19.8
Median	1.92	105	0.317	1870	1890	12.2	2.70	51.6	50.9	18.5	1.02	1.03	1.02
Min	1.53	80.5	0.117	947	948	8.0	1.90	31.0	31.5	11.8	0.809	0.701	0.700
Max	3.20	162	0.667	2700	2760	18.2	5.27	65.1	65.4	26.0	1.67	1.50	1.50
Geometric Mean	1.96	106	NC	1760	1770	12.0	2.88	50.2	51.6	17.9	1.03	1.02	1.02

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-tau=Area under the plasma concentration time curve during a dosing interval (tau) at steady-state; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time; RC=Accumulation Ratio of Cmax (repeat/initial); RAUC=Accumulation Ratio of AUC0-tau (repeat/initial); Time Dep.=Time Dependance (repeat/initial).

Table 14.2.16.21.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial CS baseline uncorrected (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
Race Group: Japanese										
3920025-1001	2.38	120	0.283	1530	1600	10.6	3.12	47.5	45.4	14.6
3920025-1002	1.88	99.4	0.417	2200	2260	18.0	2.22	57.6	57.3	25.9
3920027-1001	2.00	104	0.200	2010	2090	20.8	2.40	71.9	61.3	25.6
3920028-1001	2.30	132	0.250	2170	2230	13.3	2.25	43.2	43.2	19.2
3920029-1001	1.76	89.1	0.117	1790	1830	16.3	2.74	64.4	69.6	25.4
3920030-1001	2.20	114	0.533	1520	1540	11.5	3.26	53.8	52.9	16.3
3920031-1001	2.30	117	0.333	2480	2570	20.2	1.95	56.9	51.8	26.6
3920031-1002	2.24	118	0.333	2000	2020	10.3	2.47	36.7	40.7	16.5
3920033-1001	1.88	104	0.167	1940	2070	23.8	2.41	82.9	76.5	31.7
3920064-1001	1.91	101	0.183	2300	2380	18.9	2.10	57.4	58.5	27.8

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.21.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial CS baseline uncorrected (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
Race Group: Japanese										
n	10	10	10	10	10	10	10	10	10	10
Mean	2.08	110	NC	2000	2060	16.4	2.49	57.2	55.7	23.0
SD	0.223	12.6	NC	314	327	4.75	0.427	13.5	11.4	5.84
CV (%)	10.7	11.5	NC	15.7	15.9	29.0	17.1	23.6	20.5	25.4
Median	2.10	109	0.267	2010	2080	17.2	2.41	57.1	55.1	25.5
Min	1.76	89.1	0.117	1520	1540	10.3	1.95	36.7	40.7	14.6
Max	2.38	132	0.533	2480	2570	23.8	3.26	82.9	76.5	31.7
Geometric Mean	2.07	109	NC	1970	2030	15.7	2.46	55.8	54.7	22.2

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.21.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial CS baseline uncorrected (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
Race Group: Non-Japanese										
0360031-1001	1.86	98.7	0.217	1530	1550	11.8	3.24	55.4	56.8	17.5
0360031-1002	2.40	117	0.500	1550	1600	10.4	3.05	45.9	44.7	14.6
0360031-1003	2.54	137	0.200	3820	4010	21.9	1.26	39.8	40.0	31.8
0400001-1004	2.33	116	0.350	1120	1200	7.54	4.16	45.2	45.0	10.8
2760034-1001	1.88	103	0.333	1180	1220	9.67	4.14	57.8	56.9	13.7
2760034-1003	1.83	99.3	0.367	1910	1970	14.7	2.58	54.8	55.2	21.4
2760034-1004	1.91	100	0.417	1380	1400	13.9	3.58	71.5	66.2	18.5
2760034-1005	2.13	108	0.800	1850	1900	13.8	2.66	52.9	52.2	19.7
2760034-1006	1.62	84.6	0.417	1850	1920	14.7	2.60	55.0	59.9	23.1
2760087-1001	2.44	131	0.467	2040	2110	15.9	2.38	54.4	45.9	19.3
3480007-1002	2.36	118	0.633	2090	2130	12.3	2.35	41.7	43.9	18.7
3800023-1003	1.99	102	0.300	1490	1510	11.6	3.31	55.6	55.7	16.8
3800023-1004	1.99	102	0.417	1560	1580	11.5	3.17	52.6	53.5	16.9
3800049-1001	1.41	87.5	0.500	1690	1710	14.8	3.43	73.5	72.2	21.1
4580001-1001	1.14	75.5	0.233	1390	1430	14.0	4.29	86.6	87.5	20.4
4580001-1002	1.84	105	0.533	1270	1320	10.1	4.33	63.2	62.4	14.4
5280007-1001	1.75	90.5	0.250	1680	1730	14.3	2.86	58.9	57.9	20.2
5280007-1004	1.89	92.8	0.283	1780	1830	13.9	2.67	53.4	54.1	20.3

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.21.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial CS baseline uncorrected (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
Race Group: Non-Japanese										
6080001-1002	1.75	88.0	0.667	1560	1580	12.3	3.17	56.4	58.4	18.4
6080001-1003	1.82	107	0.367	908	932	8.93	5.39	69.5	61.6	11.4
6080001-1005	2.16	117	1.22	2360	2420	17.9	2.06	53.1	51.6	25.0
6080001-1006	2.61	131	0.700	2170	2240	15.2	2.23	48.8	49.2	22.1
6080001-1007	1.38	79.3	0.500	1350	1370	12.4	3.65	65.3	65.2	17.8
6080001-1008	0.868	62.4	0.333	991	1010	12.3	4.93	87.8	99.6	20.2
6080001-1010	0.880	45.5	0.333	642	683	11.3	7.32	119	121	16.6
6080001-1012	1.38	72.9	0.417	1510	1590	15.8	3.15	71.7	74.9	23.8
6080002-1001	1.94	97.0	0.500	1420	1440	12.8	3.47	64.0	61.1	17.6
6080002-1002	2.23	120	0.667	2170	2190	13.5	2.29	44.4	47.6	20.8
6430015-1002	1.79	118	0.500	2350	2390	16.3	2.44	57.3	57.5	23.6
7100001-1002	1.57	83.0	0.333	1620	1640	11.7	3.19	54.1	58.9	18.5
7100001-1003	1.86	118	0.200	2130	2190	14.0	2.79	56.4	56.7	20.3
7100001-1005	2.49	134	0.233	3840	4090	23.2	1.30	43.6	45.7	35.1
7100001-1006	1.54	94.2	0.00	954	971	8.41	5.79	70.3	67.3	11.6
7100001-1007	1.53	82.3	0.167	1470	1490	12.8	3.45	63.6	64.7	18.7
7100001-1008	2.15	124	0.683	2120	2160	12.3	2.67	47.3	48.3	18.1
7100001-1009	2.02	96.3	0.533	1750	1790	13.1	2.66	50.4	57.4	21.6

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.21.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial CS baseline uncorrected (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
Race Group: Non-Japanese										
7100001-1010	2.02	96.8	0.217	2570	2640	17.8	1.80	46.3	48.7	27.0
7100001-1012	1.42	82.8	0.217	2060	2090	16.0	2.75	63.7	73.0	26.5
7100001-1013	1.53	89.8	0.217	1580	1610	16.6	3.55	85.2	74.9	21.1
7100001-1015	2.29	132	0.217	2230	2300	20.3	2.07	60.7	48.6	23.5
7100001-1016	1.65	97.6	0.200	2550	2610	18.2	1.86	48.8	50.2	27.1
7240023-1001	2.00	111	0.250	2260	2300	15.9	2.17	49.9	52.3	24.0
8040005-1001	1.72	90.5	0.250	2250	2320	18.9	2.18	59.4	59.3	27.2
8040005-1003	1.81	95.3	0.250	895	956	7.57	5.23	57.1	59.1	11.3
8040005-1004	1.48	77.7	0.250	925	962	10.4	4.94	74.1	74.2	15.0
8040005-1005	1.76	87.0	0.250	2310	2390	19.4	2.02	56.3	58.1	28.8
8040005-1009	1.58	84.6	0.250	732	757	6.32	6.61	60.3	60.5	9.17
8040007-1001	1.30	74.4	1.03	1540	1590	14.0	3.37	68.3	71.6	21.2
8040007-1002	1.20	68.4	1.03	1200	1300	12.9	4.14	77.3	78.9	19.1
8400118-1001	2.78	151	0.233	2530	2600	13.7	1.93	38.1	37.1	19.3
8400184-1006	1.84	96.5	0.333	1170	1240	11.3	4.05	66.2	62.8	15.5
8400184-1008	1.36	71.2	0.417	1530	1560	16.4	3.21	75.8	75.0	23.4
8400184-1009	1.17	72.2	1.17	1020	1040	9.15	4.81	63.5	65.5	13.6
8400241-1002	2.26	125	0.467	2150	2200	12.9	2.32	43.4	43.7	18.8

Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.21.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial CS baseline uncorrected (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
Race Group: Non-Japanese										
n	54	54	54	54	54	54	54	54	54	54
Mean	1.82	98.9	NC	1740	1790	13.7	3.28	59.9	60.2	19.9
SD	0.428	21.2	NC	649	676	3.52	1.27	14.3	14.7	5.18
CV (%)	23.5	21.4	NC	37.3	37.7	25.7	38.6	23.9	24.4	26.1
Median	1.83	96.9	0.342	1600	1620	13.6	3.16	56.8	58.0	19.5
Min	0.868	45.5	0.00	642	683	6.32	1.26	38.1	37.1	9.17
Max	2.78	151	1.22	3840	4090	23.2	7.32	119	121	35.1
Geometric Mean	1.77	96.6	NC	1630	1680	13.2	3.06	58.5	58.7	19.2

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.22.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese repeat CS baseline uncorrected (PK Population)

Subject/ Statistic	IR (IU/dL/ IU/kg)	Cmax (IU/dL)	Tmax (h)	AUC0-tau (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)	RC (r)	RAUC (r)	Time Dep. (r)
Race Group: Japanese													
3920025-1001	2.43	125	0.200	1720	1720	10.6	2.90	44.5	45.0	15.5	1.05	1.08	1.07
3920027-1001	1.85	95.2	0.200	2080	2130	18.3	2.35	61.9	58.5	24.9	0.913	1.03	0.995
3920028-1001	2.28	129	0.267	1830	1840	13.9	2.71	54.6	49.4	18.2	0.971	0.826	0.820
3920029-1001	1.79	90.8	0.183	1740	1770	16.0	2.83	65.1	65.4	23.1	1.02	0.974	0.955
3920030-1001	1.83	93.6	0.417	1070	1070	8.0	4.65	54.1	55.2	11.9	0.819	0.701	0.700
3920031-1001	1.97	95.2	0.633	2160	2180	14.1	2.22	45.3	46.7	21.0	0.815	0.871	0.843
3920033-1001	1.73	93.3	0.117	2160	2290	21.1	2.18	66.4	67.4	30.9	0.901	1.11	1.05
3920064-1001	1.99	108	0.167	2460	2510	16.5	1.99	47.4	50.2	25.2	1.07	1.07	1.03
n	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean	1.98	104	NC	1900	1940	14.8	2.73	54.9	54.7	21.3	0.944	0.958	0.933
SD	0.247	15.2	NC	419	444	4.1	0.844	8.79	8.41	6.05	0.0983	0.145	0.132
CV (%)	12.5	14.7	NC	22.0	22.9	27.9	30.9	16.0	15.4	28.3	10.4	15.1	14.2
Median	1.91	95.2	0.200	1950	1980	15.0	2.53	54.4	52.7	22.1	0.942	1.00	0.975
Min	1.73	90.8	0.117	1070	1070	8.0	1.99	44.5	45.0	11.9	0.815	0.701	0.700
Max	2.43	129	0.633	2460	2510	21.1	4.65	66.4	67.4	30.9	1.07	1.11	1.07
Geometric Mean	1.97	103	NC	1860	1890	14.3	2.64	54.3	54.2	20.5	0.940	0.947	0.924

CSL Behring GmbH: CSL627_1001/CIL-GM/FINAL/PKP322P.SAS
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Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-tau=Area under the plasma concentration time curve during a dosing interval (tau) at steady-state; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time; RC=Accumulation Ratio of Cmax (repeat/initial); RAUC=Accumulation Ratio of AUC0-tau (repeat/initial); Time Dep.=Time Dependance (repeat/initial).

Table 14.2.16.22.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese repeat CS baseline uncorrected (PK Population)

Subject/ Statistic	IR (IU/dL/ IU/kg)	Cmax (IU/dL)	Tmax (h)	AUC0-tau (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)	RC (r)	RAUC (r)	Time Dep. (r)
Race Group: Non-Japanese													
0400001-1004	2.26	108	0.300	1080	1080	8.3	4.29	51.8	50.9	11.8	0.931	0.895	0.895
2760034-1005	2.36	128	0.317	2210	2210	11.9	2.26	38.6	40.4	17.9	1.19	1.17	1.16
2760087-1001	2.16	112	0.500	1960	1970	12.7	2.47	45.3	46.9	19.0	0.853	0.943	0.932
3480007-1002	2.11	106	0.633	1870	1890	13.1	2.65	50.2	50.6	19.1	0.895	0.884	0.880
3800023-1003	1.56	82.3	0.300	1300	1300	10.5	3.84	58.3	59.4	15.5	0.809	0.864	0.861
3800049-1001	1.65	105	0.417	2110	2140	14.7	2.74	58.0	61.4	22.4	1.20	1.25	1.24
4580001-1001	1.67	88.3	0.233	1270	1270	9.4	3.96	53.8	58.2	14.7	1.17	0.895	0.888
4580001-1002	1.85	112	0.200	1550	1560	10.2	3.42	50.1	51.4	15.0	1.07	1.18	1.17
6080001-1002	2.48	134	0.333	2280	2290	12.9	2.19	40.7	41.7	19.1	1.52	1.44	1.44
6080001-1003	1.78	89.2	0.667	947	948	8.5	5.27	64.9	64.1	12.1	0.836	1.02	1.02
6080002-1001	1.53	99.7	0.450	1520	1530	12.0	3.25	56.1	60.2	18.5	1.03	1.06	1.05
6080002-1002	2.01	103	0.600	2180	2190	12.5	2.27	41.0	46.5	20.5	0.864	1.01	0.997
7100001-1002	2.20	139	0.217	2410	2420	11.9	2.47	42.3	47.3	19.1	1.67	1.47	1.46
7100001-1003	1.82	103	0.583	1560	1560	12.0	3.60	62.3	58.4	16.2	0.866	0.717	0.711
7100001-1005	2.32	133	0.217	3860	4110	23.5	1.31	44.5	45.5	34.7	0.996	1.00	0.942
7100001-1006	1.38	84.5	0.167	928	928	7.6	5.99	65.7	69.9	11.7	0.897	0.956	0.956
7100001-1007	1.86	97.0	0.533	1570	1580	12.5	3.30	59.7	60.4	18.3	1.18	1.06	1.05
8040007-1001	1.78	112	0.267	2020	2040	14.1	2.63	53.4	53.2	20.2	1.51	1.28	1.27

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-tau=Area under the plasma concentration time curve during a dosing interval (tau) at steady-state; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time; RC=Accumulation Ratio of Cmax (repeat/initial); RAUC=Accumulation Ratio of AUC0-tau (repeat/initial); Time Dep.=Time Dependance (repeat/initial).

Table 14.2.16.22.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese repeat CS baseline uncorrected (PK Population)

Subject/ Statistic	IR (IU/dL/ IU/kg)	Cmax (IU/dL)	Tmax (h)	AUC0-tau (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)	RC (r)	RAUC (r)	Time Dep. (r)
Race Group: Non-Japanese													
8040007-1002	1.54	80.5	0.333	1010	1010	8.2	4.94	58.9	60.4	12.2	1.18	0.784	0.780
8400118-1001	3.20	162	0.200	2620	2630	11.3	1.90	31.0	31.5	16.6	1.08	1.01	1.01
8400184-1006	1.92	99.1	0.500	1850	1850	12.2	2.70	47.4	48.4	18.0	1.03	1.50	1.50
8400241-1002	2.18	119	0.367	2310	2360	18.2	2.12	55.4	50.2	23.7	0.953	1.06	1.05
n	22	22	22	22	22	22	22	22	22	22	22	22	22
Mean	1.98	109	NC	1840	1860	12.2	3.16	51.3	52.6	18.0	1.08	1.07	1.06
SD	0.407	20.4	NC	677	717	3.4	1.17	9.15	8.98	4.99	0.236	0.215	0.215
CV (%)	20.5	18.8	NC	36.9	38.6	28.6	37.1	17.8	17.1	27.7	21.9	20.2	20.4
Median	1.89	105	0.333	1860	1870	12.0	2.72	52.6	51.1	18.1	1.03	1.02	1.01
Min	1.38	80.5	0.167	928	928	7.6	1.31	31.0	31.5	11.7	0.809	0.717	0.711
Max	3.20	162	0.667	3860	4110	23.5	5.99	65.7	69.9	34.7	1.67	1.50	1.50
Geometric Mean	1.95	107	NC	1730	1740	11.8	2.97	50.5	51.8	17.4	1.06	1.05	1.04

Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-tau=Area under the plasma concentration time curve during a dosing interval (tau) at steady-state; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time; RC=Accumulation Ratio of Cmax (repeat/initial); RAUC=Accumulation Ratio of AUC0-tau (repeat/initial); Time Dep.=Time Dependance (repeat/initial).

Table 14.2.16.23.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial CS baseline corrected (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
Race Group: Japanese										
3920025-1001	2.38	120	0.283	1530	1600	10.6	3.12	47.5	45.4	14.6
3920025-1002	1.84	97.6	0.417	2010	2020	12.7	2.48	45.5	52.7	21.3
3920027-1001	1.98	103	0.200	1870	1900	15.7	2.64	59.5	55.8	21.2
3920028-1001	2.30	132	0.250	2170	2230	13.3	2.25	43.2	43.2	19.2
3920029-1001	1.76	89.1	0.117	1790	1830	16.3	2.74	64.4	69.6	25.4
3920030-1001	2.20	114	0.533	1520	1540	11.5	3.26	53.8	52.9	16.3
3920031-1001	2.27	115	0.333	2330	2370	14.7	2.11	44.9	48.4	22.9
3920031-1002	2.24	118	0.333	2000	2020	10.3	2.47	36.7	40.7	16.5
3920033-1001	1.82	101	0.167	1670	1690	13.9	2.96	59.6	66.7	22.5
3920064-1001	1.91	101	0.183	2300	2380	18.9	2.10	57.4	58.5	27.8

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.23.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial CS baseline corrected (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
Race Group: Japanese										
n	10	10	10	10	10	10	10	10	10	10
Mean	2.07	109	NC	1920	1960	13.8	2.61	51.2	53.4	20.8
SD	0.231	13.0	NC	296	303	2.72	0.407	8.94	9.59	4.21
CV (%)	11.2	11.9	NC	15.4	15.5	19.7	15.6	17.4	18.0	20.3
Median	2.09	109	0.267	1940	1960	13.6	2.56	50.6	52.8	21.2
Min	1.76	89.1	0.117	1520	1540	10.3	2.10	36.7	40.7	14.6
Max	2.38	132	0.533	2330	2380	18.9	3.26	64.4	69.6	27.8
Geometric Mean	2.06	108	NC	1900	1940	13.6	2.58	50.5	52.6	20.4

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.23.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial CS baseline corrected (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
Race Group: Non-Japanese										
0360031-1001	1.86	98.7	0.217	1530	1550	11.8	3.24	55.4	56.8	17.5
0360031-1002	2.40	117	0.500	1550	1600	10.4	3.05	45.9	44.7	14.6
0360031-1003	2.46	133	0.200	3430	3480	15.8	1.45	32.9	37.3	25.8
0400001-1004	2.33	116	0.350	1120	1200	7.54	4.16	45.2	45.0	10.8
2760034-1001	1.88	103	0.333	1180	1220	9.67	4.14	57.8	56.9	13.7
2760034-1003	1.83	99.3	0.367	1910	1970	14.7	2.58	54.8	55.2	21.4
2760034-1004	1.91	100	0.417	1380	1400	13.9	3.58	71.5	66.2	18.5
2760034-1005	2.13	108	0.800	1850	1900	13.8	2.66	52.9	52.2	19.7
2760034-1006	1.62	84.6	0.417	1850	1920	14.7	2.60	55.0	59.9	23.1
2760087-1001	2.44	131	0.467	2040	2110	15.9	2.38	54.4	45.9	19.3
3480007-1002	2.36	118	0.633	2090	2130	12.3	2.35	41.7	43.9	18.7
3800023-1003	1.99	102	0.300	1490	1510	11.6	3.31	55.6	55.7	16.8
3800023-1004	1.99	102	0.417	1560	1580	11.5	3.17	52.6	53.5	16.9
3800049-1001	1.41	87.5	0.500	1690	1710	14.8	3.43	73.5	72.2	21.1
4580001-1001	1.14	75.5	0.233	1390	1430	14.0	4.29	86.6	87.5	20.4
4580001-1002	1.84	105	0.533	1270	1320	10.1	4.33	63.2	62.4	14.4
5280007-1001	1.70	88.3	0.250	1500	1510	7.64	3.29	36.3	52.1	15.8
5280007-1004	1.89	92.8	0.283	1780	1830	13.9	2.67	53.4	54.1	20.3

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.23.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial CS baseline corrected (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
Race Group: Non-Japanese										
6080001-1002	1.75	88.0	0.667	1560	1580	12.3	3.17	56.4	58.4	18.4
6080001-1003	1.82	107	0.367	908	932	8.93	5.39	69.5	61.6	11.4
6080001-1005	2.16	117	1.22	2360	2420	17.9	2.06	53.1	51.6	25.0
6080001-1006	2.61	131	0.700	2170	2240	15.2	2.23	48.8	49.2	22.1
6080001-1007	1.38	79.3	0.500	1350	1370	12.4	3.65	65.3	65.2	17.8
6080001-1008	0.868	62.4	0.333	991	1010	12.3	4.93	87.8	99.6	20.2
6080001-1010	0.880	45.5	0.333	642	683	11.3	7.32	119	121	16.6
6080001-1012	1.38	72.9	0.417	1510	1590	15.8	3.15	71.7	74.9	23.8
6080002-1001	1.94	97.0	0.500	1420	1440	12.8	3.47	64.0	61.1	17.6
6080002-1002	2.23	120	0.667	2170	2190	13.5	2.29	44.4	47.6	20.8
6430015-1002	1.79	118	0.500	2350	2390	16.3	2.44	57.3	57.5	23.6
7100001-1002	1.57	83.0	0.333	1620	1640	11.7	3.19	54.1	58.9	18.5
7100001-1003	1.86	118	0.200	2130	2190	14.0	2.79	56.4	56.7	20.3
7100001-1005	2.20	118	0.233	2400	2430	12.8	2.19	40.5	43.3	19.7
7100001-1007	1.53	82.3	0.167	1470	1490	12.8	3.45	63.6	64.7	18.7
7100001-1008	1.81	105	0.683	1140	1150	2.36	5.03	17.2	47.3	9.39
7100001-1009	2.02	96.3	0.533	1750	1790	13.1	2.66	50.4	57.4	21.6
7100001-1010	2.02	96.8	0.217	2570	2640	17.8	1.80	46.3	48.7	27.0

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.23.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial CS baseline corrected (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
Race Group: Non-Japanese										
7100001-1012	1.42	82.8	0.217	2060	2090	16.0	2.75	63.7	73.0	26.5
7100001-1013	1.53	89.8	0.217	1580	1610	16.6	3.55	85.2	74.9	21.1
7100001-1015	2.27	130	0.217	2100	2130	15.1	2.24	48.7	44.2	19.8
7100001-1016	1.65	97.6	0.200	2550	2610	18.2	1.86	48.8	50.2	27.1
7240023-1001	2.00	111	0.250	2260	2300	15.9	2.17	49.9	52.3	24.0
8040005-1001	1.72	90.5	0.250	2250	2320	18.9	2.18	59.4	59.3	27.2
8040005-1003	1.81	95.3	0.250	895	956	7.57	5.23	57.1	59.1	11.3
8040005-1004	1.48	77.7	0.250	925	962	10.4	4.94	74.1	74.2	15.0
8040005-1005	1.76	87.0	0.250	2310	2390	19.4	2.02	56.3	58.1	28.8
8040005-1009	1.58	84.6	0.250	732	757	6.32	6.61	60.3	60.5	9.17
8040007-1001	1.30	74.4	1.03	1540	1590	14.0	3.37	68.3	71.6	21.2
8040007-1002	1.20	68.4	1.03	1200	1300	13.4	4.13	79.7	79.4	19.3
8400118-1001	2.78	151	0.233	2530	2600	13.7	1.93	38.1	37.1	19.3
8400184-1006	1.84	96.5	0.333	1170	1240	11.3	4.05	66.2	62.8	15.5
8400184-1008	1.36	71.2	0.417	1530	1560	16.4	3.21	75.8	75.0	23.4
8400184-1009	1.17	72.2	1.17	1020	1040	9.15	4.81	63.5	65.5	13.6
8400241-1002	2.23	123	0.467	2050	2060	10.1	2.47	36.0	41.5	16.8

Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.23.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese initial CS baseline corrected (PK Population)

Subject/ Statistic	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
Race Group: Non-Japanese										
n	53	53	53	53	53	53	53	53	53	53
Mean	1.81	98.2	NC	1690	1740	13.0	3.31	58.2	59.7	19.3
SD	0.418	20.5	NC	558	564	3.35	1.22	16.3	15.1	4.63
CV (%)	23.1	20.9	NC	32.9	32.5	25.7	36.7	27.9	25.2	24.0
Median	1.83	97.0	0.350	1560	1600	13.4	3.17	56.3	57.5	19.3
Min	0.868	45.5	0.167	642	683	2.36	1.45	17.2	37.1	9.17
Max	2.78	151	1.22	3430	3480	19.4	7.32	119	121	28.8
Geometric Mean	1.76	96.0	NC	1600	1650	12.4	3.12	56.0	58.1	18.7

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.16.24.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese repeat CS baseline corrected (PK Population)

Subject/ Statistic	IR (IU/dL/ IU/kg)	Cmax (IU/dL)	Tmax (h)	AUC0-tau (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)	RC (r)	RAUC (r)	Time Dep. (r)
Race Group: Japanese													
3920025-1001	2.43	125	0.200	1720	1720	10.6	2.90	44.5	45.0	15.5	1.05	1.08	1.07
3920027-1001	1.82	93.8	0.200	1930	1950	13.9	2.57	51.6	54.1	21.1	0.912	1.03	1.02
3920028-1001	2.28	129	0.267	1830	1840	13.9	2.71	54.6	49.4	18.2	0.971	0.826	0.820
3920029-1001	1.79	90.8	0.183	1740	1770	16.0	2.83	65.1	65.4	23.1	1.02	0.974	0.955
3920030-1001	1.83	93.6	0.417	1070	1070	8.0	4.65	54.1	55.2	11.9	0.819	0.701	0.700
3920031-1001	1.94	93.8	0.633	2020	2030	10.9	2.39	37.6	44.8	18.8	0.813	0.867	0.856
3920033-1001	1.67	90.5	0.117	1890	1930	16.5	2.60	61.6	61.5	23.7	0.899	1.13	1.12
3920064-1001	1.99	108	0.167	2460	2510	16.5	1.99	47.4	50.2	25.2	1.07	1.07	1.03
n	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean	1.97	103	NC	1830	1850	13.3	2.83	52.1	53.2	19.7	0.943	0.960	0.947
SD	0.259	15.8	NC	386	398	3.1	0.790	8.93	7.41	4.50	0.0989	0.148	0.144
CV (%)	13.1	15.3	NC	21.0	21.5	23.5	27.9	17.1	13.9	22.9	10.5	15.5	15.2
Median	1.88	93.8	0.200	1860	1880	13.9	2.66	52.9	52.1	19.9	0.941	1.00	0.987
Min	1.67	90.5	0.117	1070	1070	8.0	1.99	37.6	44.8	11.9	0.813	0.701	0.700
Max	2.43	129	0.633	2460	2510	16.5	4.65	65.1	65.4	25.2	1.07	1.13	1.12
Geometric Mean	1.95	102	NC	1790	1810	12.9	2.75	51.4	52.8	19.2	0.939	0.949	0.937

CSL Behring GmbH: CSL627_1001/CIL-GM/FINAL/PKP322P.SAS
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Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-tau=Area under the plasma concentration time curve during a dosing interval (tau) at steady-state; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time; RC=Accumulation Ratio of Cmax (repeat/initial); RAUC=Accumulation Ratio of AUC0-tau (repeat/initial); Time Dep.=Time Dependance (repeat/initial).

Table 14.2.16.24.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese repeat CS baseline corrected (PK Population)

Subject/ Statistic	IR (IU/dL/ IU/kg)	Cmax (IU/dL)	Tmax (h)	AUC0-tau (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)	RC (r)	RAUC (r)	Time Dep. (r)
Race Group: Non-Japanese													
0400001-1004	2.26	108	0.300	1080	1080	8.3	4.29	51.8	50.9	11.8	0.931	0.895	0.895
2760034-1005	2.36	128	0.317	2210	2210	11.9	2.26	38.6	40.4	17.9	1.19	1.17	1.16
2760087-1001	2.16	112	0.500	1960	1970	12.7	2.47	45.3	46.9	19.0	0.853	0.943	0.932
3480007-1002	2.11	106	0.633	1870	1890	13.1	2.65	50.2	50.6	19.1	0.895	0.884	0.880
3800023-1003	1.56	82.3	0.300	1300	1300	10.5	3.84	58.3	59.4	15.5	0.809	0.864	0.861
3800049-1001	1.65	105	0.417	2110	2140	14.7	2.74	58.0	61.4	22.4	1.20	1.25	1.24
4580001-1001	1.67	88.3	0.233	1270	1270	9.4	3.96	53.8	58.2	14.7	1.17	0.895	0.888
4580001-1002	1.85	112	0.200	1550	1560	10.2	3.42	50.1	51.4	15.0	1.07	1.18	1.17
6080001-1002	2.48	134	0.333	2280	2290	12.9	2.19	40.7	41.7	19.1	1.52	1.44	1.44
6080001-1003	1.78	89.2	0.667	947	948	8.5	5.27	64.9	64.1	12.1	0.836	1.02	1.02
6080002-1001	1.53	99.7	0.450	1520	1530	12.0	3.25	56.1	60.2	18.5	1.03	1.06	1.05
6080002-1002	2.01	103	0.600	2180	2190	12.5	2.27	41.0	46.5	20.5	0.864	1.01	0.997
7100001-1002	2.20	139	0.217	2410	2420	11.9	2.47	42.3	47.3	19.1	1.67	1.47	1.46
7100001-1003	1.82	103	0.583	1560	1560	12.0	3.60	62.3	58.4	16.2	0.866	0.717	0.711
7100001-1005	2.03	118	0.217	2700	2760	18.2	1.95	51.3	50.7	26.0	0.995	1.11	1.11
7100001-1007	1.86	97.0	0.533	1570	1580	12.5	3.30	59.7	60.4	18.3	1.18	1.06	1.05
8040007-1001	1.78	112	0.267	2020	2040	14.1	2.63	53.4	53.2	20.2	1.51	1.28	1.27
8040007-1002	1.54	80.5	0.333	1010	1010	8.2	4.94	58.9	60.4	12.2	1.18	0.782	0.778

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-tau=Area under the plasma concentration time curve during a dosing interval (tau) at steady-state; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time; RC=Accumulation Ratio of Cmax (repeat/initial); RAUC=Accumulation Ratio of AUC0-tau (repeat/initial); Time Dep.=Time Dependance (repeat/initial).

Table 14.2.16.24.1 Part 3 - FVIII PK Parameters of CSL627, Japanese vs non-Japanese repeat CS baseline corrected (PK Population)

Subject/ Statistic	IR (IU/dL/ IU/kg)	Cmax (IU/dL)	Tmax (h)	AUC0-tau (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)	RC (r)	RAUC (r)	Time Dep. (r)
Race Group: Non-Japanese													
8400118-1001	3.20	162	0.200	2620	2630	11.3	1.90	31.0	31.5	16.6	1.08	1.01	1.01
8400184-1006	1.92	99.1	0.500	1850	1850	12.2	2.70	47.4	48.4	18.0	1.03	1.50	1.50
8400241-1002	2.15	117	0.367	2170	2180	13.4	2.29	44.3	46.4	20.3	0.953	1.05	1.05
n	21	21	21	21	21	21	21	21	21	21	21	21	21
Mean	2.00	109	NC	1820	1830	11.9	3.07	50.5	51.8	17.7	1.09	1.08	1.07
SD	0.387	19.5	NC	518	526	2.3	0.958	8.72	8.26	3.46	0.238	0.219	0.218
CV (%)	19.4	17.9	NC	28.5	28.8	19.4	31.2	17.3	15.9	19.5	22.0	20.3	20.4
Median	1.92	106	0.333	1870	1890	12.0	2.70	51.3	50.9	18.3	1.03	1.05	1.05
Min	1.53	80.5	0.200	947	948	8.2	1.90	31.0	31.5	11.8	0.809	0.717	0.711
Max	3.20	162	0.667	2700	2760	18.2	5.27	64.9	64.1	26.0	1.67	1.50	1.50
Geometric Mean	1.96	108	NC	1740	1750	11.7	2.94	49.7	51.1	17.4	1.06	1.06	1.05

Source: Listing 16.2.9.6.6
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-tau=Area under the plasma concentration time curve during a dosing interval (tau) at steady-state; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time; RC=Accumulation Ratio of Cmax (repeat/initial); RAUC=Accumulation Ratio of AUC0-tau (repeat/initial); Time Dep.=Time Dependance (repeat/initial).

Table 14.3.2.1 Summary of Adverse Events
(Safety Population)

	Total (N=174) n	(%)	E
Any Adverse Events	121	(69.5)	325
Any Treatment-Emergent Adverse Events	113	(64.9)	292
Any Treatment-Emergent Adverse Events Leading to Study Drug Withdrawal	0		
Treatment-Emergent Adverse Event Severity			
Mild	94	(54.0)	225
Moderate	43	(24.7)	61
Severe	5	(2.9)	6
Any Treatment-Emergent Adverse Events Related to Study Drug	13	(7.5)	19
Treatment-Emergent Adverse Event Outcome			
Death Related to Adverse Event	0		
Not Recovered/Not Resolved	22	(12.6)	25
Recovered/Resolved	104	(59.8)	256
Recovered/Resolved With Sequelae	1	(0.6)	1
Recovering/Resolving	9	(5.2)	10
Unknown	0		

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group

Table 14.3.2.1 Summary of Adverse Events
(Safety Population)

	Total (N=174) n	(%)	E
Any Serious Adverse Events	8	(4.6)	10
Any Treatment-Emergent Serious Adverse Events	7	(4.0)	9
Any Treatment-Emergent Serious Adverse Events Leading to Study Drug Withdrawal	0		
Treatment-Emergent Serious Adverse Event Severity			
Mild	1	(0.6)	2
Moderate	2	(1.1)	2
Severe	4	(2.3)	5
Any Treatment-Emergent Serious Adverse Events Related to Study Drug	1	(0.6)	1
Treatment-Emergent Serious Adverse Event Outcome			
Death Related to Adverse Event	0		
Not Recovered/Not Resolved	0		
Recovered/Resolved	7	(4.0)	9
Recovered/Resolved With Sequelae	0		
Recovering/Resolving	0		
Unknown	0		

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Any Treatment-Emergent Adverse Events	113	(64.9)	292
Infections and infestations	45	(25.9)	61
Nasopharyngitis	18	(10.3)	22
Upper respiratory tract infection	6	(3.4)	6
Influenza	4	(2.3)	4
Viral infection	3	(1.7)	4
Sinusitis	3	(1.7)	3
Gastroenteritis	2	(1.1)	2
Gastroenteritis viral	2	(1.1)	2
Pharyngitis	2	(1.1)	2
Viral upper respiratory tract infection	2	(1.1)	2
Bronchitis	1	(0.6)	1
Ear infection	1	(0.6)	1
Fungal skin infection	1	(0.6)	1
Furuncle	1	(0.6)	1
Lower respiratory tract infection	1	(0.6)	1
Oral fungal infection	1	(0.6)	1
Oral herpes	1	(0.6)	1
Otitis media	1	(0.6)	1
Perirectal abscess	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Infections and infestations (continued)			
Respiratory tract infection	1	(0.6)	1
Rhinitis	1	(0.6)	1
Tonsillitis	1	(0.6)	1
Tooth abscess	1	(0.6)	1
Urinary tract infection	1	(0.6)	1
Musculoskeletal and connective tissue disorders	26	(14.9)	46
Arthralgia	17	(9.8)	19
Back pain	5	(2.9)	6
Haemophilic arthropathy	3	(1.7)	11
Pain in extremity	2	(1.1)	3
Groin pain	1	(0.6)	1
Joint range of motion decreased	1	(0.6)	1
Joint swelling	1	(0.6)	1
Lumbar spinal stenosis	1	(0.6)	1
Muscle spasms	1	(0.6)	1
Neck pain	1	(0.6)	1
Synovial cyst	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Injury, poisoning and procedural complications	26	(14.9)	34
Joint injury	3	(1.7)	4
Fall	3	(1.7)	3
Limb injury	2	(1.1)	3
Contusion	2	(1.1)	2
Laceration	2	(1.1)	2
Ligament sprain	2	(1.1)	2
Post-traumatic pain	2	(1.1)	2
Thermal burn	2	(1.1)	2
Wound	2	(1.1)	2
Ankle fracture	1	(0.6)	1
Arthropod bite	1	(0.6)	1
Chillblains	1	(0.6)	1
Conjunctival abrasion	1	(0.6)	1
Hand fracture	1	(0.6)	1
Muscle strain	1	(0.6)	1
Road traffic accident	1	(0.6)	1
Sunburn	1	(0.6)	1
Tendon rupture	1	(0.6)	1
Tongue injury	1	(0.6)	1
Traumatic haematoma	1	(0.6)	1
Wound haemorrhage	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Nervous system disorders	19	(10.9)	25
Headache	12	(6.9)	13
Dizziness	4	(2.3)	5
Paraesthesia	2	(1.1)	2
Somnolence	1	(0.6)	3
Hypoaesthesia	1	(0.6)	1
Migraine	1	(0.6)	1
Gastrointestinal disorders	17	(9.8)	23
Toothache	6	(3.4)	8
Dental caries	3	(1.7)	3
Abdominal pain	2	(1.1)	3
Constipation	1	(0.6)	1
Diarrhoea	1	(0.6)	1
Gastritis	1	(0.6)	1
Haematochezia	1	(0.6)	1
Haemorrhoidal haemorrhage	1	(0.6)	1
Loose tooth	1	(0.6)	1
Oesophagitis	1	(0.6)	1
Umbilical hernia	1	(0.6)	1
Varices oesophageal	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Skin and subcutaneous tissue disorders	17	(9.8)	21
Rash	7	(4.0)	8
Acne	2	(1.1)	2
Actinic keratosis	1	(0.6)	1
Dermatitis	1	(0.6)	1
Dermatitis allergic	1	(0.6)	1
Dermatitis atopic	1	(0.6)	1
Dermatitis contact	1	(0.6)	1
Dyshidrosis	1	(0.6)	1
Ecchymosis	1	(0.6)	1
Erythema	1	(0.6)	1
Heat rash	1	(0.6)	1
Petechiae	1	(0.6)	1
Pruritus	1	(0.6)	1
General disorders and administration site conditions	17	(9.8)	20
Pyrexia	4	(2.3)	5
Asthenia	2	(1.1)	2
Chest pain	2	(1.1)	2
Injection site pain	2	(1.1)	2
Chills	1	(0.6)	2

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
General disorders and administration site conditions (continued)			
Adverse drug reaction	1	(0.6)	1
Feeling hot	1	(0.6)	1
Local swelling	1	(0.6)	1
Localised oedema	1	(0.6)	1
Malaise	1	(0.6)	1
Oedema peripheral	1	(0.6)	1
Pain	1	(0.6)	1
Respiratory, thoracic and mediastinal disorders	9	(5.2)	17
Cough	5	(2.9)	6
Oropharyngeal pain	3	(1.7)	3
Nasal congestion	2	(1.1)	2
Rhinorrhoea	2	(1.1)	2
Nasal mucosal disorder	1	(0.6)	1
Pharyngeal erythema	1	(0.6)	1
Sneezing	1	(0.6)	1
Tonsillar haemorrhage	1	(0.6)	1
Investigations	9	(5.2)	13

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Investigations (continued)			
Liver function test abnormal	2	(1.1)	2
Blood uric acid increased	1	(0.6)	3
Blood glucose increased	1	(0.6)	2
Blood lactate dehydrogenase increased	1	(0.6)	1
Blood triglycerides increased	1	(0.6)	1
Blood urea increased	1	(0.6)	1
C-reactive protein increased	1	(0.6)	1
Drug specific antibody present	1	(0.6)	1
Gamma-glutamyltransferase increased	1	(0.6)	1
Vascular disorders	7	(4.0)	7
Hypertension	5	(2.9)	5
Capillary fragility	1	(0.6)	1
Haematoma	1	(0.6)	1
Blood and lymphatic system disorders	6	(3.4)	7
Anaemia	2	(1.1)	2
Leukocytosis	2	(1.1)	2
Eosinophilia	1	(0.6)	1
Iron deficiency anaemia	1	(0.6)	1
Thrombocytopenia	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Immune system disorders	3	(1.7)	4
Hypersensitivity	2	(1.1)	3
Seasonal allergy	1	(0.6)	1
Renal and urinary disorders	3	(1.7)	3
Haematuria	1	(0.6)	1
Pollakiuria	1	(0.6)	1
Renal colic	1	(0.6)	1
Eye disorders	2	(1.1)	2
Conjunctivitis	2	(1.1)	2
Metabolism and nutrition disorders	2	(1.1)	2
Hyperuricaemia	1	(0.6)	1
Iron deficiency	1	(0.6)	1
Surgical and medical procedures	1	(0.6)	2
Tooth extraction	1	(0.6)	2
Cardiac disorders	1	(0.6)	1
Arrhythmia	1	(0.6)	1

Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.3.2.4 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	Total (N=174) n	(%)	E
Ear and labyrinth disorders	1	(0.6)	1
Ear pain	1	(0.6)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.6)	1
Gastrointestinal tract adenoma	1	(0.6)	1
Psychiatric disorders	1	(0.6)	1
Suicidal ideation	1	(0.6)	1
Reproductive system and breast disorders	1	(0.6)	1
Penile discharge	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)
[2] Percentages are based on the number of subjects in the respective group
[3] Events with onset date during the surgical period are excluded from this summary
[4] Adverse Events were coded using MedDRA Version 14.1

Table 14.1.1.2J Japanese Subject Populations
(Japanese Enrolled Population)

	Total n
Enrolled	10
Safety Population	10
Efficacy Population	10
Prophylaxis	9
On-demand	1
PP Population	9
PK Population	10
PK Part 1	0
PK Part 3	10
Surgical Population	0

Table 14.1.5.1J Japanese Demographics
(Japanese Efficacy Population)

	On-Demand (N=1)	Prophylaxis (N=9)	Total (N=10)
Age (years)			
n	1	9	10
Mean (SD)	29.0 ( )	28.2 (12.33)	28.3 (11.62)
Median	29.0	34.0	31.5
Min, Max	29, 29	12, 46	12, 46
Age Group [n (%)]			
12 to <18 years	0	2 (22.2)	2 (20.0)
>=18 to <=65 years	1(100.0)	7 (77.8)	8 (80.0)
Race [n (%)]			
American Indian/Alaska Native	0	0	0
Asian	1 (100.0)	9 (100.0)	10 (100.0)
Black or African American	0	0	0
Native Hawaiian/Other Pacific Islander	0	0	0
White	0	0	0
Other	0	0	0
Ethnicity [n (%)]			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	1 (100.0)	9 (100.0)	10 (100.0)
Not Reported	0	0	0
Unknown	0	0	0
Country [n (%)]			
Japan	1 (100.0)	9 (100.0)	10 (100.0)

Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.

Table 14.1.5.1J Japanese Demographics
(Japanese Efficacy Population)

	On-Demand (N=1)	Prophylaxis (N=9)	Total (N=10)
Geographical Region [n (%)]			
Japan	1 (100.0)	9 (100.0)	10 (100.0)
Height (cm)			
n	1	9	10
Mean (SD)	160.0 ( )	166.6 (5.85)	165.9 (5.89)
Median	160.0	169.7	166.1
Min, Max	160, 160	159, 174	159, 174
Weight (kg)			
n	1	9	10
Mean (SD)	59.1 ( )	57.6 (11.47)	57.7 (10.83)
Median	59.1	59.5	59.3
Min, Max	59, 59	38, 74	38, 74
BMI (kg/m^2)			
n	1	9	10
Mean (SD)	23.1 ( )	20.6 (3.31)	20.9 (3.22)
Median	23.1	19.8	20.4
Min, Max	23, 23	15, 25	15, 25
BMI Category [n (%)]			
<30 kg/m2	1 (100.0)	9 (100.0)	10 (100.0)
>=30 kg/m2	0	0	0

Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.

Table 14.2.1.1J Japanese Investigator's Overall Assessment of Hemostatic Efficacy
(Japanese Efficacy Population)

Bleeding Type Assessment	On-Demand (N=1)	Prophylaxis (N=9)	Total (N=10)
Total			
Number of Bleeding Events	8	27	35
Number of Treated Bleeding Events	7	22	29
Excellent	4 (57.1)	17 (77.3)	21 (72.4)
Good	2 (28.6)	3 (13.6)	5 (17.2)
Moderate	1 (14.3)	2 (9.1)	3 (10.3)
Poor/No Response	0	0	0
Missing	0	0	0
Success (a)	6 (85.7)	20 (90.9)	26 (89.7)
Rate of Success	85.7	90.9	89.7
95% CI for Rate	(85.7, 85.7)	(69.6, 97.8)	(74.7, 96.2)
Success (b)	6 (85.7)	20 (90.9)	26 (89.7)
Rate of Success	85.7	90.9	89.7
95% CI for Rate	(85.7, 85.7)	(69.6, 97.8)	(74.7, 96.2)
Success (c)	6 (85.7)	20 (90.9)	26 (89.7)
Rate of Success	85.7	90.9	89.7
95% CI for Rate	(85.7, 85.7)	(69.6, 97.8)	(74.7, 96.2)

Source: Listing 16.2.6.2
Notes: [1] Success is defined as a rating of excellent or good. [a] Primary analysis: missing counted as failure;
[b] Sensitivity analysis: all missing excluded. [c] Sensitivity analysis: missing counted as success.
[2] 95% CI based on a generalized linear model to account for within-subject correlation.
[3] Table presents number and percentage of bleeding events [n(%)].
[4] Percentages are based on the number of treated bleeding events.

Table 14.2.2.2.1J Japanese Summary of Annualized Bleeding Rates
(Japanese Efficacy Population)

	On-Demand (N=1)	Prophylaxis (N=9)
Spontaneous Bleeds		
n	1	9
Mean (SD)	3.55	1.83 (4.268)
Median	3.55	0.00
Q1, Q3	3.6, 3.6	0.0, 1.1
Min, Max	3.6, 3.6	0.0, 13.0
Number of bleeds per year (95% CI)	3.6 (1.3, 9.5)	2.0 (1.2, 3.3)
Traumatic Bleeds		
n	1	9
Mean (SD)	2.67	0.68 (1.590)
Median	2.67	0.00
Q1, Q3	2.7, 2.7	0.0, 0.0
Min, Max	2.7, 2.7	0.0, 4.7
Number of bleeds per year (95% CI)	2.7 (0.9, 8.3)	0.9 (0.4, 2.0)
Total Bleeds		
n	1	9
Mean (SD)	6.22	2.51 (4.556)
Median	6.22	0.00
Q1, Q3	6.2, 6.2	0.0, 1.4
Min, Max	6.2, 6.2	0.0, 13.0
Number of bleeds per year (95% CI)	6.2 (3.0, 13.0)	2.9 (1.9, 4.5)
Number of subjects with zero bleeds [n(%)]	0	5 (55.6)

Source: Listing 16.2.6.2
Notes: [1] Number of bleeds per year (95% CI) is based on a Poisson distribution.

Table 14.2.5.1J Japanese Consumption of CSL627 During Routine Prophylaxis
(Japanese Efficacy Population, Assigned Modality = Prophylaxis)

	Prophylaxis (N=9)
Number of Subjects on Routine Prophylaxis Treatment [n (%)]	9 (100.0)
Total Number of Prophylaxis Infusions	731
Prophylaxis Dose Administered per Subject Per Month (IU/kg)	
n	9
Mean (SD)	318.9 (120.58)
Median	292.8
Min, Max	198, 592
Total Dose Administered per Subject Per Month (IU/kg)	
n	9
Mean (SD)	332.5 (127.08)
Median	292.8
Min, Max	198, 621

Source: Listing 16.2.6.4
Notes: [1] Prophylaxis infusions are those recorded as administered for 'Routine/Prophylaxis'. Total infusions also include those recorded as administered for 'Bleeding Event', 'Surgery', 'Post Surgery' 'Prevention Prior to Activity', and 'Additional Treatment'.

Table 14.2.5.1J Japanese Consumption of CSL627 During Routine Prophylaxis
(Japanese Efficacy Population, Assigned Modality = Prophylaxis)

	Prophylaxis (N=9)
Prophylaxis Dose Administered per Subject Per Year (IU/kg)	
n	9
Mean (SD)	3827.3 (1447.01)
Median	3514.0
Min, Max	2379, 7108
Total Dose Administered per Subject Per Year (IU/kg)	
n	9
Mean (SD)	3990.2 (1524.98)
Median	3514.0
Min, Max	2379, 7454
Prophylaxis IU per Month	
n	9
Mean (SD)	18224.7 (6836.88)
Median	16997.5
Min, Max	7593, 29736
Total IU per Month	
n	9
Mean (SD)	18853.2 (6850.02)
Median	17423.7
Min, Max	8677, 31184

Source: Listing 16.2.6.4
Notes: [1] Prophylaxis infusions are those recorded as administered for 'Routine/Prophylaxis'. Total infusions also include those recorded as administered for 'Bleeding Event', 'Surgery', 'Post Surgery' 'Prevention Prior to Activity', and 'Additional Treatment'.

Table 14.3.2.1J Summary of Adverse Events
(Japanese and Global Safety Population)

	Japanese (N=10)			Global (N=174)		
	n	(%)	E	n	(%)	E
Any Adverse Events	8	(80.0)	20	121	(69.5)	325
Any Treatment-Emergent Adverse Events	8	(80.0)	20	113	(64.9)	292
Any Treatment-Emergent Adverse Events Leading to Study Drug Withdrawal	0		0	0		0
Treatment-Emergent Adverse Event Severity						
Mild	8	(80.0)	18	94	(54.0)	225
Moderate	2	(20.0)	2	43	(24.7)	61
Severe	0		0	5	(2.9)	6
Any Treatment-Emergent Adverse Events Related to Study Drug	1	(10.0)	1	13	(7.5)	19
Treatment-Emergent Adverse Event Outcome						
Death Related to Adverse Event	0		0	0		0
Not Recovered/Not Resolved	3	(30.0)	3	22	(12.6)	25
Recovered/Resolved	8	(80.0)	17	104	(59.8)	256
Recovered/Resolved With Sequelae	0		0	1	(0.6)	1
Recovering/Resolving	0		0	9	(5.2)	10
Unknown	0		0	0		0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).

Table 14.3.2.1J Summary of Adverse Events
(Japanese and Global Safety Population)

	Japanese (N=10)			Global (N=174)		
	n	(%)	E	n	(%)	E
Any Serious Adverse Events	0		0	8	(4.6)	10
Any Treatment-Emergent Serious Adverse Events	0		0	7	(4.0)	9
Any Treatment-Emergent Serious Adverse Events Leading to Study Drug Withdrawal	0		0	0		0
Any Treatment-Emergent Serious Adverse Events Related to Study Drug	0		0	1	(0.6)	1
Treatment-Emergent Serious Adverse Event Severity						
Mild	0		0	1	(0.6)	2
Moderate	0		0	2	(1.1)	2
Severe	0		0	4	(2.3)	5
Treatment-Emergent Serious Adverse Event Outcome						
Death Related to Adverse Event	0		0	0		0
Not Recovered/Not Resolved	0		0	0		0
Recovered/Resolved	0		0	7	(4.0)	9
Recovered/Resolved With Sequelae	0		0	0		0
Recovering/Resolving	0		0	0		0
Unknown	0		0	0		0

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).

Table 14.3.2.4J Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Japanese and Global Safety Population)

System Organ Class Preferred Term	Japanese (N=10) n	(%)	E	Global (N=174) n	(%)	E
Any Treatment-Emergent Adverse Events	8	(80.0)	20	113	(64.9)	292
Infections and infestations	6	(60.0)	9	45	(25.9)	61
Nasopharyngitis	4	(40.0)	4	18	(10.3)	22
Upper respiratory tract infection	0		0	6	(3.4)	6
Influenza	2	(20.0)	2	4	(2.3)	4
Viral infection	0		0	3	(1.7)	4
Sinusitis	1	(10.0)	1	3	(1.7)	3
Gastroenteritis	0		0	2	(1.1)	2
Gastroenteritis viral	0		0	2	(1.1)	2
Pharyngitis	0		0	2	(1.1)	2
Viral upper respiratory tract infection	0		0	2	(1.1)	2
Bronchitis	0		0	1	(0.6)	1
Ear infection	0		0	1	(0.6)	1
Fungal skin infection	0		0	1	(0.6)	1
Furuncle	0		0	1	(0.6)	1
Lower respiratory tract infection	0		0	1	(0.6)	1
Oral fungal infection	0		0	1	(0.6)	1
Oral herpes	1	(10.0)	1	1	(0.6)	1
Otitis media	1	(10.0)	1	1	(0.6)	1
Perirectal abscess	0		0	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse Events were coded using MedDRA Version 14.1.

Table 14.3.2.4J Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Japanese and Global Safety Population)

System Organ Class Preferred Term	Japanese (N=10) n	(%)	E	Global (N=174) n	(%)	E
Infections and infestations (continued)						
Respiratory tract infection	0		0	1	(0.6)	1
Rhinitis	0		0	1	(0.6)	1
Tonsillitis	0		0	1	(0.6)	1
Tooth abscess	0		0	1	(0.6)	1
Urinary tract infection	0		0	1	(0.6)	1
Musculoskeletal and connective tissue disorders	0		0	26	(14.9)	46
Arthralgia	0		0	17	(9.8)	19
Back pain	0		0	5	(2.9)	6
Haemophilic arthropathy	0		0	3	(1.7)	11
Pain in extremity	0		0	2	(1.1)	3
Groin pain	0		0	1	(0.6)	1
Joint range of motion decreased	0		0	1	(0.6)	1
Joint swelling	0		0	1	(0.6)	1
Lumbar spinal stenosis	0		0	1	(0.6)	1
Muscle spasms	0		0	1	(0.6)	1
Neck pain	0		0	1	(0.6)	1
Synovial cyst	0		0	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse Events were coded using MedDRA Version 14.1.

Table 14.3.2.4J Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Japanese and Global Safety Population)

System Organ Class Preferred Term	Japanese (N=10) n	(%)	E	Global (N=174) n	(%)	E
Injury, poisoning and procedural complications	3	(30.0)	4	26	(14.9)	34
Joint injury	0		0	3	(1.7)	4
Fall	0		0	3	(1.7)	3
Limb injury	0		0	2	(1.1)	3
Contusion	0		0	2	(1.1)	2
Laceration	0		0	2	(1.1)	2
Ligament sprain	0		0	2	(1.1)	2
Post-traumatic pain	0		0	2	(1.1)	2
Thermal burn	0		0	2	(1.1)	2
Wound	0		0	2	(1.1)	2
Ankle fracture	0		0	1	(0.6)	1
Arthropod bite	0		0	1	(0.6)	1
Chillblains	1	(10.0)	1	1	(0.6)	1
Conjunctival abrasion	1	(10.0)	1	1	(0.6)	1
Hand fracture	0		0	1	(0.6)	1
Muscle strain	0		0	1	(0.6)	1
Road traffic accident	0		0	1	(0.6)	1
Sunburn	1	(10.0)	1	1	(0.6)	1
Tendon rupture	0		0	1	(0.6)	1
Tongue injury	1	(10.0)	1	1	(0.6)	1
Traumatic haematoma	0		0	1	(0.6)	1
Wound haemorrhage	0		0	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse Events were coded using MedDRA Version 14.1.

Table 14.3.2.4J Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Japanese and Global Safety Population)

System Organ Class Preferred Term	Japanese (N=10) n	(%)	E	Global (N=174) n	(%)	E
Nervous system disorders	2	(20.0)	2	19	(10.9)	25
Headache	1	(10.0)	1	12	(6.9)	13
Dizziness	1	(10.0)	1	4	(2.3)	5
Paraesthesia	0		0	2	(1.1)	2
Somnolence	0		0	1	(0.6)	3
Hypoaesthesia	0		0	1	(0.6)	1
Migraine	0		0	1	(0.6)	1
Gastrointestinal disorders	0		0	17	(9.8)	23
Toothache	0		0	6	(3.4)	8
Dental caries	0		0	3	(1.7)	3
Abdominal pain	0		0	2	(1.1)	3
Constipation	0		0	1	(0.6)	1
Diarrhoea	0		0	1	(0.6)	1
Gastritis	0		0	1	(0.6)	1
Haematochezia	0		0	1	(0.6)	1
Haemorrhoidal haemorrhage	0		0	1	(0.6)	1
Loose tooth	0		0	1	(0.6)	1
Oesophagitis	0		0	1	(0.6)	1
Umbilical hernia	0		0	1	(0.6)	1
Varices oesophageal	0		0	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse Events were coded using MedDRA Version 14.1.

Table 14.3.2.4J Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Japanese and Global Safety Population)

System Organ Class Preferred Term	Japanese (N=10) n	(%)	E	Global (N=174) n	(%)	E
Skin and subcutaneous tissue disorders	3	(30.0)	4	17	(9.8)	21
Rash	1	(10.0)	1	7	(4.0)	8
Acne	1	(10.0)	1	2	(1.1)	2
Actinic keratosis	0		0	1	(0.6)	1
Dermatitis	0		0	1	(0.6)	1
Dermatitis allergic	0		0	1	(0.6)	1
Dermatitis atopic	0		0	1	(0.6)	1
Dermatitis contact	0		0	1	(0.6)	1
Dyshidrosis	1	(10.0)	1	1	(0.6)	1
Ecchymosis	0		0	1	(0.6)	1
Erythema	0		0	1	(0.6)	1
Heat rash	1	(10.0)	1	1	(0.6)	1
Petechiae	0		0	1	(0.6)	1
Pruritus	0		0	1	(0.6)	1
General disorders and administration site conditions	0		0	17	(9.8)	20
Pyrexia	0		0	4	(2.3)	5
Asthenia	0		0	2	(1.1)	2
Chest pain	0		0	2	(1.1)	2
Injection site pain	0		0	2	(1.1)	2
Chills	0		0	1	(0.6)	2

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse Events were coded using MedDRA Version 14.1.

Table 14.3.2.4J Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Japanese and Global Safety Population)

System Organ Class Preferred Term	Japanese (N=10) n	(%)	E	Global (N=174) n	(%)	E
General disorders and administration site conditions (continued)						
Adverse drug reaction	0		0	1	(0.6)	1
Feeling hot	0		0	1	(0.6)	1
Local swelling	0		0	1	(0.6)	1
Localised oedema	0		0	1	(0.6)	1
Malaise	0		0	1	(0.6)	1
Oedema peripheral	0		0	1	(0.6)	1
Pain	0		0	1	(0.6)	1
Respiratory, thoracic and mediastinal disorders	0		0	9	(5.2)	17
Cough	0		0	5	(2.9)	6
Oropharyngeal pain	0		0	3	(1.7)	3
Nasal congestion	0		0	2	(1.1)	2
Rhinorrhoea	0		0	2	(1.1)	2
Nasal mucosal disorder	0		0	1	(0.6)	1
Pharyngeal erythema	0		0	1	(0.6)	1
Sneezing	0		0	1	(0.6)	1
Tonsillar haemorrhage	0		0	1	(0.6)	1
Investigations	0		0	9	(5.2)	13

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse Events were coded using MedDRA Version 14.1.

Table 14.3.2.4J Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Japanese and Global Safety Population)

System Organ Class Preferred Term	Japanese (N=10) n	(%)	E	Global (N=174) n	(%)	E
Investigations (continued)						
Liver function test abnormal	0		0	2	(1.1)	2
Blood uric acid increased	0		0	1	(0.6)	3
Blood glucose increased	0		0	1	(0.6)	2
Blood lactate dehydrogenase increased	0		0	1	(0.6)	1
Blood triglycerides increased	0		0	1	(0.6)	1
Blood urea increased	0		0	1	(0.6)	1
C-reactive protein increased	0		0	1	(0.6)	1
Drug specific antibody present	0		0	1	(0.6)	1
Gamma-glutamyltransferase increased	0		0	1	(0.6)	1
Vascular disorders	0		0	7	(4.0)	7
Hypertension	0		0	5	(2.9)	5
Capillary fragility	0		0	1	(0.6)	1
Haematoma	0		0	1	(0.6)	1
Blood and lymphatic system disorders	0		0	6	(3.4)	7
Anaemia	0		0	2	(1.1)	2
Leukocytosis	0		0	2	(1.1)	2
Eosinophilia	0		0	1	(0.6)	1
Iron deficiency anaemia	0		0	1	(0.6)	1
Thrombocytopenia	0		0	1	(0.6)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse Events were coded using MedDRA Version 14.1.

Table 14.3.2.4J Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Japanese and Global Safety Population)

System Organ Class Preferred Term	Japanese (N=10) n	(%)	E	Global (N=174) n	(%)	E
Immune system disorders	0		0	3	(1.7)	4
Hypersensitivity	0		0	2	(1.1)	3
Seasonal allergy	0		0	1	(0.6)	1
Renal and urinary disorders	0		0	3	(1.7)	3
Haematuria	0		0	1	(0.6)	1
Pollakiuria	0		0	1	(0.6)	1
Renal colic	0		0	1	(0.6)	1
Eye disorders	0		0	2	(1.1)	2
Conjunctivitis	0		0	2	(1.1)	2
Metabolism and nutrition disorders	1	(10.0)	1	2	(1.1)	2
Hyperuricaemia	1	(10.0)	1	1	(0.6)	1
Iron deficiency	0		0	1	(0.6)	1
Surgical and medical procedures	0		0	1	(0.6)	2
Tooth extraction	0		0	1	(0.6)	2
Cardiac disorders	0		0	1	(0.6)	1
Arrhythmia	0		0	1	(0.6)	1

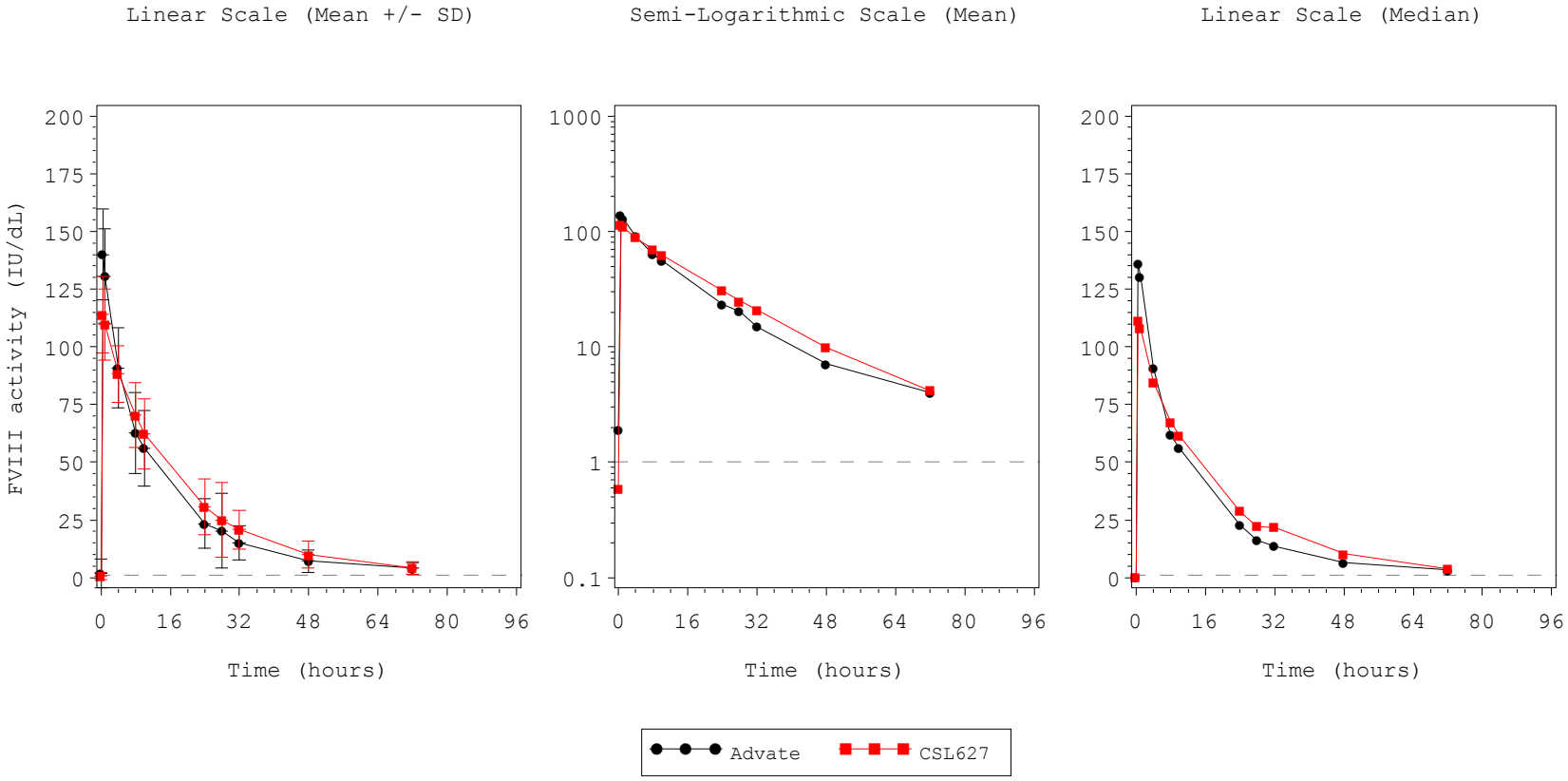
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse Events were coded using MedDRA Version 14.1.

Table 14.3.2.4J Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Japanese and Global Safety Population)

System Organ Class Preferred Term	Japanese (N=10) n	(%)	E	Global (N=174) n	(%)	E
Ear and labyrinth disorders	0		0	1	(0.6)	1
Ear pain	0		0	1	(0.6)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0		0	1	(0.6)	1
Gastrointestinal tract adenoma	0		0	1	(0.6)	1
Psychiatric disorders	0		0	1	(0.6)	1
Suicidal ideation	0		0	1	(0.6)	1
Reproductive system and breast disorders	0		0	1	(0.6)	1
Penile discharge	0		0	1	(0.6)	1

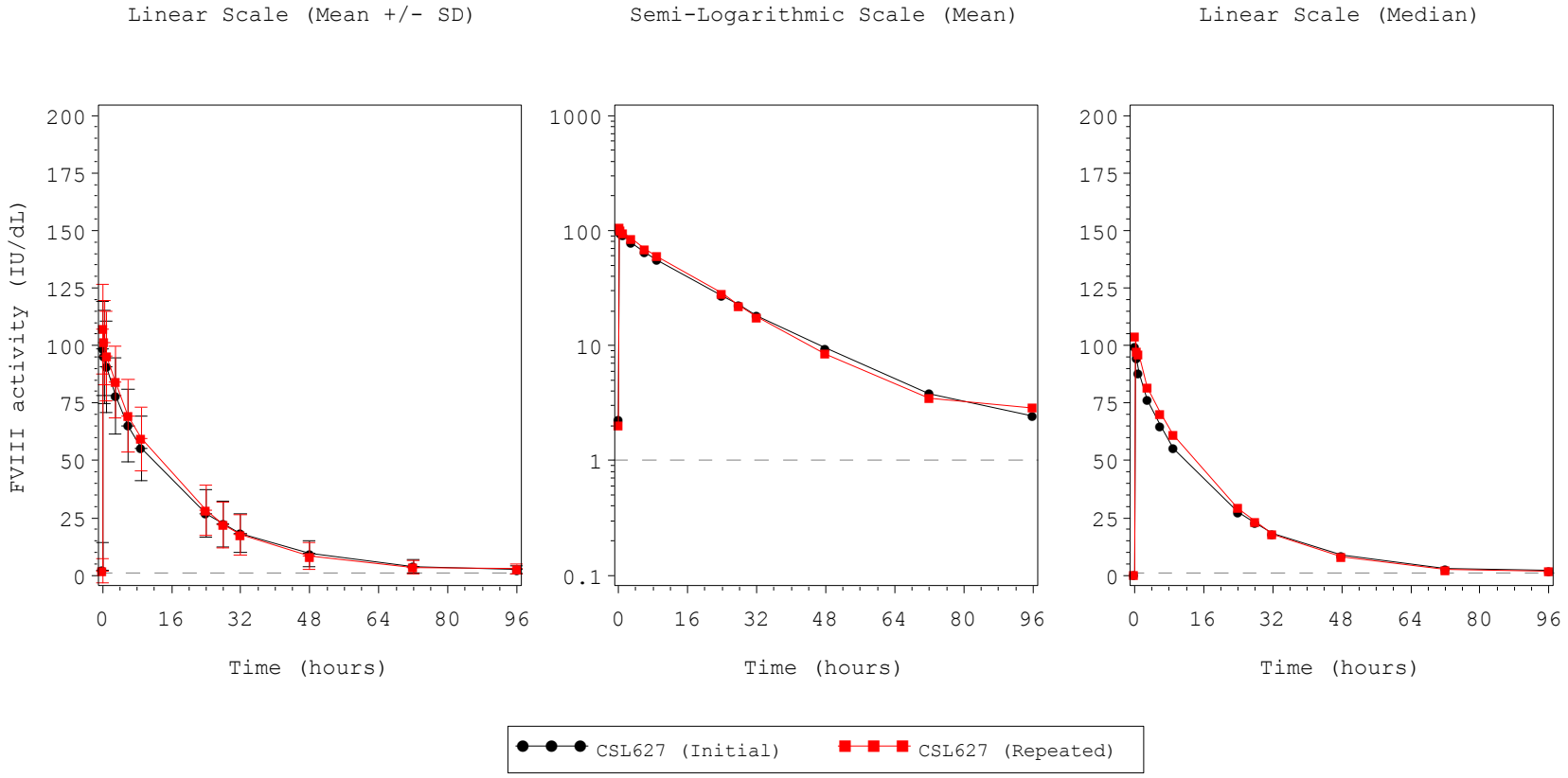
Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Events with onset date during the surgical period are excluded from this summary.
[3] Adverse Events were coded using MedDRA Version 14.1.

Figure 14.2.1.1.2 Part 1 - CS Assay Baseline Uncorrected FVIII Activities by Treatment
(PK Population - Patients whose dosing is within +/- 10% range of planned dose)



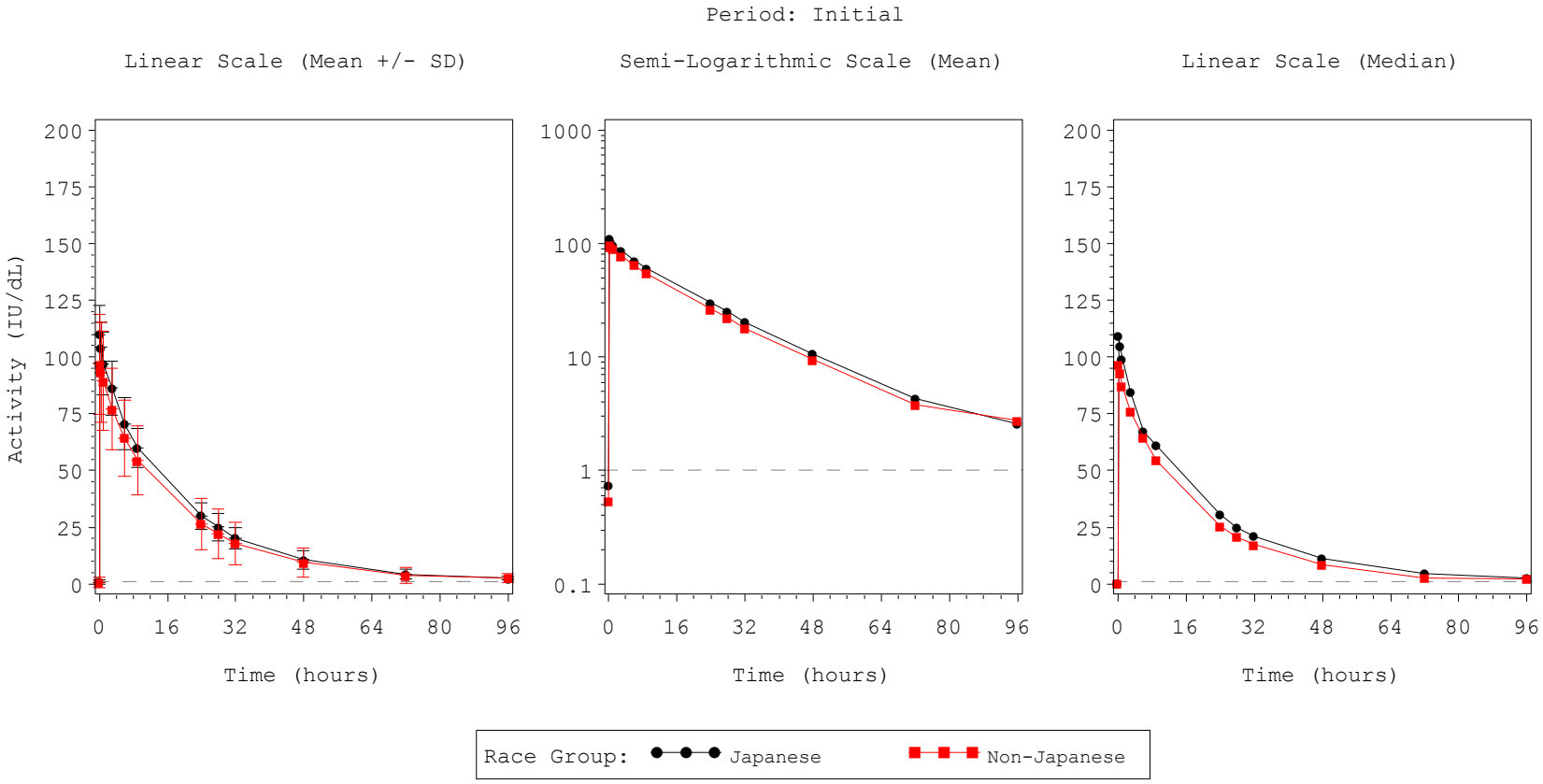
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Produced: [redacted] 20[redacted], 11:10
Source: Listing 16.2.9.6.1
Notes: [1] ---- Lower Limit of Quantification (LLOQ): 1.00 IU/dL.

Figure 14.2.4.1.1 Part 3 - CS Assay Baseline Uncorrected FVIII Activities (PK Population)



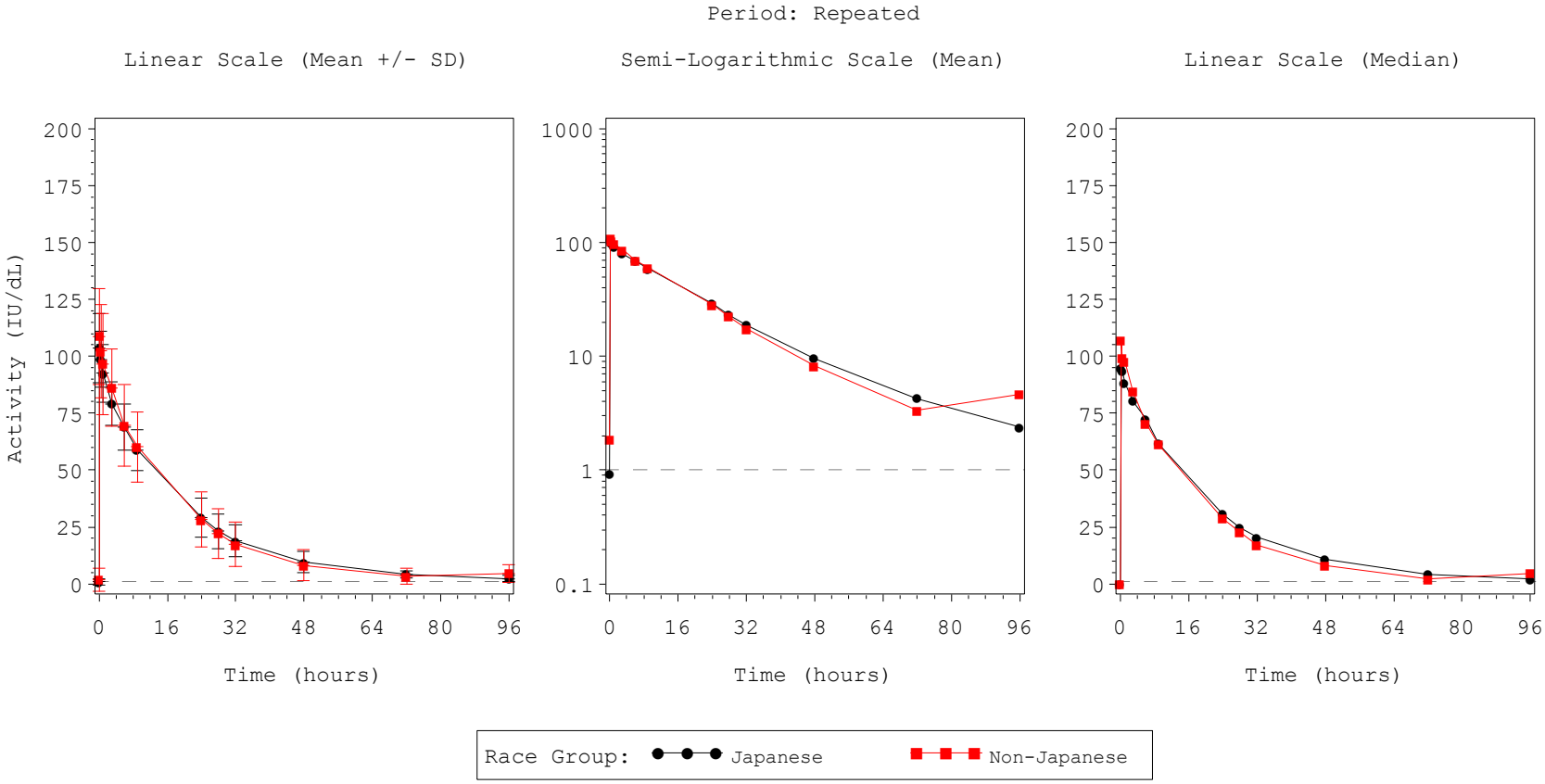
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Produced: [redacted] 20[redacted], 11:13
Source: Listing 16.2.9.6.5
Notes: [1] ---- Lower Limit of Quantification (LLOQ): 1.00 IU/dL.

Figure 14.2.7.1.2 Part 3 - CS Assay Baseline Uncorrected FVIII Activities By Race Group
(PK Population - Patients whose dosing is within +/- 10% range of planned dose)



CSL Behring GmbH: CSL627_1001/CIL-GM/FINAL/CONC04F.SAS
Produced: [redacted] 20[redacted], 16:57
Source: Listing 16.2.9.6.5
Notes: [1] ---- Lower Limit of Quantification (LLOQ): 1.00 IU/dL.

Figure 14.2.7.1.2 Part 3 - CS Assay Baseline Uncorrected FVIII Activities By Race Group
(PK Population - Patients whose dosing is within +/- 10% range of planned dose)



CSL Behring GmbH: CSL627_1001/CIL-GM/FINAL/CONC04F.SAS
Produced: [redacted] 20[redacted], 16:57
Source: Listing 16.2.9.6.5
Notes: [1] ---- Lower Limit of Quantification (LLOQ): 1.00 IU/dL.

Table 14.1.1.2 Subject Populations
(Enrolled Population)

	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Number of Subjects			
Enrolled	35	49	84
Safety Population	35	49	84
Efficacy Population	35	48	83
Per Protocol Population	31	44	75
PK Population	20	19	39

Table 14.1.2.1 Subject Disposition
(Safety Population)

	<6 years (N=35) n (%)	>=6 to <12 years (N=49) n (%)	Total (N=84) n (%)
Completed Study	27 (77.1)	38 (77.6)	65 (77.4)
Discontinued from Study	8 (22.9)	11 (22.4)	19 (22.6)
Reasons for Discontinuation			
Adverse Event(s)	0	1 (2.0)	1 (1.2)
Death	0	0	0
Lack of Efficacy	0	0	0
Lost to Follow-up	0	0	0
Other	0	0	0
Physician Decision	1 (2.9)	0	1 (1.2)
Protocol Violation	0	0	0
Study Terminated by Sponsor	7 (20.0)	10 (20.4)	17 (20.2)
Withdrawal by Subject	0	0	0
Unknown	0	0	0

Source: Listing 16.2.1.2
Notes: [1] Table presents number and percentage of subjects [n (%)].
[2] Subjects with reason Study Terminated by Sponsor are subjects who were discontinued because the study cohort reached the primary objective (25 subjects with 50 EDs).

Table 14.1.2.2 Subject Disposition
(Efficacy Population)

	On-Demand			Prophylaxis			
	<6 years (N=0) n (%)	>=6 to <12 years (N=3) n (%)	Total (N=3) n (%)	<6 years (N=35) n (%)	>=6 to <12 years (N=45) n (%)	Total (N=80) n (%)	Total (N=83) n (%)
Completed Study	0	2 (66.7)	2 (66.7)	27 (77.1)	35 (77.8)	62 (77.5)	64 (77.1)
Discontinued from Study	0	1 (33.3)	1 (33.3)	8 (22.9)	10 (22.2)	18 (22.5)	19 (22.9)
Reasons for Discontinuation							
Adverse Event(s)	0	0	0	0	1 (2.2)	1 (1.3)	1 (1.2)
Death	0	0	0	0	0	0	0
Lack of Efficacy	0	0	0	0	0	0	0
Lost to Follow-up	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0
Physician Decision	0	0	0	1 (2.9)	0	1 (1.3)	1 (1.2)
Protocol Violation	0	0	0	0	0	0	0
Study Terminated by Sponsor	0	1 (33.3)	1 (33.3)	7 (20.0)	9 (20.0)	16 (20.0)	17 (20.5)
Withdrawal by Subject	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0

Source: Listing 16.2.1.2
Notes: [1] Table presents number and percentage of subjects [n (%)].
[2] Subjects with reason Study Terminated by Sponsor are subjects who were discontinued because the study cohort reached the primary objective (25 subjects with 50 EDs).

Table 14.1.3.2.1 Exclusions from the Per Protocol Population
(Efficacy Population)

	On-Demand (N=3) n (%)	Prophylaxis (N=80) n (%)	Total (N=83) n (%)
Any Exclusion from Per Protocol Population	0	8 (10.0)	8 (9.6)
Subject was non-compliant to their prescribed dose	0	5 (6.3)	5 (6.0)
Subject was non-compliant to their prescribed regimen	0	4 (5.0)	4 (4.8)

Source: Listing 16.2.2
Notes: [1] Table presents number and percentage of subjects [n(%)].

Table 14.1.4.1 Demographics
(Safety Population)

	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Age (years)			
n	35	49	84
Mean (SD)	3.5 (1.34)	8.8 (1.77)	6.6 (3.11)
Median	4.0	9.0	7.0
Min, Max	1, 5	6, 11	1, 11
Race [n (%)]			
American Indian/Alaska Native	0	0	0
Asian	9 (25.7)	13 (26.5)	22 (26.2)
Black or African American	0	0	0
Native Hawaiian/Other Pacific Islander	0	0	0
White	25 (71.4)	36 (73.5)	61 (72.6)
Other	1 (2.9)	0	1 (1.2)
Ethnicity [n (%)]			
Hispanic or Latino	1 (2.9)	1 (2.0)	2 (2.4)
Not Hispanic or Latino	33 (94.3)	48 (98.0)	81 (96.4)
Not Reported	1 (2.9)	0	1 (1.2)
Unknown	0	0	0

Source: Listing 16.2.4.2.1, 16.2.4.2.2
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.

Table 14.1.4.1 Demographics
(Safety Population)

	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Country [n (%)]			
Australia	1 (2.9)	2 (4.1)	3 (3.6)
Austria	1 (2.9)	2 (4.1)	3 (3.6)
France	5 (14.3)	2 (4.1)	7 (8.3)
Georgia	2 (5.7)	3 (6.1)	5 (6.0)
Germany	2 (5.7)	3 (6.1)	5 (6.0)
Italy	1 (2.9)	0	1 (1.2)
Lebanon	2 (5.7)	4 (8.2)	6 (7.1)
Malaysia	0	4 (8.2)	4 (4.8)
Netherlands	3 (8.6)	3 (6.1)	6 (7.1)
Philippines	4 (11.4)	4 (8.2)	8 (9.5)
Poland	1 (2.9)	1 (2.0)	2 (2.4)
Portugal	0	2 (4.1)	2 (2.4)
Romania	1 (2.9)	0	1 (1.2)
Spain	0	2 (4.1)	2 (2.4)
Switzerland	0	1 (2.0)	1 (1.2)
Thailand	5 (14.3)	5 (10.2)	10 (11.9)
Turkey	3 (8.6)	5 (10.2)	8 (9.5)
Ukraine	2 (5.7)	4 (8.2)	6 (7.1)
United States of America	2 (5.7)	2 (4.1)	4 (4.8)
Geographical Region [n (%)]			
United States	2 (5.7)	2 (4.1)	4 (4.8)
Europe	21 (60.0)	28 (57.1)	49 (58.3)
Rest Of The World	12 (34.3)	19 (38.8)	31 (36.9)

Source: Listing 16.2.4.2.1, 16.2.4.2.2
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.

Table 14.1.4.1 Demographics
(Safety Population)

	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Height (cm)			
n	35	49	84
Mean (SD)	102.2 (10.75)	136.9 (11.22)	122.5 (20.41)
Median	102.0	137.0	124.8
Min, Max	80, 121	117, 172	80, 172
Weight (kg)			
n	35	49	84
Mean (SD)	16.62 (3.566)	35.45 (12.361)	27.60 (13.447)
Median	16.00	32.00	25.00
Min, Max	10.0, 26.2	18.7, 87.5	10.0, 87.5
BMI (kg/m^2)			
n	35	49	84
Mean (SD)	15.81 (1.660)	18.50 (4.018)	17.38 (3.500)
Median	15.63	17.60	16.80
Min, Max	13.4, 20.0	11.9, 29.6	11.9, 29.6

Source: Listing 16.2.4.2.1, 16.2.4.2.2
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.

Table 14.1.8.5.1 Extent of Exposure to CSL627
(Safety Population)

	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Exposure Days (EDs)			
n	35	49	84
Mean (SD)	56.7 (18.90)	66.4 (27.64)	62.4 (24.73)
Median	52.0	59.0	58.5
Min, Max	4, 98	9, 142	4, 142
<50 EDs [n (%)]	8 (22.9)	11 (22.4)	19 (22.6)
>=50 EDs [n (%)]	27 (77.1)	38 (77.6)	65 (77.4)
>=100 EDs [n (%)]	0	8 (16.3)	8 (9.5)

CSL Behring GmbH: CSL627_3002/CIL-MJ/FINAL/EXT01P.SAS
Produced: [redacted] 20[redacted], 10:00
Source: Listing 16.2.5.1, 16.2.5.2, 16.2.5.5
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.
[2] In one subject, the reporting of bleeding events and factor administration by the caregiver was deemed unreliable and not included. Only factor administration by a health care professional or those witnessed by a health care professional were included in the analysis.

Table 14.1.8.5.1 Extent of Exposure to CSL627
(Safety Population)

	<6 years (N=35)	>=6 to <12 years (N=49)	Total (N=84)
Number of Infusions			
n	35	49	84
Mean (SD)	56.9 (19.20)	67.8 (28.93)	63.3 (25.77)
Median	52.0	60.0	59.0
Min, Max	4, 100	9, 145	4, 145
Total Number of Infusions	1991	3322	5313
Dose Per Infusion Administered (IU/kg)			
n	1991	3322	5313
Mean (SD)	38.3 (11.21)	35.0 (12.11)	36.3 (11.89)
Median	37.7	30.8	33.0
Min, Max	16, 76	11, 93	11, 93
Total IU Administered			
n	35	49	84
Mean (SD)	2263.5 (1011.13)	2471.8 (1371.59)	2385.0 (1231.84)
Median	2079.1	2124.2	2079.2
Min, Max	176, 5918	222, 7831	176, 7831

Source: Listing 16.2.5.1, 16.2.5.2, 16.2.5.5
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.
[2] In one subject, the reporting of bleeding events and factor administration by the caregiver was deemed unreliable and not included. Only factor administration by a health care professional or those witnessed by a health care professional were included in the analysis.

Table 14.1.10.2.1 Summary of Dose Assignment and Dose Adjustment
(Efficacy Population, Age 0 to <6 Years)

	On-Demand	Initial Assigned Prophylaxis Regimen				Total
	On-Demand Regimen (N=0)	Every 2nd Day (N=2)	Three Times Per Week (N=10)	Two Times Per Week (N=16)	Other Regimen (N=7)	(N=35)
Initial Assigned Dose (IU/kg)						
n	0	2	10	16	7	35
Mean (SD)		33.5 (9.19)	34.2 (8.59)	38.6 (7.88)	44.6 (13.89)	38.3 (9.89)
Median		33.5	34.5	38.0	50.0	38.0
Min, Max		27, 40	22, 50	25, 52	23, 55	22, 55
Number of subjects assigned a dose <15 IU/kg anytime during the study [n (%)]	0	0	0	0	0	0
Number of subjects assigned a dose >50 IU/kg anytime during the study [n (%)]	0	0	0	2 (12.5)	3 (42.9)	5 (14.3)
Number of Dose Adjustments per Subject [n (%)]						
0	0	1 (50.0)	6 (60.0)	11 (68.8)	6 (85.7)	24 (68.6)
1	0	1 (50.0)	4 (40.0)	4 (25.0)	1 (14.3)	10 (28.6)
2	0	0	0	0	0	0
>2	0	0	0	1 (6.3)	0	1 (2.9)
Reason for Dose Adjustment [n (%)]						
Physician Decision	0	1 (50.0)	3 (30.0)	4 (25.0)	1 (14.3)	9 (25.7)
Lack of Efficacy	0	0	0	0	0	0
Other	0	0	1 (10.0)	1 (6.3)	0	2 (5.7)

Source: Listing 16.2.5.3
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.

Table 14.2.1.1.1 Investigator's Overall Assessment of Hemostatic Efficacy
(Efficacy Population)

	On-Demand (N=3)	Prophylaxis (N=80)	Total (N=83)
Number of Bleeding Events	133	256	389
Number of Treated Bleeding Events	132	215	347
Excellent	132 (100.0)	164 (76.3)	296 (85.3)
Good	0	38 (17.7)	38 (11.0)
Moderate	0	12 (5.6)	12 (3.5)
Poor/No Response	0	1 (0.5)	1 (0.3)
Success (a)	132	202	334
Rate of Success	100.0	94.0	96.3
95% CI for Rate	N/A	(87.8, 97.1)	(91.3, 98.4)
Success (b)	132	202	334
Rate of Success	100.0	94.0	96.3
95% CI for Rate	N/A	(87.8, 97.1)	(91.3, 98.4)
Success (c)	132	202	334
Rate of Success	100.0	94.0	96.3
95% CI for Rate	N/A	(87.8, 97.1)	(91.3, 98.4)

Source: Listing 16.2.6.2
Notes: [1] Success is defined as a rating of excellent or good. [a] Primary analysis: missing counted as failure;
[b] Sensitivity analysis: all missing excluded; [c] Sensitivity analysis: missing counted as success.
[2] 95% CI based on a generalized linear model to account for within-subject correlation.
[3] Table presents number and percentage of bleeding events [(n(%)].
[4] Percentages are based on the number of treated bleeding events.

Table 14.1.10.3.1 Summary of Dose Assignment and Dose Adjustment
(Efficacy Population, Age >=6 to <12 Years)

	On-Demand	Initial Assigned Prophylaxis Regimen				Total
	On-Demand Regimen (N=3)	Every 2nd Day (N=1)	Three Times Per Week (N=14)	Two Times Per Week (N=27)	Other Regimen (N=3)	(N=48)
Initial Assigned Dose (IU/kg)						
n	3	1	14	27	3	48
Mean (SD)	26.0 (2.65)	50.0 ()	33.6 (10.64)	32.4 (10.72)	39.3 (11.02)	33.2 (10.60)
Median	25.0	50.0	31.0	28.0	40.0	30.0
Min, Max	24, 29	50, 50	19, 50	20, 57	28, 50	19, 57
Number of subjects assigned a dose <15 IU/kg anytime during the study [n (%)]	0	0	0	0	0	0
Number of subjects assigned a dose >50 IU/kg anytime during the study [n (%)]	0	0	0	2 (7.4)	0	2 (4.2)
Number of Dose Adjustments per Subject [n (%)]						
0	2 (66.7)	1 (100.0)	8 (57.1)	15 (55.6)	1 (33.3)	27 (56.3)
1	1 (33.3)	0	3 (21.4)	6 (22.2)	1 (33.3)	11 (22.9)
2	0	0	3 (21.4)	2 (7.4)	0	5 (10.4)
>2	0	0	0	4 (14.8)	1 (33.3)	5 (10.4)
Reason for Dose Adjustment [n (%)]						
Physician Decision	1 (33.3)	0	5 (35.7)	9 (33.3)	2 (66.7)	17 (35.4)
Lack of Efficacy	0	0	0	1 (3.7)	0	1 (2.1)
Other	0	0	3 (21.4)	3 (11.1)	0	6 (12.5)

Source: Listing 16.2.5.3
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.

Table 14.2.2.3 Summary of Annualized Bleeding Rates
(Efficacy Population, Age 0 to <6 Years)

	On-Demand (N=0)	Prophylaxis (N=35)
Total Bleeds		
n	0	35
Mean (SD)		3.00 (3.932)
Median		2.12
Q1, Q3		0.00, 4.54
Min, Max		0.0, 17.0
Number of bleeds per year (95% CI)		3.0 (2.3, 4.0)
Spontaneous Bleeds		
n	0	35
Mean (SD)		0.81 (1.499)
Median		0.00
Q1, Q3		0.00, 1.46
Min, Max		0.0, 5.4
Number of bleeds per year (95% CI)		0.9 (0.5, 1.5)
Traumatic Bleeds		
n	0	35
Mean (SD)		1.48 (1.919)
Median		0.00
Q1, Q3		0.00, 2.52
Min, Max		0.0, 7.2
Number of bleeds per year (95% CI)		1.4 (1.0, 2.2)

Source: Listing 16.2.6.3.1
Notes: [1] Number of bleeds per year (95% CI) based on a Poisson distribution.

Table 14.2.2.3 Summary of Annualized Bleeding Rates
(Efficacy Population, Age 0 to <6 Years)

	On-Demand (N=0)	Prophylaxis (N=35)
Joint Bleeds		
n	0	35
Mean (SD)		1.13 (1.864)
Median		0.00
Q1, Q3		0.00, 1.89
Min, Max		0.0, 6.2
Number of bleeds per year (95% CI)		1.1 (0.7, 1.8)
Number of subjects with zero treated bleeds [n(%)]	0	14 (40.0)

Source: Listing 16.2.6.3.1
Notes: [1] Number of bleeds per year (95% CI) based on a Poisson distribution.

Table 14.2.2.4 Summary of Annualized Bleeding Rates
(Efficacy Population, Age >=6 to <12 Years)

	On-Demand (N=3)	Prophylaxis (N=45)
Total Bleeds		
n	3	45
Mean (SD)	66.77 (27.702)	6.94 (6.047)
Median	78.56	5.11
Q1, Q3	35.12, 86.62	2.52, 10.50
Min, Max	35.1, 86.6	0.0, 23.7
Number of bleeds per year (95% CI)	71.5 (60.3, 84.8)	7.4 (6.3, 8.6)
Spontaneous Bleeds		
n	3	45
Mean (SD)	24.83 (22.191)	2.39 (3.607)
Median	31.76	0.00
Q1, Q3	0.00, 42.73	0.00, 3.20
Min, Max	0.0, 42.7	0.0, 14.0
Number of bleeds per year (95% CI)	28.7 (21.9, 37.6)	2.6 (2.0, 3.3)
Traumatic Bleeds		
n	3	45
Mean (SD)	28.95 (11.320)	2.90 (2.871)
Median	35.12	2.52
Q1, Q3	15.88, 35.84	0.00, 4.81
Min, Max	15.9, 35.8	0.0, 10.0
Number of bleeds per year (95% CI)	28.2 (21.5, 37.0)	3.3 (2.6, 4.1)

Source: Listing 16.2.6.3.1
Notes: [1] Number of bleeds per year (95% CI) based on a Poisson distribution.

Table 14.2.2.4 Summary of Annualized Bleeding Rates
(Efficacy Population, Age >=6 to <12 Years)

	On-Demand (N=3)	Prophylaxis (N=45)
Joint Bleeds		
n	3	45
Mean (SD)	43.51 (22.544)	4.30 (4.802)
Median	43.31	2.31
Q1, Q3	21.07, 66.16	0.00, 6.87
Min, Max	21.1, 66.2	0.0, 20.5
Number of bleeds per year (95% CI)	47.1 (38.2, 58.2)	4.8 (4.0, 5.8)
Number of subjects with zero treated bleeds [n(%)]	0	7 (15.6)

Source: Listing 16.2.6.3.1
Notes: [1] Number of bleeds per year (95% CI) based on a Poisson distribution.

Table 14.2.2.16 Summary of Annualized Bleeding Rates for Prophylaxis
(Efficacy Population, Initial Dose Assignment 15-50 IU/kg, Age 0 to <6 Years)

	Every 2nd Day (N=2)	Three Times Per Week (N=10)	Two Times Per Week (N=14)	Other Regimen (N=4)	Total (N=30)
Total Bleeds					
n	2	10	14	4	30
Mean (SD)	2.70 (3.817)	2.42 (5.270)	3.84 (3.579)	2.92 (3.384)	3.16 (4.060)
Median	2.70	0.00	2.63	2.77	2.31
Q1, Q3	0.00, 5.40	0.00, 2.52	1.89, 4.54	0.00, 5.84	0.00, 4.54
Min, Max	0.0, 5.4	0.0, 17.0	0.0, 11.9	0.0, 6.2	0.0, 17.0
Number of bleeds per year (95% CI)	4.6 (1.5, 14.3)	2.5 (1.4, 4.7)	3.7 (2.5, 5.4)	2.7 (1.3, 5.7)	3.2 (2.4, 4.3)
Spontaneous Bleeds					
n	2	10	14	4	30
Mean (SD)	2.70 (3.817)	0.70 (1.176)	0.75 (1.416)	1.04 (2.075)	0.90 (1.589)
Median	2.70	0.00	0.00	0.00	0.00
Q1, Q3	0.00, 5.40	0.00, 1.63	0.00, 1.46	0.00, 2.08	0.00, 1.63
Min, Max	0.0, 5.4	0.0, 3.0	0.0, 4.8	0.0, 4.2	0.0, 5.4
Number of bleeds per year (95% CI)	4.6 (1.5, 14.3)	0.8 (0.2, 2.4)	0.7 (0.3, 1.8)	1.2 (0.4, 3.6)	1.0 (0.6, 1.7)
Traumatic Bleeds					
n	2	10	14	4	30
Mean (SD)	0.00 (0.000)	0.50 (1.045)	2.36 (1.872)	1.88 (2.921)	1.52 (1.915)
Median	0.00	0.00	2.39	0.69	0.69
Q1, Q3	0.00, 0.00	0.00, 0.00	1.54, 2.91	0.00, 3.77	0.00, 2.52
Min, Max	0.0, 0.0	0.0, 2.5	0.0, 7.2	0.0, 6.2	0.0, 7.2
Number of bleeds per year (95% CI)	0.0 (0.0,)	0.5 (0.1, 2.0)	2.2 (1.3, 3.6)	1.5 (0.6, 4.1)	1.5 (1.0, 2.3)

Source: Listing 16.2.6.3.1
Notes: [1] Number of bleeds per year (95% CI) based on a Poisson distribution.

Table 14.2.2.16 Summary of Annualized Bleeding Rates for Prophylaxis
(Efficacy Population, Initial Dose Assignment 15-50 IU/kg, Age 0 to <6 Years)

	Every 2nd Day (N=2)	Three Times Per Week (N=10)	Two Times Per Week (N=14)	Other Regimen (N=4)	Total (N=30)
Joint Bleeds					
n	2	10	14	4	30
Mean (SD)	2.70 (3.817)	0.66 (1.085)	1.08 (1.712)	1.54 (3.078)	1.11 (1.852)
Median	2.70	0.00	0.00	0.00	0.00
Q1, Q3	0.00, 5.40	0.00, 1.63	0.00, 1.89	0.00, 3.08	0.00, 1.89
Min, Max	0.0, 5.4	0.0, 2.5	0.0, 4.8	0.0, 6.2	0.0, 6.2
Number of bleeds per year (95% CI)	4.6 (1.5, 14.3)	0.8 (0.2, 2.4)	1.0 (0.5, 2.2)	1.2 (0.4, 3.6)	1.1 (0.7, 1.9)
Number of subjects with zero treated bleeds [n(%)]	1 (50.0)	6 (60.0)	2 (14.3)	2 (50.0)	11 (36.7)

Source: Listing 16.2.6.3.1
Notes: [1] Number of bleeds per year (95% CI) based on a Poisson distribution.

Table 14.2.2.17 Summary of Annualized Bleeding Rates for Prophylaxis
(Efficacy Population, Initial Dose Assignment 15-50 IU/kg, Age >=6 to <12 Years)

	Every 2nd Day (N=1)	Three Times Per Week (N=14)	Two Times Per Week (N=26)	Other Regimen (N=3)	Total (N=44)
Total Bleeds					
n	1	14	26	3	44
Mean (SD)	4.27 ()	8.21 (6.794)	6.57 (6.094)	5.46 (4.429)	6.97 (6.114)
Median	4.27	8.11	5.06	3.71	5.09
Q1, Q3	4.27, 4.27	2.08, 14.81	2.75, 8.16	2.17, 10.50	2.35, 10.82
Min, Max	4.3, 4.3	0.0, 18.0	0.0, 23.7	2.2, 10.5	0.0, 23.7
Number of bleeds per year (95% CI)	4.3 (1.1, 17.1)	7.8 (5.9, 10.2)	7.5 (6.2, 9.1)	5.4 (2.7, 10.8)	7.4 (6.3, 8.6)
Spontaneous Bleeds					
n	1	14	26	3	44
Mean (SD)	2.14 ()	2.61 (3.370)	2.09 (3.890)	4.76 (3.242)	2.44 (3.630)
Median	2.14	1.25	0.00	3.71	0.00
Q1, Q3	2.14, 2.14	0.00, 3.34	0.00, 2.15	2.17, 8.40	0.00, 3.27
Min, Max	2.1, 2.1	0.0, 10.3	0.0, 14.0	2.2, 8.4	0.0, 14.0
Number of bleeds per year (95% CI)	2.1 (0.3, 15.2)	2.5 (1.5, 4.1)	2.5 (1.8, 3.5)	4.7 (2.3, 10.0)	2.6 (2.0, 3.4)
Traumatic Bleeds					
n	1	14	26	3	44
Mean (SD)	2.14 ()	2.92 (3.363)	3.14 (2.684)	0.00 (0.000)	2.83 (2.870)
Median	2.14	2.08	2.80	0.00	2.33
Q1, Q3	2.14, 2.14	0.00, 5.07	0.00, 4.65	0.00, 0.00	0.00, 4.73
Min, Max	2.1, 2.1	0.0, 10.0	0.0, 8.7	0.0, 0.0	0.0, 10.0
Number of bleeds per year (95% CI)	2.1 (0.3, 15.2)	3.1 (2.0, 4.8)	3.6 (2.7, 4.8)	0.0 (0.0,)	3.2 (2.5, 4.0)

Source: Listing 16.2.6.3.1
Notes: [1] Number of bleeds per year (95% CI) based on a Poisson distribution.

Table 14.2.2.17 Summary of Annualized Bleeding Rates for Prophylaxis
(Efficacy Population, Initial Dose Assignment 15-50 IU/kg, Age >=6 to <12 Years)

	Every 2nd Day (N=1)	Three Times Per Week (N=14)	Two Times Per Week (N=26)	Other Regimen (N=3)	Total (N=44)
Joint Bleeds					
n	1	14	26	3	44
Mean (SD)	2.14 ()	4.72 (4.798)	4.25 (5.063)	4.22 (5.540)	4.35 (4.844)
Median	2.14	3.69	2.63	2.17	2.42
Q1, Q3	2.14, 2.14	0.00, 9.87	0.00, 6.87	0.00, 10.50	0.00, 6.90
Min, Max	2.1, 2.1	0.0, 12.5	0.0, 20.5	0.0, 10.5	0.0, 20.5
Number of bleeds per year (95% CI)	2.1 (0.3, 15.2)	4.5 (3.1, 6.5)	5.2 (4.2, 6.6)	4.1 (1.8, 9.1)	4.9 (4.0, 5.9)
Number of subjects with zero treated bleeds [n(%)]	0	3 (21.4)	4 (15.4)	0	7 (15.9)

Notes: [1] Number of bleeds per year (95% CI) based on a Poisson distribution.

Table 14.2.3.1 Number of CSL627 Infusions Required to Achieve Hemostasis
(Efficacy Population)

	On-Demand (N=3)	Prophylaxis (N=80)	Total (N=83)
Number of Bleeds	133	256	389
Number of Treated Bleeds	132	215	347
Number of Subjects with >=1 Bleed	3	63	66
Number of Subjects with >=1 Treated Bleeds	3	59	62
Number of Infusions Required to Achieve Hemostasis (n (%))			
1 Infusion	131 (99.2)	167 (77.7)	298 (85.9)
2 Infusions	0	34 (15.8)	34 (9.8)
3 Infusions	1 (0.8)	7 (3.3)	8 (2.3)
>3 Infusions	0	7 (3.3)	7 (2.0)
Unknown	0	0	0
Total IU per Bleed			
n	132	215	347
Mean (SD)	879.1 (343.92)	1606.1 (1823.95)	1329.6 (1492.42)
Median	1009.0	1072.0	1009.0
Min, Max	536, 3111	276, 16355	276, 16355
Total IU/kg per Bleed			
n	132	215	347
Mean (SD)	27.8 (7.70)	47.2 (36.88)	39.8 (30.86)
Median	25.9	37.0	27.6
Min, Max	21, 78	16, 282	16, 282

Source: Listing 16.2.6.2
Notes: [1] n=number of treated bleeds.
[2] Percentages for bleeding episodes are based on the total number of treated bleeds.

Table 14.2.3.1 Number of CSL627 Infusions Required to Achieve Hemostasis
(Efficacy Population)

	On-Demand (N=3)	Prophylaxis (N=80)	Total (N=83)
Total IU per Infusion per Bleed			
n	132	215	347
Mean (SD)	863.4 (283.19)	1123.2 (620.32)	1024.4 (533.21)
Median	1009.0	1009.0	1009.0
Min, Max	536, 2186	276, 3320	276, 3320
Total IU/kg per Infusion per Bleed			
n	132	215	347
Mean (SD)	27.4 (6.33)	34.1 (11.41)	31.5 (10.30)
Median	25.9	30.0	27.3
Min, Max	21, 57	16, 76	16, 76

Source: Listing 16.2.6.2
Notes: [1] n=number of treated bleeds.
[2] Percentages for bleeding episodes are based on the total number of treated bleeds.

Table 14.2.5.2 Consumption of CSL627 for Prophylaxis Subjects
(Efficacy Population, Assigned Modality = Prophylaxis, Age 0 to <6 Years)

	Two Times Per Week (N=16)	Three Times Per Week (N=10)	All Frequencies (N=35)
Number of Subjects on Routine Prophylaxis Treatment [n (%)]	16 (100.0)	10 (100.0)	35 (100.0)
Total Number of Prophylaxis Infusions	835	598	1863
Prophylaxis Dose Administered per Subject Per Month (IU/kg)			
n	16	10	35
Mean (SD)	363.76 (93.846)	449.96 (126.163)	369.41 (125.743)
Median	339.15	426.95	339.16
Min, Max	232.0, 546.6	315.6, 716.7	70.7, 716.7
Prophylaxis Dose Administered per Subject Per Year (IU/kg)			
n	16	10	35
Mean (SD)	4365.17 (1126.151)	5399.52 (1513.955)	4432.98 (1508.914)
Median	4069.83	5123.37	4069.88
Min, Max	2784.6, 6559.6	3787.6, 8601.0	848.4, 8601.0
Prophylaxis IU per Month			
n	16	10	35
Mean (SD)	6065.27 (1598.031)	6935.33 (1703.869)	6047.91 (1969.409)
Median	6007.05	6953.60	6361.44
Min, Max	3853.1, 8885.7	3559.6, 10679.6	869.6, 10679.6

Source: Listing 16.2.6.3
Notes: [1] Prophylaxis infusions are those recorded as administered for 'Routine/Prophylaxis'. Total infusions also include those recorded as administered for 'Bleeding Event', 'Prevention Prior to Activity', 'Additional Treatment', 'PK' and 'Post Surgery'.

Table 14.2.5.2 Consumption of CSL627 for Prophylaxis Subjects
(Efficacy Population, Assigned Modality = Prophylaxis, Age 0 to <6 Years)

	Two Times Per Week (N=16)	Three Times Per Week (N=10)	All Frequencies (N=35)
Total Number of Infusions	885	633	1991
Total Dose Administered per Subject Per Month (IU/kg)			
n	16	10	35
Mean (SD)	386.05 (93.591)	478.61 (132.526)	397.97 (129.350)
Median	357.97	455.71	368.86
Min, Max	263.8, 560.1	334.6, 785.9	153.2, 785.9
Total Dose Administered per Subject Per Year (IU/kg)			
n	16	10	35
Mean (SD)	4632.59 (1123.096)	5743.36 (1590.314)	4775.59 (1552.200)
Median	4295.68	5468.57	4426.33
Min, Max	3166.0, 6721.2	4014.9, 9430.7	1838.6, 9430.7
Total IU per Month			
n	16	10	35
Mean (SD)	6465.32 (1748.902)	7425.55 (1965.357)	6529.33 (2132.938)
Median	6374.54	7297.75	6486.45
Min, Max	4302.9, 9928.1	3688.6, 11709.8	1884.5, 11709.8

Source: Listing 16.2.6.3
Notes: [1] Prophylaxis infusions are those recorded as administered for 'Routine/Prophylaxis'. Total infusions also include those recorded as administered for 'Bleeding Event', 'Prevention Prior to Activity', 'Additional Treatment', 'PK' and 'Post Surgery'.

Table 14.2.5.3 Consumption of CSL627 for Prophylaxis Subjects
(Efficacy Population, Assigned Modality = Prophylaxis, Age >=6 to <12 Years)

	Two Times Per Week (N=27)	Three Times Per Week (N=14)	All Frequencies (N=45)
Number of Subjects on Routine Prophylaxis Treatment [n (%)]	27 (100.0)	14 (100.0)	45 (100.0)
Total Number of Prophylaxis Infusions	1519	921	2661
Prophylaxis Dose Administered per Subject Per Month (IU/kg)			
n	27	14	45
Mean (SD)	302.28 (99.495)	430.90 (123.083)	351.52 (123.915)
Median	262.76	391.66	345.62
Min, Max	178.5, 525.0	279.6, 656.3	178.5, 656.3
Prophylaxis Dose Administered per Subject Per Year (IU/kg)			
n	27	14	45
Mean (SD)	3627.31 (1193.941)	5170.74 (1476.993)	4218.19 (1486.976)
Median	3153.18	4699.87	4147.48
Min, Max	2141.9, 6299.7	3355.6, 7875.2	2141.9, 7875.2
Prophylaxis IU per Month			
n	27	14	45
Mean (SD)	10686.26 (5420.256)	15289.31 (5372.846)	12590.47 (6148.523)
Median	9006.12	15874.06	10916.01
Min, Max	4462.4, 28790.7	6543.5, 23165.4	4462.4, 28955.0

Source: Listing 16.2.6.3
Notes: [1] Prophylaxis infusions are those recorded as administered for 'Routine/Prophylaxis'. Total infusions also include those recorded as administered for 'Bleeding Event', 'Prevention Prior to Activity', 'Additional Treatment', 'PK' and 'Post Surgery'.

Table 14.2.5.3 Consumption of CSL627 for Prophylaxis Subjects
(Efficacy Population, Assigned Modality = Prophylaxis, Age >=6 to <12 Years)

	Two Times Per Week (N=27)	Three Times Per Week (N=14)	All Frequencies (N=45)
Total Number of Infusions	1705	1071	3097
Total Dose Administered per Subject Per Month (IU/kg)			
n	27	14	45
Mean (SD)	346.91 (116.885)	518.37 (161.378)	427.33 (212.177)
Median	310.10	463.10	406.89
Min, Max	185.2, 580.4	307.3, 872.7	185.2, 1393.9
Total Dose Administered per Subject Per Year (IU/kg)			
n	27	14	45
Mean (SD)	4162.97 (1402.623)	6220.49 (1936.541)	5127.94 (2546.122)
Median	3721.26	5557.24	4882.70
Min, Max	2222.6, 6964.5	3687.2, 10472.8	2222.6, 16727.1
Total IU per Month			
n	27	14	45
Mean (SD)	12090.04 (5722.241)	18634.51 (7931.927)	15295.45 (9242.645)
Median	11145.40	19111.27	12805.64
Min, Max	4815.7, 30373.4	7190.1, 34394.6	4815.7, 51575.4

Notes: [1] Prophylaxis infusions are those recorded as administered for 'Routine/Prophylaxis'. Total infusions also include those recorded as administered for 'Bleeding Event', 'Prevention Prior to Activity', 'Additional Treatment', 'PK' and 'Post Surgery'.

Table 14.2.12.2 Summary of FVIII PK Parameters By Age
(PK Population)

Assay Baseline Adjustment Age Cohort	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
CS										
Baseline Uncorrected										
0 to <6 years										
n	20	20	20	20	20	20	20	20	20	20
Mean	1.61	80.9	NC	1010	1080	10.4	5.07	70.7	71.0	12.4
SD	0.327	16.0	NC	286	334	2.98	1.50	8.43	8.38	3.10
CV (%)	20.3	19.8	NC	28.4	31.0	28.7	29.6	11.9	11.8	25.0
>=6 to <12 years										
n	19	19	19	19	19	19	19	19	19	19
Mean	1.67	83.8	NC	1090	1170	10.2	4.63	66.4	67.1	12.3
SD	0.321	16.0	NC	287	307	1.99	1.37	15.8	14.9	2.07
CV (%)	19.3	19.1	NC	26.4	26.3	19.4	29.5	23.8	22.3	16.8
0 to <12 years										
n	39	39	39	39	39	39	39	39	39	39
Mean	1.64	82.3	NC	1050	1120	10.3	4.86	68.6	69.1	12.4
SD	0.321	15.9	NC	286	320	2.51	1.43	12.6	12.0	2.62
CV (%)	19.6	19.3	NC	27.3	28.6	24.4	29.5	18.4	17.4	21.2

Source: Listing 16.2.5.7
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.12.2 Summary of FVIII PK Parameters By Age
(PK Population)

Assay Baseline Adjustment Age Cohort	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
CS										
Baseline Corrected										
0 to <6 years										
n	20	20	20	20	20	20	20	20	20	20
Mean	1.60	80.2	NC	957	1030	10.1	5.17	71.3	71.8	12.0
SD	0.337	16.5	NC	224	256	2.52	1.40	8.30	8.53	2.76
CV (%)	21.1	20.6	NC	23.4	24.8	25.0	27.0	11.7	11.9	23.1
>=6 to <12 years										
n	19	19	19	19	19	19	19	19	19	19
Mean	1.66	83.5	NC	1070	1140	9.85	4.76	65.1	66.4	12.1
SD	0.326	16.2	NC	293	317	2.03	1.45	14.7	14.2	2.00
CV (%)	19.7	19.5	NC	27.3	27.7	20.6	30.4	22.5	21.4	16.6
0 to <12 years										
n	39	39	39	39	39	39	39	39	39	39
Mean	1.63	81.8	NC	1010	1090	9.98	4.97	68.3	69.2	12.0
SD	0.329	16.3	NC	263	289	2.27	1.42	12.1	11.8	2.39
CV (%)	20.2	19.9	NC	26.0	26.6	22.7	28.5	17.7	17.1	19.9

Source: Listing 16.2.5.7
Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.12.2 Summary of FVIII PK Parameters By Age
(PK Population)

Assay Baseline Adjustment Age Cohort	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
OS										
Baseline Uncorrected										
0 to <6 years										
n	20	20	20	20	20	20	20	20	20	20
Mean	0.889	44.9	NC	545	610	10.9	10.8	147	142	12.2
SD	0.726	36.1	NC	260	379	5.30	6.31	62.1	50.6	3.90
CV (%)	81.7	80.3	NC	47.7	62.1	48.6	58.6	42.2	35.7	31.8
>=6 to <12 years										
n	19	19	19	19	19	19	19	19	19	19
Mean	0.848	42.6	NC	635	683	10.3	8.44	116	121	12.8
SD	0.169	8.45	NC	205	227	2.74	3.58	29.1	26.2	2.25
CV (%)	20.0	19.8	NC	32.3	33.2	26.6	42.4	25.1	21.7	17.5
0 to <12 years										
n	39	39	39	39	39	39	39	39	39	39
Mean	0.869	43.8	NC	588	646	10.6	9.63	132	132	12.5
SD	0.527	26.2	NC	236	312	4.20	5.23	50.7	41.5	3.18
CV (%)	60.6	59.8	NC	40.1	48.4	39.7	54.3	38.5	31.5	25.3

Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.2.12.2 Summary of FVIII PK Parameters By Age
(PK Population)

Assay Baseline Adjustment Age Cohort	IR ([IU/dL]/ [IU/kg])	Cmax (IU/dL)	Tmax (h)	AUC0-last (IU*h/dL)	AUC0-∞ (IU*h/dL)	t1/2 (h)	CL (mL/h/kg)	Vz (mL/kg)	Vss (mL/kg)	MRT (h)
OS										
Baseline Corrected										
0 to <6 years										
n	20	20	20	20	20	20	20	20	20	20
Mean	0.865	43.7	NC	483	517	9.41	11.4	147	145	11.5
SD	0.730	36.3	NC	171	173	2.02	5.92	63.7	51.9	3.24
CV (%)	84.4	83.0	NC	35.5	33.5	21.4	52.0	43.4	35.7	28.2
>=6 to <12 years										
n	19	19	19	19	19	19	19	19	19	19
Mean	0.841	42.3	NC	615	656	9.39	8.83	108	118	12.4
SD	0.170	8.50	NC	203	222	3.06	3.80	25.4	24.4	2.39
CV (%)	20.3	20.1	NC	33.0	33.9	32.6	43.1	23.6	20.7	19.2
0 to <12 years										
n	39	39	39	39	39	39	39	39	39	39
Mean	0.853	43.0	NC	547	585	9.40	10.1	128	132	12.0
SD	0.529	26.3	NC	197	208	2.54	5.11	52.2	42.6	2.86
CV (%)	62.1	61.2	NC	36.0	35.6	27.1	50.4	40.9	32.3	24.0

Notes: [1] SD=Standard Deviation; CV=Coefficient of Variation; NC=Not Calculated.
[2] PK Parameters: IR=Incremental Recovery; Cmax=Maximum observed concentration/activity; Tmax=Time corresponding to Cmax; AUC0-last=Area under the activity-time curve from zero (time of drug administration) to the time of last measurable (positive) activity; AUC0-∞=Area Under the activity-time curve from zero (time of drug administration) to infinity with extrapolation of the terminal phase; t1/2=Terminal elimination half-life of the compound; CL=Total plasma clearance; Vz=Volume of distribution during terminal phase; Vss=Volume of distribution at steady state; MRT=Mean residence time.

Table 14.3.1.1 Summary of Adverse Events
(Safety Population)

	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Any Adverse Events	28	(80.0)	85	36	(73.5)	108	64	(76.2)	193
Any Treatment Emergent Adverse Events	28	(80.0)	79	36	(73.5)	104	64	(76.2)	183
Any Treatment Emergent Adverse Events Leading to Withdrawal	0			1	(2.0)	1	1	(1.2)	1
Any Treatment Emergent Adverse Events of Potential Special Interest	6	(17.1)	9	8	(16.3)	11	14	(16.7)	20
Treatment Emergent Adverse Event Severity									
Mild	22	(62.9)	57	30	(61.2)	80	52	(61.9)	137
Moderate	11	(31.4)	19	14	(28.6)	23	25	(29.8)	42
Severe	3	(8.6)	3	1	(2.0)	1	4	(4.8)	4
Any Treatment Emergent Adverse Events Related to Study Drug	0			1	(2.0)	1	1	(1.2)	1

Source: Listing 16.2.7.1, 16.2.7.5
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)

Table 14.3.1.1 Summary of Adverse Events
(Safety Population)

	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Treatment Emergent Adverse Event Outcome									
Death Related to Adverse Event	0			0			0		
Not Recovered/Not Resolved	3	(8.6)	3	3	(6.1)	6	6	(7.1)	9
Recovered/Resolved	26	(74.3)	74	35	(71.4)	94	61	(72.6)	168
Recovered/Resolved With Sequelae	0			0			0		
Recovering/Resolving	1	(2.9)	1	3	(6.1)	3	4	(4.8)	4
Unknown	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Any Serious Adverse Events	4	(11.4)	6	5	(10.2)	6	9	(10.7)	12
Any Treatment Emergent Serious Adverse Events	4	(11.4)	6	5	(10.2)	5	9	(10.7)	11
Any Treatment Emergent SAEs Leading to Withdrawal	0			0			0		
Treatment Emergent Serious Adverse Event Severity									
Mild	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Moderate	1	(2.9)	3	3	(6.1)	3	4	(4.8)	6
Severe	2	(5.7)	2	1	(2.0)	1	3	(3.6)	3
Any Treatment Emergent Serious Adverse Events Related to Study Drug	0			0			0		

Source: Listing 16.2.7.1, 16.2.7.5
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)

Table 14.3.1.1 Summary of Adverse Events
(Safety Population)

	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Treatment Emergent Serious Adverse Event Outcome									
Death Related to Adverse Event	0			0			0		
Not Recovered/Not Resolved	0			0			0		
Recovered/Resolved	4	(11.4)	6	5	(10.2)	5	9	(10.7)	11
Recovered/Resolved With Sequelae	0			0			0		
Recovering/Resolving	0			0			0		
Unknown	0			0			0		

Source: Listing 16.2.7.1, 16.2.7.5
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E)

Table 14.3.1.4.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Any Treatment Emergent Adverse Events	28	(80.0)	79	36	(73.5)	104	64	(76.2)	183
Infections and infestations	18	(51.4)	29	20	(40.8)	31	38	(45.2)	60
Nasopharyngitis	6	(17.1)	7	8	(16.3)	8	14	(16.7)	15
Upper respiratory tract infection	2	(5.7)	3	2	(4.1)	2	4	(4.8)	5
Rhinitis	0		0	4	(8.2)	4	4	(4.8)	4
Ear infection	1	(2.9)	1	2	(4.1)	2	3	(3.6)	3
Lower respiratory tract infection	1	(2.9)	2	1	(2.0)	1	2	(2.4)	3
Device related infection	2	(5.7)	2	0		0	2	(2.4)	2
Gastroenteritis	2	(5.7)	2	0		0	2	(2.4)	2
Pharyngitis	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Skin infection	0		0	2	(4.1)	2	2	(2.4)	2
Viral infection	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Acute tonsillitis	1	(2.9)	1	0		0	1	(1.2)	1
Bacteraemia	0		0	1	(2.0)	1	1	(1.2)	1
Bronchitis	1	(2.9)	1	0		0	1	(1.2)	1
Croup infectious	1	(2.9)	1	0		0	1	(1.2)	1
Gastroenteritis viral	0		0	1	(2.0)	1	1	(1.2)	1
Hordeolum	0		0	1	(2.0)	1	1	(1.2)	1
Infection parasitic	0		0	1	(2.0)	1	1	(1.2)	1
Laryngitis	1	(2.9)	1	0		0	1	(1.2)	1
Otitis externa	1	(2.9)	1	0		0	1	(1.2)	1
Otitis media	0		0	1	(2.0)	1	1	(1.2)	1
Otitis media acute	0		0	1	(2.0)	1	1	(1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.4.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Infections and infestations (continued)									
Paronychia	0		0	1	(2.0)	1	1	(1.2)	1
Parotitis	0		0	1	(2.0)	1	1	(1.2)	1
Pneumonia	1	(2.9)	1	0		0	1	(1.2)	1
Respiratory tract infection	0		0	1	(2.0)	1	1	(1.2)	1
Tonsillitis	1	(2.9)	1	0		0	1	(1.2)	1
Tracheobronchitis	1	(2.9)	1	0		0	1	(1.2)	1
Urinary tract infection	0		0	1	(2.0)	1	1	(1.2)	1
Viral myositis	1	(2.9)	1	0		0	1	(1.2)	1
Viral upper respiratory tract infection	1	(2.9)	1	0		0	1	(1.2)	1
Injury, poisoning and procedural complications	10	(28.6)	15	10	(20.4)	17	20	(23.8)	32
Head injury	3	(8.6)	3	2	(4.1)	3	5	(6.0)	6
Fall	3	(8.6)	3	1	(2.0)	1	4	(4.8)	4
Contusion	0		0	3	(6.1)	6	3	(3.6)	6
Laceration	1	(2.9)	1	2	(4.1)	3	3	(3.6)	4
Ligament sprain	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Limb injury	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Excoriation	1	(2.9)	1	0		0	1	(1.2)	1
Hand fracture	0		0	1	(2.0)	1	1	(1.2)	1
Joint injury	1	(2.9)	1	0		0	1	(1.2)	1
Lip injury	1	(2.9)	1	0		0	1	(1.2)	1
Splenic rupture	0		0	1	(2.0)	1	1	(1.2)	1
Tongue injury	1	(2.9)	1	0		0	1	(1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.4.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Injury, poisoning and procedural complications (continued)									
Upper limb fracture	1	(2.9)	1	0		0	1	(1.2)	1
Wound	1	(2.9)	1	0		0	1	(1.2)	1
Musculoskeletal and connective tissue disorders	4	(11.4)	4	11	(22.4)	14	15	(17.9)	18
Arthralgia	3	(8.6)	3	5	(10.2)	5	8	(9.5)	8
Pain in extremity	0		0	4	(8.2)	4	4	(4.8)	4
Musculoskeletal pain	0		0	2	(4.1)	2	2	(2.4)	2
Back pain	0		0	1	(2.0)	1	1	(1.2)	1
Flank pain	0		0	1	(2.0)	1	1	(1.2)	1
Synovial cyst	0		0	1	(2.0)	1	1	(1.2)	1
Synovial disorder	1	(2.9)	1	0		0	1	(1.2)	1
Respiratory, thoracic and mediastinal disorders	3	(8.6)	8	9	(18.4)	11	12	(14.3)	19
Cough	2	(5.7)	3	5	(10.2)	7	7	(8.3)	10
Oropharyngeal pain	1	(2.9)	1	2	(4.1)	2	3	(3.6)	3
Rhinitis allergic	1	(2.9)	1	2	(4.1)	2	3	(3.6)	3
Asthma	1	(2.9)	2	0		0	1	(1.2)	2
Tonsillar disorder	1	(2.9)	1	0		0	1	(1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.4.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	<6 years (N=35) n (%)	E	>=6 to <12 years (N=49) n (%)	E	Total (N=84) n (%)	E
Nervous system disorders	1 (2.9)	1	7 (14.3)	13	8 (9.5)	14
Headache	1 (2.9)	1	6 (12.2)	8	7 (8.3)	9
Convulsion	0	0	1 (2.0)	2	1 (1.2)	2
Dizziness	0	0	1 (2.0)	1	1 (1.2)	1
Paraesthesia	0	0	1 (2.0)	1	1 (1.2)	1
Post-traumatic headache	0	0	1 (2.0)	1	1 (1.2)	1
General disorders and administration site conditions	5 (14.3)	5	3 (6.1)	3	8 (9.5)	8
Pyrexia	4 (11.4)	4	1 (2.0)	1	5 (6.0)	5
Device occlusion	0	0	1 (2.0)	1	1 (1.2)	1
Pain	0	0	1 (2.0)	1	1 (1.2)	1
Systemic inflammatory response syndrome	1 (2.9)	1	0	0	1 (1.2)	1
Gastrointestinal disorders	3 (8.6)	3	4 (8.2)	5	7 (8.3)	8
Dental caries	1 (2.9)	1	1 (2.0)	1	2 (2.4)	2
Vomiting	1 (2.9)	1	1 (2.0)	1	2 (2.4)	2
Abdominal pain	0	0	1 (2.0)	1	1 (1.2)	1
Dyspepsia	1 (2.9)	1	0	0	1 (1.2)	1
Nausea	0	0	1 (2.0)	1	1 (1.2)	1
Tooth loss	0	0	1 (2.0)	1	1 (1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.4.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Blood and lymphatic system disorders	2	(5.7)	4	4	(8.2)	4	6	(7.1)	8
Anaemia	1	(2.9)	3	2	(4.1)	2	3	(3.6)	5
Iron deficiency anaemia	0		0	2	(4.1)	2	2	(2.4)	2
Hypochromic anaemia	1	(2.9)	1	0		0	1	(1.2)	1
Skin and subcutaneous tissue disorders	3	(8.6)	3	1	(2.0)	1	4	(4.8)	4
Dry skin	1	(2.9)	1	0		0	1	(1.2)	1
Ecchymosis	0		0	1	(2.0)	1	1	(1.2)	1
Eczema	1	(2.9)	1	0		0	1	(1.2)	1
Rash erythematous	1	(2.9)	1	0		0	1	(1.2)	1
Ear and labyrinth disorders	2	(5.7)	2	1	(2.0)	1	3	(3.6)	3
Ear pain	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Cerumen impaction	1	(2.9)	1	0		0	1	(1.2)	1
Eye disorders	2	(5.7)	2	1	(2.0)	1	3	(3.6)	3
Blepharitis	1	(2.9)	1	0		0	1	(1.2)	1
Conjunctivitis	1	(2.9)	1	0		0	1	(1.2)	1
Diplopia	0		0	1	(2.0)	1	1	(1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.

Table 14.3.1.4.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class Preferred Term	<6 years (N=35) n	(%)	E	>=6 to <12 years (N=49) n	(%)	E	Total (N=84) n	(%)	E
Investigations	1	(2.9)	1	1	(2.0)	1	2	(2.4)	2
Cardiac murmur	1	(2.9)	1	0		0	1	(1.2)	1
Haemoglobin decreased	0		0	1	(2.0)	1	1	(1.2)	1
Cardiac disorders	0		0	1	(2.0)	1	1	(1.2)	1
Sinus arrhythmia	0		0	1	(2.0)	1	1	(1.2)	1
Immune system disorders	0		0	1	(2.0)	1	1	(1.2)	1
Hypersensitivity	0		0	1	(2.0)	1	1	(1.2)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(2.9)	1	0		0	1	(1.2)	1
Skin papilloma	1	(2.9)	1	0		0	1	(1.2)	1
Reproductive system and breast disorders	1	(2.9)	1	0		0	1	(1.2)	1
Balanitis	1	(2.9)	1	0		0	1	(1.2)	1

Source: Listing 16.2.7.1
Notes: [1] Table presents number and percentage of subjects [n (%)] with at least one specified event and number of specified events (E).
[2] Adverse Events were coded using MedDRA Version 16.1.