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ツロクトコグ アルファ ペゴル（遺伝子組換え）

2.7.4 臨床的安全性

ノボ ノルディスク ファーマ株式会社

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略語一覧

aPTT	:	activated partial thromboplastin time（活性化部分トロンボプラスチン時間）
BU	:	Bethesda unit（ベセスダ単位）
CHO	:	Chinese hamster ovary（チャイニーズハムスター卵巣）
ECG	:	electrocardiogram（心電図）
ED	:	exposure day（曝露日数）
EMA	:	European Medicines Agency（欧州医薬品庁）
FVIII	:	coagulation factor VIII（血液凝固第 VIII 因子）
HCP	:	host cell protein（宿主細胞由来タンパク）
ISTH	:	International Society on Thrombosis and Haemostasis （国際血栓止血学会）
kDa	:	kilodalton（キロダルトン）
N8	:	turoctocog alfa（ツロクトコグ アルファ）
N8-GP	:	turoctocog alfa pegol（ツロクトコグ アルファ ペゴル）
MedDRA	:	Medical Dictionary for Regulatory Activities（ICH 国際医薬用語集）
NNMQ	:	Novo Nordisk specific MedDRA query（ノボ ノルディスク社が定義した MedDRA 標準検索式）
pdFVIII	:	plasma-derived coagulation factor VIII（血漿由来血液凝固第 VIII 因子）
PEG	:	polyethylene glycol（ポリエチレングリコール）
PK	:	pharmacokinetics（薬物動態）
PYE	:	patient years of exposure（曝露量：人・年）
rFVIII	:	recombinant coagulation factor VIII（遺伝子組換え血液凝固第 VIII 因子）
rFVIIa	:	recombinant activated coagulation factor VII（遺伝子組換え活性型血液凝固第 VII 因子）
SD	:	standard deviation（標準偏差）
SMQ	:	standardised MedDRA query（MedDRA 標準検索式）

臨床試験の表記：

本臨床概要では、個々の臨床試験（NN7088-xxxx）を「xxxx 試験」と表記する（例：「NN7088-3859」の場合、「3859 試験」と表記する）。

2.7.4.1 医薬品への曝露

2.7.4.1.1 序文

本申請で示すデータは、ツロクトコグ アルファ ペゴル（N8-GP）の血友病 A〔先天性血液凝固第 VIII 因子（FVIII）欠乏症〕患者に対する使用を支持するものである。N8-GP は、既承認の遺伝子組換え血液凝固第 VIII 因子（rFVIII）製剤であるノボエイト®（ツロクトコグ アルファ）を基盤とした新規 rFVIII 製剤であり、ツロクトコグ アルファの B ドメイン上の *O* 型糖鎖に 40 kDa ポリエチレングリコール（PEG）を共有結合させることで半減期を延長させている[1,2]。N8-GP の作用機序は、血友病 A 患者において不足又は欠乏している FVIII を補充することである。

2018 年 2 月に米国及び欧州、同年 3 月にスイス、同年 7 月にカナダにおいて N8-GP の製造販売承認申請を行った。

2.7.4.1.2 総括的安全性評価計画及び安全性試験の記述

2.7.4.1.2.1 臨床的安全性の概要に含めた試験

本臨床概要には、N8-GP のすべての実施中及び完了した臨床試験で得られたデータが含まれる。

治療歴のある患者を対象とした試験

- 3776 試験：成人患者（年齢：18 歳以上）を対象とした第 1 相試験（ヒトへの初回投与試験）
- 3859 試験：青年及び成人患者（年齢：12 歳以上）を対象とした第 3 相試験（主要期間及び 2 つの延長期間で構成される）
- 3860 試験：青年及び成人患者（年齢：12 歳以上）を対象とした第 3 相試験（手術試験）
- 3885 試験：小児患者（年齢：12 歳未満）を対象とした第 3 相試験（主要期間及び 1 つの延長期間で構成される）
- 4033 試験：青年及び成人患者（年齢：12 歳以上）を対象とした第 1 相試験

治療歴のない患者を対象とした試験

- 3908 試験：小児患者（年齢：6 歳未満）を対象とした第 3 相試験

N8-GP の安全性を評価した臨床試験の概要を表 2.7.4.1-1 に示す。

表 2.7.4.1-1　　N8-GP の安全性を評価した臨床試験の概要

試験 ID／状況（cut-off 時点）	試験デザイン	N8-GP の用量及び投与方法 [a]	被験者数 [b]／年齢の範囲
治療歴のある患者を対象とした試験			
3776 試験 完了	ヒトへの初回投与試験：重症型血友病 A 患者を対象として、3 用量の N8-GP 単回投与後の安全性及び薬物動態を検討する、多施設、国際共同、非盲検、用量漸増試験	薬物動態：25、50 及び 75 IU/kg の単回投与	26 例 20～60 歳
3859 試験 主要パート（中間報告）：完了	主要試験：重症型血友病 A 患者を対象として、長期予防治療及び出血時治療における N8-GP の安全性、有効性及び薬物動態を検討する、多施設、国際共同、非盲検、非無作為化試験	予防治療：50 IU/kg の 3～4 日毎投与 出血時治療：20～75 IU/kg 薬物動態（サブグループ）：50 IU/kg の単回投与（2 回）	186 例 12～66 歳
延長期間パート 1（中間報告）：完了		予防治療：50 IU/kg の 3～4 日毎投与又は 75 IU/kg の 7 日毎投与 出血時治療：20～75 IU/kg	150 例 12～66 歳
延長期間パート 2（中間報告）：実施中		予防治療：50 IU/kg の 3～4 日毎投与又は 75 IU/kg の 7 日毎投与 出血時治療群：20～75 IU/kg	139 例 12～66 歳
3860 試験 （中間報告）：実施中	手術試験：重症型血友病 A 患者を対象として、大手術における N8-GP の有効性及び安全性を検討する、多施設、国際共同、非盲検、非無作為化試験	手術前期間： FVIII 活性 80%～100%を目標とした投与 手術後期間： 手術後 1～6 日：FVIII 活性 50%超を目標とした投与（治験責任医師の判断による） 手術後 7～14 日：治験責任医師の判断による投与	34 例 （手術 45 件） 15～69 歳
3885 試験 主要期間（中間報告）：完了 延長期間（中間報告）：実施中	小児試験：小児重症型血友病 A 患者を対象として、予防治療及び出血時治療における N8-GP の安全性、有効性及び薬物動態を検討する、多施設、国際共同、非盲検、非対照試験	予防治療：約 60 IU/kg（50～75 IU/kg）の週 2 回投与（必要に応じて 3 日毎投与に調節[*]） 出血時治療：20～75 IU/kg 薬物動態：50 IU/kg の単回投与	68 例 1～11 歳
4033 試験 完了	2 つの原薬製造工程による N8-GP の薬物動態及び安全性の比較検討試験：重症型血友病 A 患者を対象として、N8-GP（[redacted]実生産工程）及び N8-GP（[redacted]実生産工程）の単回投与後の薬物動態及び安全性を検討する、多施設、国際共同、二重盲検、無作為割り付け、クロスオーバー比較試験	薬物動態：50 IU/kg の単回投与 来院間では、3859 試験の予防治療の実施が認められた [c]	21 例 25～71 歳
治療歴のある患者の総数（重複排除）			計 270 例

試験 ID／ 状況（cut-off 時点）	試験デザイン	N8-GP の用量及び投与方法 [a]	被験者数 [b]／ 年齢の範囲
治療歴のない患者を対象とした試験			
3908 試験 実施中	治療歴のない患者の試験：重症型血友病 A 小児患者を対象として、N8-GP の安全性及び有効性を検討する、多施設、非盲検、非対照試験	予防治療：50～75 IU/kg の 3 日毎、週 2 回又は 7 日毎投与 出血時治療：20～75 IU/kg	32 例（予定被験者数は、6 歳未満の小児患者 125 例）

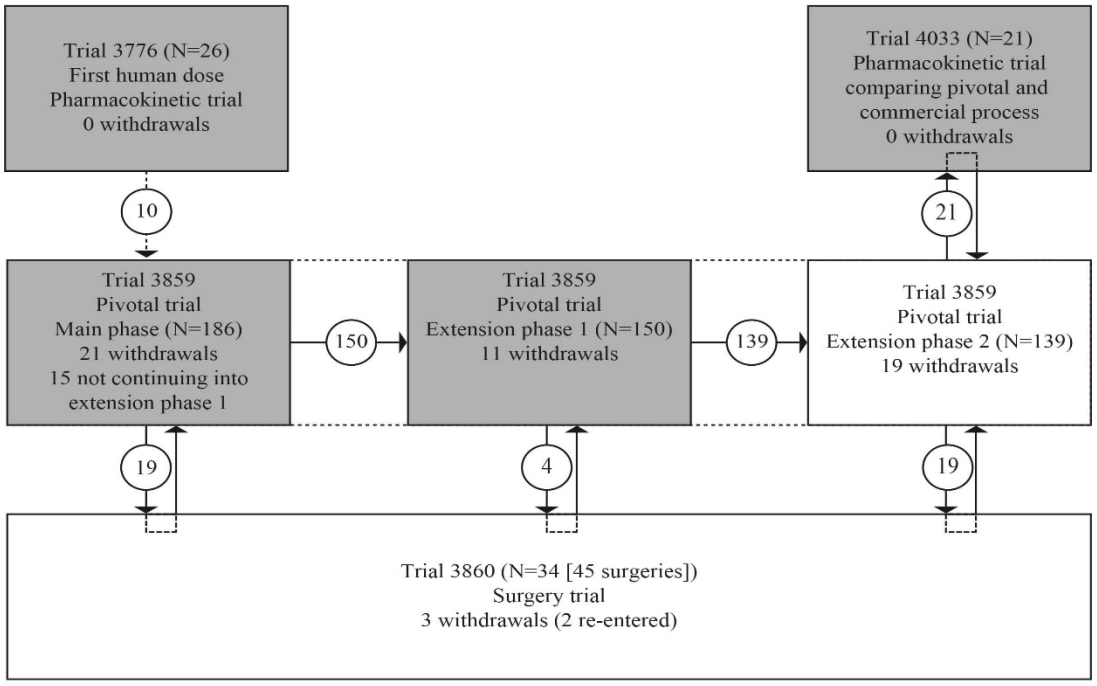
3～4 日毎投与：4 日毎投与で開始したが、その後は週 2 回投与へ変更することができた。
*：投与方法は、個々の被験者の反応に応じて治験責任医師の判断により変更することができた。
a：すべての N8-GP の投与は静脈注射により行われた。治験責任医師の判断で追加投与を行うことができた。
b：すべての被験者は重症型血友病 A 患者（FVIII 活性 1%未満）であった。
c：4033 試験の被験者は 3859 試験から組み入れられ、試験完了後に 3859 試験へ復帰した（図 2.7.4.1-1）。そのため、4033 試験の来院間では、3859 試験の予防治療の実施が認められた。

本申請の cut-off date（2017 年 8 月）時点で、2 つの第 1 相試験（3776 及び 4033 試験）が完了していた。第 3 相試験については、3859 試験（青年及び成人患者対象）の主要期間、ならびに 3885 試験（小児患者対象）の主要期間が完了していた。3859 試験は延長期間パート 1 も完了し、延長期間パート 2 を実施中であった。また、3885 試験は延長期間を実施中であった。3860 試験（手術試験）は、3859 試験の被験者が大手術を受ける場合の参加を可能にするために実施中であった。現在、3859 及び 3885 試験は 1 つの第 3 相試験（4410 試験）に統合して実施中である。さらに、治療歴のない患者を対象とした第 3 相試験（3908 試験）も実施中である。

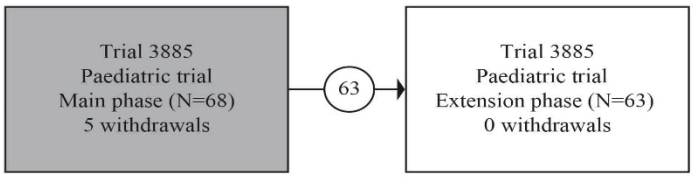
本臨床概要には、治療歴のある患者を対象とした実施中及び完了した臨床試験で N8-GP の投与を受けたすべての被験者の安全性情報が含まれる。実施中の臨床試験については、cut-off date である 2017 年 7 月 18 日（3885 試験）及び 2017 年 8 月 15 日（3859 及び 3860 試験）前の最終来院時までに得られたデータを含めた。さらに、治療歴のない患者を対象とした実施中の試験（3908 試験）では、cut-off date である 2017 年 8 月 15 日までに得られた安全性調査データベース（死亡例、重篤な有害事象及び特に注目すべき医学的事象）のデータを含めた。

3776、3859 及び 3885 試験では、治療歴のある患者を組み入れた。多くの被験者が複数の試験に参加しており、各試験の被験者数の合計は、本臨床開発プログラム全体の被験者総数（重複排除）と比べて多くなっている。本臨床開発プログラムにおける患者の流れを図 2.7.4.1-1 に示す。計 270 例の治療歴のある患者が N8-GP の投与を受けた。

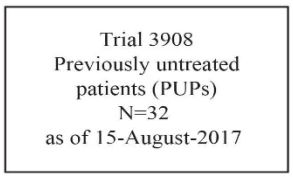
Previously treated patients (PTPs), adults and adolescents

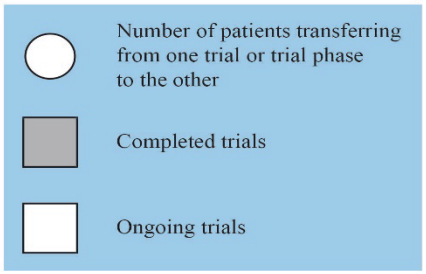


Previously treated patients, paediatric patients



Previously untreated patients





N: Number of exposed patients.

The figure shows the flow of patients through the trials. Prior to entering the extension phase(s) of the trials, patients had to re-consent to continue. Those who did not re-consent are denoted as 'not continuing' in the figure.

All the patients enrolled in trials 3860 and 4033 were recruited from trial 3859 and re-entered trial 3859 upon completion of trial 3860 or trial 4033. Three (3) patients withdrew from trial 3860 as they had their surgery postponed/cancelled of whom 2 patients re-entered trial 3860 to have surgery done at a later stage. Nine (9) patients entered trial 3860 more than once from different phases of trial 3859.

図 2.7.4.1-1　　N8-GP 臨床開発プログラムにおける患者の流れ

3776 試験（ヒトへの初回投与試験）の目的は、N8-GP の安全性を検討すること、ならびに被験者が組み入れ時に使用していた前治療の FVIII 製剤〔血漿由来 FVIII（pdFVIII）製剤又は遺伝子組換え FVIII（rFVIII）製剤〕と N8-GP の薬物動態を比較することであった。3859 及び 3885 試験の主要目的は N8-GP の免疫原性を評価することであり、3859 試験では N8-GP の予防治療の臨床的有効性の評価も行った。3860 試験（手術試験）の主要目的は、手術中の N8-GP の止血効果を評価することであった。

本臨床開発プログラムの期間中に、N8-GP 原薬の製造を[redacted]し、原薬製造工程を最適化した。第 3 相試験（青年及び成人患者を対象とした 3859 試験、ならびに小児患者を対象とした 3885 試験）では、変更前の N8-GP〔以下、N8-GP（[redacted]実生産工程）〕から変更後の N8-GP〔以下、N8-GP（[redacted]実生産工程）〕へ切り替えた。本臨床概要の cut-off date 時点で、両試験の 254 例中 92 例が N8-GP（[redacted]実生産工程）へ切り替えている（表 2.7.4.1-4）。両試験では 2 つの原薬製造工程による N8-GP の安全性データを別々に提示しており、それらの反復投与後の安全性プロファイルを定性的に比較することが可能である。4033 試験では、青年及び成人患者を対象として 2 つの原薬製造工程による N8-GP の単回投与後の薬物動態及び安全性を検討した。原薬製造工程の変更の詳細は、Module 2.7.1.1.3 を参照のこと。

N8-GP の臨床開発の根拠は、Module 2.5（臨床に関する概括評価）を参照のこと。

各試験の概要は、Module 2.7.6（個々の試験のまとめ）を参照のこと。各試験の治験総括報告書は、Module 5 を参照のこと。

治療歴のある患者を対象とした試験における死亡例、重篤な有害事象を発現した被験者及び治験を中止した被験者について、詳細な叙述及び完全な症例報告書（CRF）を含めた。特に注目すべき医学的事象（MESI：投薬過誤、FVIII インヒビター発生、血栓塞栓性事象、アナフィラキシーを含むアレルギー反応、治験薬を介する感染因子伝播の疑い）についても、叙述及び CRF を含めた（特に注目すべき医学的事象の定義の詳細は、2.7.4.2.1.1.1 を参照のこと）。

2.7.4.1.2.2　安全性の要約方法の概要

定義

- 1 曝露日は、被験者が N8-GP の投与を少なくとも 1 回受けた日と定義した。N8-GP の投与には、出血時治療、予防治療、手術及び薬物動態評価のための投与が含まれる。
- 治験薬投与下で発現した有害事象は、N8-GP 投与後に発現したすべての有害事象と定義した。本臨床概要には治験薬投与下で発現した有害事象のみを含めており、以降は治験薬投与下で発現した有害事象を「有害事象」と記載する。
- 安全性解析対象集団には、N8-GP の投与を少なくとも 1 回受けたすべての被験者が含まれる。本臨床概要に示す安全性データは、安全性解析対象集団に基づく。

有害事象の定義、ならびに有害事象の記録及び追跡に関する詳細は、2.7.4.2.1 を参照のこと。

データのグループ化及び併合

- 臨床試験では、N8-GP の安全性プロファイルについて、年齢グループ及び投与方法による明らかな違いはみられなかった〔3859 試験延長期間パート 2（Module 5.3.5.2, Sections 12.3 to 12.5）及び 3885 試験延長期間（Module 5.3.5.2, Sections 12.3 to 12.5）〕。そのため、治療歴のある患者を対象とした実施中及び完了した臨床試験〔3776、3859、4033 及び 3885 試験。3860 試験（手術試験）を除く〕の安全性データを併合し、N8-GP の安全性について包括的に評価した。
- 大手術を受ける患者の医学的状態は予防治療及び出血時治療を受けている患者とは異なっており、予測された通り、手術中は異なる有害事象の傾向がみられた（3860 試験）。そのため、手術中の安全性は別途提示し、併合データには含めなかった（FVIII インヒビター発生率の算出を除く）（2.7.4.1.2.3.4）。
- 臨床検査値、バイタルサイン及び身体所見は試験ごとに提示した。
- 4033 試験では薬物動態セッション（単回投与）の間に予防治療の実施が認められていたため、本試験のデータは単回投与ではなく予防治療として集計した。
- 3859 試験から 4033 試験へ移行し、その後 3859 試験へ復帰した被験者では、前の試験の最終来院と後の試験の初回来院は同日である。この場合、重複する来院日の曝露日数は 1 日として集計した。
- 3859 試験では N8-GP の投与方法を変更することができたため、1 例の被験者が複数の投与方法のデータに寄与している場合がある。
- 本臨床概要の各項では、年少児（0～5 歳）、年長児（6～11 歳）、青年（12～17 歳）及び成人（18 歳以上）の年齢グループ別にデータを提示した。
- 本臨床開発プログラムへの組み入れ時点で、6 例の年少児は 2 歳未満（0～1 歳）であった。これらの被験者における安全性は別途提示した。
- 本臨床プログラムへの組み入れ時点で、3 例の成人患者は高齢者（65 歳以上）であった。これらの被験者における安全性は別途提示した。
- 日本人患者における安全性は別途提示した。日本人患者は、日本国内の施設で組み入れられたアジア人と定義した。

2.7.4.1.2.3　試験デザイン及び安全性モニタリングの叙述

2.7.4.1.2.3.1　投与方法

すべての臨床試験において、N8-GP の投与は静脈内ボーラス注射により行われた。

単回投与

3776 試験（ヒトへの初回投与試験）は、第 3 相試験での N8-GP の開始用量を決定するための安全性及び薬物動態試験であり、N8-GP は安全であると考えられ、かつ FVIII 活性プロファイルに基づく潜在的な有効性が示された。本試験で検討した N8-GP の単回投与の用量は、25、50 及び 75 IU/kg であった。

4033 試験では、被験者は N8-GP（[redacted]実生産工程）及び N8-GP（[redacted]実生産工程）の単回投与（50 IU/kg）を受けた。本試験の来院間では、3859 試験の予防治療の実施が認められた。

予防治療

3859 試験では、青年及び成人患者を対象として N8-GP の予防治療（50 IU/kg の 4 日毎投与及び 75 IU/kg の 7 日毎投与）について検討した。治験責任医師の判断により、投与方法を 4 日毎投与から 3～4 日毎投与又は 7 日毎投与へ変更することが可能であった。また、本試験では、4 日毎投与での出血率が低かった被験者は、7 日毎投与又は 4 日毎投与への無作為割り付けを受けることができた。詳細は、Module 2.7.3.1.3.1.1 を参照のこと。

ノボ ノルディスク社は、N8-GP の予防治療を開始する際に推奨される投与方法は、4 日毎投与であると考える。7 日毎投与への切り替えは、治療による負担を軽減する目的で、出血率が低い患者に対してのみ検討されるべきである。投与方法の変更は、すべて主治医との合意に基づき行うべきである。

3885 試験では、小児患者を対象として N8-GP の予防治療〔約 60 IU/kg（50～75 IU/kg）の 3～4 日毎投与（以下、週 2 回投与）〕について検討した。治験責任医師の判断により、投与方法を週 2 回投与から 3 日毎投与へ変更することが可能であった。詳細は、Module 2.7.3.1.3.1.2 を参照のこと。

出血エピソードの治療

出血エピソードの治療に用いる N8-GP の用量は 20～75 IU/kg（出血の重症度及び部位に応じて設定）とし、繰り返しの投与を可とした。詳細は、Module 2.7.3.1.3.1.1 を参照のこと。

出血時治療

出血時治療には、上記の出血エピソードの治療が含まれた。

周術期の止血管理

3860 試験では、大手術における N8-GP の投与を検討した。手術当日（0 日目）は、血漿中 FVIII 活性 80%～100%を目標とした手術前投与を行った。手術後 1～6 日目は、血漿中 FVIII 活性 50%超の維持を目標とした投与を行った。手術後 7～14 日目は、WFH ガイドラインを参考にして、治験責任医師の判断で投与を行った。詳細は、Module 2.7.3.1.3.1.3 を参照のこと。

2.7.4.1.2.3.2　治験中の併用禁止薬

治験期間中、以下の薬剤は併用禁止とした：

- 活性型遺伝子組換え第 VII 因子（rFVIIa）製剤
- 血漿由来プロトロンビン複合体濃縮製剤
- 血漿由来活性型プロトロンビン複合体濃縮製剤
- 他の FVIII 製剤及び抗凝固剤（ただし、中心静脈カテーテルのヘパリンロックのみ許可された）

2.7.4.1.2.3.3　安全性評価

N8-GP の臨床試験において、以下の安全性情報を収集した：

- 有害事象
- 以下の安全性に関する臨床検査：
  - FVIII インヒビター発生の評価
  - 血液学的検査
  - 血液生化学的検査
  - 凝固関連パラメータ（3776、3859 及び 3860 試験のみ）
  - 尿検査〔3776 及び 3859 試験（ベースライン時）のみ〕
  - 抗チャイニーズハムスター卵巣宿主細胞（CHO HCP）抗体（すべての試験で、重度のアレルギー／アナフィラキシー反応が発生した場合に実施した。3859 及び 3885 試験においても、複数の時点で抗体 CHO HCP 抗体の評価を行った）
  - 抗 N8-GP 抗体
  - 抗 PEG 抗体
- 身体所見
- バイタルサイン
- 心電図〔3776、3859、3860 及び 4033 試験（ベースライン時）のみ〕

2.7.4.1.2.3.4　統計手法

安全性データは、主に記述統計量を用いて提示した。有害事象の表は、ICH 国際医薬用語集（MedDRA）バージョン 20.0 の器官別大分類及び基本語を用いて作成した。

エンドポイントである FVIII インヒビター（0.6 BU 以上）の発生率について、統計解析を実施した。インヒビター発生率の推定値を算出し、二項分布による精密計算に基づき、片側 97.5%信頼区間の上限を算出した。分母には N8-GP の投与を 50 曝露日数以上受けた被験者、ならびに曝露日数に関わらず FVIII インヒビターが発生した被験者を含めた。

すべての被験者が男性重症型血友病 A 患者であるため、性別ごとの安全性の解析は実施できなかった。また、治験対象集団である血友病 A の患者数が限られていることから、N8-GP の安全性への人種の影響について詳細な解析を行うことはできなかった。

2.7.4.1.2.4　安全性に関する重要な考察

2.7.4.1.2.4.1　非臨床における所見

一般的な安全性薬理試験及び反復投与毒性試験で得られた非臨床データからは、ヒトにおける N8-GP の安全性上の懸念は認められなかった。非臨床における安全性評価には PEG 関連の安全性も含まれた（2.7.4.2.1.8）。非臨床評価の詳細は、Module 2.4（非臨床試験の概括評価）を参照のこと。

2.7.4.1.2.4.2　薬理学的クラス効果

N8-GP は血液凝固因子製剤に分類され、その薬理学的クラス効果は抗 FVIII 中和抗体（FVIII インヒビター）の発生及びアレルギー反応である。

2.7.4.1.2.4.3　免疫原性

FVIII インヒビター

血友病 A 患者の治療における最大の懸念は FVIII インヒビターの発生である[3]。インヒビターが発生した患者では、FVIII 補充療法に対する臨床反応が不十分となる（有効性の欠如）ため症状が顕著になり、出血リスクの増加、ならびに血友病性関節症及び筋萎縮症の発症・進展リスクの増加により QOL の著しい低下に繋がる。インヒビター発生のリスクは、軽症型及び中等症型と比較して重症型の血友病 A 患者で高い[4]。特定の遺伝子変異は、血友病 A 患者におけるインヒビターの発生リスクの増加と関連している。すべての N8-GP の臨床試験において、各国の法規制で認められており、かつ被験者の同意が得られた場合、被験者の遺伝子変異について記録した。市販の FVIII 製剤におけるインヒビターの累積発生率は 24%～45%であり[3,5,6,7,8]、主に治療歴のない患者で報告されている。通常、治療歴のない患者におけるインヒビター発生は投与開始後 20 日までに観察され[9]、100 曝露日数以降に発生する可能性は低いと考えられている[4]。インヒビターが発生した患者の約 3 分の 1 では、同一製剤による治療を継続した場合にインヒビターが消滅している[9]。治療歴のある患者のうち、インヒビターを保有しておらず、かつその既往歴がない患者において FVIII 製剤投与後にインヒビターが発生するリスクは、約 2～3 件／1,000 人・年と予測されている[10,11]。

すべての N8-GP の臨床試験において、被験者は予定来院において FVIII インヒビターの検査を受けた。インヒビターの検出には Bethesda 法の Nijmegen 変法を用いた[12]。インヒビター発生の定義は、初回の検査結果が 0.6 ベセスダ単位（BU）以上であり、その後 2 週間以内に採取した 2 回目の検体で確

定されたこととした。検査方法の詳細は、Integrated summary of immunogenicity（Module 5.3.5.3, Section 3.2.1）を参照のこと。

すべての FVIII インヒビター（0.6 BU 以上）の発生は、有害事象及び特に注目すべき医学的事象として報告された（2.7.4.2.1）。

その他の抗体

N8-GP の原薬は、特性が十分に解明されている哺乳類の CHO 細胞株内で産生され、マウス免疫グロブリン G（IgG）を用いて精製される。すべての N8-GP の臨床試験において、重度のアレルギー／アナフィラキシー反応が生じた場合に抗 CHO HCP 抗体の検査を実施した。3859 及び 3885 試験では、抗 CHO HCP 抗体の評価を定期的に実施した。また、すべての臨床試験において、非中和性抗 N8-GP 抗体及び抗 PEG 抗体検査を行った。抗体検査方法の詳細は、Integrated summary of immunogenicity（Module 5.3.5.3, Section 3.2）を参照のこと。

2.7.4.1.2.4.4　アレルギー反応

他の静脈内投与製剤と同様、アレルギー反応は特に重要な事象である。市販の FVIII 製剤では、アナフィラキシーを含むアレルギー反応が報告されている。

注射後のアナフィラキシー反応は極めて稀であるが、血友病治療において、軽度のアレルギー反応は血栓塞栓性事象及び FVIII インヒビター以外で最も一般的な有害事象である。Franchini らによる血友病 A 患者を対象としたすべての前向き研究のシステマティック・レビューでは、過去 20 年間における計 226,603 回の注射で確認されたアナフィラキシーは 1 件のみであった[13,14]。また、同研究では、非重篤な有害事象に分類されたアレルギー反応の発現頻度は、0.06%（1,574 回の注射あたりに 1 件）であった。さらに、ヨーロッパ血友病安全性監視システムにおけるアレルギー／急性反応の報告件数及び各調査年の登録患者数に基づくと、血友病 A 患者におけるアレルギー反応の発現件数は 1.9～2.6 件／1,000 人・年と予測される[13]。

アレルギー反応の既往歴を有する患者、もしくは有効成分、PEG を含む添加物又はハムスター由来タンパク質に対する過敏症を有する患者は、アレルギー反応の発現リスクが高い。

本臨床開発プログラムにおいて、アレルギー反応の発現は特に注視され、有害事象及び特に注目すべき医学的事象として報告された（2.7.4.2.1）。

2.7.4.1.3　全体的な曝露量

曝露量の概要（3776、3859、4033 及び 3885 試験の併合データ）

N8-GP の累積曝露量の概要を表 2.7.4.1-2 に示す。

表 2.7.4.1-2　　N8-GP の累積曝露量 – 治療法別（3776、3859、4033 及び 3885 試験）

Trial Treatment type	Number of patients	Patient years of exposure	Exposure days
Trial 3776			
Phase 1 single dose	26	1.77	26
Total	26	1.77	26
Trial 3859			
Prophylaxis multiple dose	177	610.92	53267
On-demand	12	33.44	1405
Total	186	644.36	54672
Trial 4033			
Prophylaxis multiple dose	21	1.93	127
Total	21	1.93	127
Trial 3885			
Prophylaxis multiple dose	68	234.07	24621
Total	68	234.07	24621
All Trials			
Phase 1 single dose	26	1.77	26
Prophylaxis multiple dose	245	846.92	78015
On-demand	12	33.44	1405
Total	270	882.13	79446

An exposure day is a day when the patient received at least one dose of N8-GP.
Patients in trial 4033 were recruited from 3859 and returned to 3859 after completion of the trial. Prophylaxis treatment was allowed in between visits in 4033. Therefore exposure for 4033 is summarised under prophylaxis.
Patients might be included in multiple treatment types and therefore the number of patients in the rows might not necessarily add up to the Totals.

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3776、3859、4033 及び 3885 試験では、計 270 例（重複排除）の治療歴のある患者に対して N8-GP が投与された。総曝露日数は 79,446 日であり、これは 882 人・年に相当した（表 2.7.4.1-2）。多くの被験者が複数の試験に参加しており、各試験の被験者数の合計は、本臨床開発プログラム全体の被験者総数（重複排除）と比べて多くなっている。本臨床開発プログラム全体の被験者の流れは、図 2.7.4.1-1 を参照のこと。N8-GP の曝露の大部分は、3859 及び 3885 試験におけるものであった。各試験における治療、年齢グループ、人種及び民族別の累積曝露量の詳細は、付録 1、表 2.7.4.7.1-1～4 を参照のこと。

3776、3859、4033 及び 3885 試験における年齢グループ別の N8-GP の総曝露日数を表 2.7.4.1-3 及び図 2.7.4.1-2 に示す。年齢グループ及び治療法別の曝露期間及び曝露日数は、付録 1、表 2.7.4.7.1-7～9 を参照のこと。

本臨床開発プログラム全体で、N8-GP の投与を 2 年以上受けた被験者は 201 例、3 年以上受けた被験者は 192 例、4 年以上受けた被験者は 139 例、5 年以上受けた被験者は 18 例であった（表 2.7.4.1-3）。

表 2.7.4.1-3　　N8-GP の曝露期間 – 期間別及び年齢グループ別（3776、3859、4033 及び 3885 試験）

Duration interval	0-5 years N	6-11 years N	12-17 years N	>=18 years N	Total N
0 - <3months	4	-	1	23	28
3 - <6months	1	-	-	3	4
6 - <12months	-	-	4	6	10
12 - <18months	-	-	1	12	13
18 - <24months	-	-	3	11	14
24 - <30months	-	-	1	1	2
30 - <36months	-	-	1	6	7
36 - <42months	6	-	1	2	9
42 - <48months	16	26	-	2	44
48 - <54months	7	8	6	52	73
54 - <60months	-	-	6	42	48
60 - <66months	-	-	1	17	18

Duration intervals are based on patient years of exposure.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.

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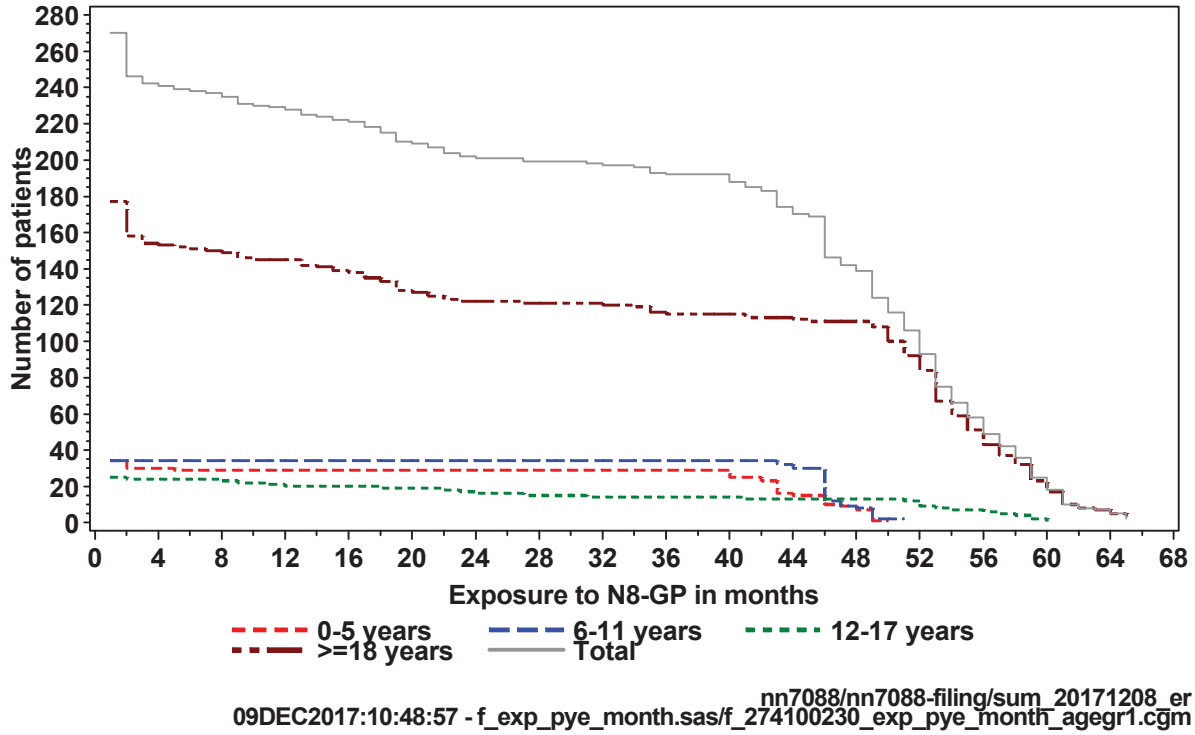


図 2.7.4.1-2　　N8-GP の曝露期間 – 年齢グループ別（3776、3859、4033 及び 3885 試験）

N8-GP の曝露の詳細は、付録 1、表 2.7.4.7.1-12（年齢グループ別）及び表 2.7.4.7.1-13（日本人患者）を参照のこと。

曝露量の概要（3860 試験）

手術試験（3860 試験）では、計 34 例（すべて 3859 試験に参加した被験者）が追加で N8-GP の投与を 979 曝露日数（6.4 人・年に相当）受けた（付録 1、表 2.7.4.7.1-14）。

市販予定製剤の曝露

3859 試験の延長期間及び 3885 試験の延長期間では、N8-GP（[redacted]実生産工程）を導入した。Cut-off date までに、両試験の 254 例中 92 例が治験薬の使用製剤を N8-GP（[redacted]実生産工程）から N8-GP（[redacted]実生産工程）へ切り替えた。2 つの原薬製造工程による N8-GP の曝露の概要を表 2.7.4.1-4 に示す。

表 2.7.4.1-4　　N8-GP の曝露 – 年齢グループ別及び原薬製造工程別（3859 及び 3885 試験）

	Pivotal process			Commercial			Total		
Age group	Number of patients	PYE	ED	Number of patients	PYE	ED	Number of patients	PYE	ED
0-5 years	34	93.07	9791	21	12.96	1349	34	106.03	11140
6-11 years	34	115.25	12142	22	12.79	1339	34	128.04	13481
12-17 years	25	72.10	6189	6	4.27	397	25	76.37	6586
>=18 years	161	543.60	45954	43	24.39	2132	161	567.99	48086
Total	254	824.02	74076	92	54.40	5217	254	878.43	79293

ED: exposure days
PYE: Patient years of exposure
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
Exposure to N8-GP from the different production methods is accounted from the scheduled visit where product was first dispensed.

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各試験における N8-GP の原薬製造工程別の曝露の詳細は、付録 1、表 2.7.4.7.1-15 を参照のこと。

4033 試験では、21 例における N8-GP（[redacted]実生産工程）及び N8-GP（[redacted]実生産工程）の単回投与（50 IU/kg）のデータが得られ、それぞれの薬物動態及び安全性を比較した〔4033 試験（Module 5.3.5.2, Section 10.1）〕。

2.7.4.1.4　治験対象集団の人口統計学的特性及びその他の特性

2.7.4.1.4.1　被験者の組み入れ基準

N8-GP の臨床試験における被験者の組み入れ基準は、欧州医薬品庁（EMA）の遺伝子組換え及び血漿由来 FVIII 製剤の臨床試験に関するガイドライン[4]、ならびに国際血栓止血学会（ISTH）の血液凝固因子の薬物動態試験のデザイン及び解析に関するガイドライン[15]に準拠して設定した。

3908 試験を除くすべての試験において、FVIII インヒビターの既往歴がなく、治療歴のある重症型血友病 A 患者（FVIII 活性 1%未満）を対象とした。また、FVIII 製剤による治療歴は、150 曝露日数以上（6 歳未満の小児患者を対象とした 3885 試験では 50 曝露日数以上）とした。3776 試験（ヒトへの初回投与試験）では、成人患者（18～65 歳）を組み入れた。3859（主要試験）、3860（手術試験）及び 4033 試験（薬物動態試験）では、青年及び成人患者（12 歳以上）を組み入れた。3885 試験（小児試験）では、小児患者（0～11 歳）を組み入れた。

治療歴のない患者〔凝固製剤を含む精製 FVIII 製剤による治療歴がない（血液製剤 5 曝露日数までは可）〕を対象とした 3908 試験では、小児患者（6 歳未満）を組み入れた。

安全性に関する主な除外基準は、以下の通りであった：

- 治験薬に対する過敏症又はその疑いを有する患者（ハムスター由来タンパク質又は関連薬剤に対するアレルギー反応を含む）

- FVIII インヒビターの既往歴を有する患者
- 血友病 A 以外の先天性又は後天性凝固障害を有する患者
- 重篤な血栓塞栓性事象の既往歴を有する患者
- 免疫抑制剤又は化学療法剤を投与中又は試験期間中に投与を予定している患者
- 被験者を危険にさらす可能性があり、治験参加又は治験結果の妨げとなる疾患（肝臓、腎臓、炎症、及び精神疾患を含む）又は健康状態を有する患者（治験責任医師の判断による）

被験者の組み入れ基準の詳細は、Module 2.7.3.1.3.5 及び個々の治験総括報告書〔3776 試験（Module 5.3.5.2, Section 9.3）、3859 試験（Module 5.3.5.2, Section 9.3）、3885 試験（Module 5.3.5.2, Section 9.3）、3860 試験（Module 5.3.5.2, Section 9.3）及び 4033 試験（Module 5.3.5.2, Section 9.3）〕を参照のこと。

2.7.4.1.4.2　ベースライン特性

ベースライン特性（3776、3859、4033 及び 3885 試験の併合データ）

3776、3859、4033 及び 3885 試験に参加した被験者（計 270 例）のベースライン特性を表 2.7.4.1-5 に示す。すべての被験者は重症型血友病 A の診断を受けており、FVIII 活性 1%未満であった。年齢の平均は 25 歳（範囲：1～66 歳）であった。人種について、大部分の被験者は白人（75%）であり、次いで多いのはアジア人（16%）、黒人又はアフリカ系アメリカ人（6%）であった。

ベースライン時に、18 歳未満の被験者（小児及び青年患者）では、C 型肝炎、B 型肝炎及び HIV 陽性の被験者はいなかった。一方、18 歳以上の被験者（成人患者）では、177 例中 120 例が C 型肝炎陽性、6 例が B 型肝炎陽性（3 例は C 型肝炎も陽性）であり、HIV のデータが得られた患者のうち 13 例が HIV 陽性であった（付録 1、表 2.7.4.7.1-55）。

ベースライン特性の詳細は、Module 2.7.3.3.1.2 を参照のこと。

表 2.7.4.1-5　　ベースライン特性 – 年齢グループ別（3776、3859、4033 及び 3885 試験）

	0-5 years	6-11 years	12-17 years	>=18 years	Total
Number of patients	34	34	25	177	270
Age at baseline in first trial (year)					
N	34	34	25	177	270
Mean (SD)	3.0 (1.3)	8.9 (1.7)	14.9 (1.6)	33.8 (11.8)	25.1 (15.7)
Median	3.0	9.0	15.0	31.0	24.0
Min ; Max	1 ; 5	6 ; 11	12 ; 17	18 ; 66	1 ; 66
Country, N (%)					
N	34 (100.0)	34 (100.0)	25 (100.0)	177 (100.0)	270 (100.0)
Australia	[redacted]				4 (1.5)
Brazil					4 (1.5)
Canada					2 (0.7)
Croatia					3 (1.1)
Denmark					6 (2.2)
France					11 (4.1)
Germany					20 (7.4)
Greece					1 (0.4)
Hungary					10 (3.7)
Israel					6 (2.2)
Italy					8 (3.0)
Japan					19 (7.0)
Korea, Republic of					5 (1.9)
Lithuania					5 (1.9)
Malaysia					7 (2.6)
Netherlands					7 (2.6)
Norway					2 (0.7)
Portugal					2 (0.7)
Russia					5 (1.9)
Spain					2 (0.7)
Sweden					1 (0.4)
Switzerland					11 (4.1)
Taiwan					5 (1.9)
Turkey					16 (5.9)
Ukraine					6 (2.2)
United Kingdom					32 (11.9)
United States of America					70 (25.9)
Ethnicity, N (%)					
N	34 (100.0)	34 (100.0)	25 (100.0)	177 (100.0)	270 (100.0)
Hispanic or Latino	-	3 (8.8)	3 (12.0)	10 (5.6)	16 (5.9)
Not Hispanic or Latino	34 (100.0)	30 (88.2)	22 (88.0)	167 (94.4)	253 (93.7)
NA	-	1 (2.9)	-	-	1 (0.4)
Race, N (%)					
N	34 (100.0)	34 (100.0)	25 (100.0)	177 (100.0)	270 (100.0)
Asian	1 (2.9)	4 (11.8)	1 (4.0)	37 (20.9)	43 (15.9)
Black or African American	2 (5.9)	1 (2.9)	3 (12.0)	9 (5.1)	15 (5.6)
White	30 (88.2)	25 (73.5)	19 (76.0)	129 (72.9)	203 (75.2)
Other	1 (2.9)	1 (2.9)	2 (8.0)	1 (0.6)	5 (1.9)
NA	-	3 (8.8)	-	1 (0.6)	4 (1.5)

Baseline is defined for each patient as entry in the first trial

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ベースライン特性（3860 試験）

手術試験（3860 試験）に参加した 34 例における組み入れ時の年齢の平均は、40 歳（範囲：15～69 歳）であった。1 例は青年患者（15 歳）、その他の被験者は成人患者（18 歳以上）であった。人種について、大部分の被験者は白人（82%）であり、残りの被験者はアジア人（15%）、黒人又はアフリカ系アメリカ人（3%）であった〔3860 試験（Module 5.3.5.2, Section 10.2）〕。

2.7.4.2 有害事象

2.7.4.2.1 有害事象の解析

2.7.4.2.1.1 解析方法

2.7.4.2.1.1.1 有害事象の定義、記録及び報告

有害事象は、医薬品の使用と時間的に関連のある、あらゆる好ましくない又は意図しない徴候（臨床検査の異常所見を含む）、症状又は疾患と定義した（当該医薬品との因果関係の有無は問わない）。有害事象には、被験者が同意書に署名した後の最初の治験関連手順から治験実施計画書で規定した投与後のフォローアップ期間までに観察された事象が含まれた。

また、治験責任医師により臨床的に問題があると判定された臨床検査値異常（疾患又は臓器に対する毒性が示唆され、治験薬の用量変更又は投与中止、追跡調査又は診断検査の追加等、積極的な管理を要する異常）も、有害事象として記録された。

さらに、併発疾患の悪化も有害事象として記録された。継続中の有害事象が悪化した場合、その重篤性及び重症度についての再評価が行われ、新規の有害事象として報告された。

以下は有害事象として記録されなかった：

- 事前に予定された処置（ただし、被験者が同意書に署名した後の最初の治験関連手順以降に、その処置に関連した症状が悪化した場合を除く）
- スクリーニング検査で観察された徴候、症状。これらは既往歴／併発疾患として記録された

重篤な有害事象の定義

投与状況を問わず、以下のいずれかに該当した事象は「重篤な有害事象（SAE）」とした：

- 死に至るもの
- 生命を脅かすもの [a)]
- 入院又は入院期間の延長が必要となるもの [b)]
- 永続的又は顕著な障害又は機能不全に陥るもの [c)]
- 先天性異常又は出生異常を来すもの
- その他医学的に重要な状態 [d)]：「死に至るもの」、「生命を脅かすもの」又は「入院が必要となるもの」に至らなくとも、被験者が危険な状態となり、上記の結果に至らぬように内科的又は外科的処置を要した場合は、適切な医学的判断に基づき重篤な有害事象とした
- 治験薬を介した感染性物質伝播の疑い及びFVIIIインヒビター発生 [e)]

a：「生命を脅かす」とは、当該事象の発現中に被験者が死の危険にさらされていたという意味であり、当該事象がより重症なものであった場合は死に至っていたかもしれないという仮定的な意味ではない。

b：「入院」は、被験者が以下に該当した場合に用いた：

- 身体的な滞在時間に関係なく、入院した又は入院患者となった
- 入院しなかった又は入院患者とはならなかったが、治療又は観察のために24時間以上病院に滞在した。

入院については常に医学的な判定を実施し、疑わしい場合の病院受診は入院と判断した。管理上の入院、治験関連の入院及び社会的理由による入院は有害事象に該当せず、有害事象又は重篤な有害事象としての報告は不要であった。同様に、治験前に予定された外科処置を目的とした入院も有害事象又は重篤な有害事象に該当しなかった。

c：「障害又は機能不全」とは、被験者の身体機能、身体構造、身体活動及び生活の質（QOL）において、重大で永続的又は恒久的な変化、障害、損傷又は失調を生じることである。

d：「その他医学的に重要な状態」とは、被験者が危険な状態となり、重篤な有害事象の定義に至らぬように処置を要した場合とした（例：薬物相互作用、禁忌又は使用上の注意に反する使用、悪性腫瘍の発現、ならびに薬物依存又は薬物中毒の進行等、被験者に重大な危害を及ぼす又は被験者を危険にさらすような有害事象）。

e：3859、3860 及び 3885 試験では、「治験薬を介した感染性物質伝播の疑い及び FVIII インヒビターの発生は、すべて重篤な有害事象とみなす」旨を治験実施計画書に追記した。

非重篤な有害事象の定義

重篤な有害事象の定義に該当しない有害事象は、すべて非重篤な有害事象とした。

重症度の定義

- 軽度（Mild）：無症状又は一時的な症状であり、被験者の日常の活動を妨げるものではない程度
- 中等度（Moderate）：顕著な症状であり、被験者の日常の活動を中程度に妨げる程度
- 重度（Severe）：被験者の日常の活動に対しかなりの妨げとなるもので、受け入れ難い程度

治験薬との因果関係の定義

- あり（Probable）：因果関係があると断言できる確かな理由や十分な証拠がある
- 可能性あり（Possible）：治験薬との因果関係の可能性が考えられ、否定できない
- なし（Unlikely）：事象は治験薬以外の病因に関連するものである可能性が高い

転帰の分類及び定義

- 回復（Recovered）：被験者が完全に回復した場合。もしくは、内科的又は外科的処置により、被験者の同意書署名後の最初の治験関連手順実施時に認められた状態まで回復した場合
- 軽快（Recovering）：状態が改善されつつあり、被験者が事象から回復すると予測される場合。本用語は、被験者が試験を終了した場合にのみ用いた
- 回復したが後遺症あり（Recovered with sequelae）：有害事象の結果として、永続的かつ顕著な障害又は機能不全（失明、聴力喪失、麻痺等）を被験者が被った場合。後遺症が重篤な有害事象の定義に該当する場合、当該事象は重篤な有害事象として報告された
- 未回復（Not recovered）
- 死亡（Fatal）
- 不明（Unknown）：本用語は、被験者が追跡不可能となった場合にのみ用いた

特に注目すべき医学的事象

特に注目すべき医学的事象とは、ノボ ノルディスク社が継続してモニターする、科学的及び医学的に懸念される注目すべき事象（重篤又は非重篤）である。特に注目すべき医学的事象は、必ずしも N8-GP との因果関係があるとは限らない。

N8-GP 臨床試験において、以下の事象が特に注目すべき医学的事象とみなされた：

- 投薬過誤
  - 誤った薬剤の投与又は医療機器の使用
  - 誤った経路による投与（例：静脈内投与と筋肉内投与の間違い）
  - 偶発的な過量投与（重篤な有害事象の定義に合致するか否かにかかわらず、治験責任医師により重大な健康上の問題につながると判断される用量）
  - 危害を引き起こすことを意図した高用量の投与（例：自殺企図）
- FVIII インヒビター発生
  - FVIII インヒビター測定のために採取した血液検体は、ノボ ノルディスク社が選定した中央検査機関で分析された。結果が陽性（0.6 BU 以上）であった場合は、特に注目すべき医学的事象として報告された。連続する 2 回のインヒビター検査（可能な限り 2 週間以内に実施）で陽性であった場合にのみ、インヒビター陽性（0.6 BU 以上）と判定した。
- アナフィラキシーを含むアレルギー反応（Sampson ら[16]の定義による）
  - アレルギー反応には Sampson らの定義に合致しない免疫グロブリン E（IgE）依存性反応又は遅発性過敏症（臨床徴候として様々な種類の皮膚がある）も含まれるが、これに限定されるものではない。特に注目すべき医学的事象として報告されたすべての過敏症反応は、hypersensitivity follow up form を用いて追跡された。
- 血栓塞栓性事象
  - 心筋梗塞、肺塞栓症、脳梗塞／脳血栓、深部静脈血栓症、ならびにその他の臨床的に問題となる血栓塞栓性事象及び末梢動脈閉塞を含む、動脈血栓性及び静脈血栓性の臨床徴候又はそれを示唆する臨床検査値〔定義は個々の治験総括報告書（Module 5）を参照のこと〕。
- 治験薬を介した感染性物質伝播の疑い

有害事象の収集、記録及び報告

すべての有害事象は、治験責任医師の観察によるもの又は患者からの報告によるものを問わず、治験責任医師が記録し、評価した。ノボノルディスク社による予測性の評価は、当該事象発現時点での最新の治験薬概要書に記載された安全性参照情報に準拠して行われた。

有害事象のコーディング

治験総括報告書に記載されているすべての重篤及び非重篤な有害事象のコーディングには、データベースロック時点での最新版の MedDRA を用いた。本臨床概要は、MedDRA バージョン 20.0 に準拠している。MedDRA の旧版からバージョン 20.0 までに基本語が変更されたすべての有害事象を付録 1、表 2.7.4.7.1-76 に示す。

有害事象の治療及び追跡調査

治験中に発現したすべての有害事象は、適切な標準治療により治療された。

非重篤な有害事象は、転帰が「回復」、「軽快」又は「回復したが後遺症あり」となり、かつ当該事象に関連するすべての疑問が解決するまで追跡調査を実施した。慢性疾患又は癌、もしくは被験者の死亡（他の有害事象に起因する死亡）時に継続中であった有害事象については、「軽快」又は「未回復」の転帰をもって追跡調査を終了することが可能であった。

すべての重篤な有害事象及び特に注目すべき医学的事象は、転帰が「回復」、「回復したが後遺症あり」又は「死亡」となり、かつ当該事象に関連するすべての疑問が解決するまで追跡調査を実施した。慢性疾患又は癌、もしくは被験者の死亡（他の有害事象に起因する死亡）時に継続中であった有害事象については、「回復」又は「未回復」の転帰をもって追跡調査を終了することが可能であった。また、被験者が治験を完了し、治験責任医師により事象の回復が予期された場合は、「軽快」の転帰をもって追跡調査を終了することが可能であった。

2.7.4.2.1.1.2　有害事象の提示

N8-GP の投与を受けた被験者において報告された有害事象の要約及び一覧表を付録 1 に提示した。治験責任医師により有害事象に関連する症状として記録された事象は、要約表に含めていない。すべての事象（有害事象及び症状）を一覧表に提示し、症状には「related to diagnosis」のフラグを立てた。

比較的よく見られる有害事象（2.7.4.2.1.2）及び重篤な有害事象（2.7.4.2.1.4）の記述及び評価では、有害事象を報告した被験者の割合、有害事象の発現件数／単位時間あたりの発現件数、重症度、事象の種類、治験薬との因果関係及び転帰に注目した。有害事象の結果は原則として併合データ（3776、3859、4033 及び 3885 試験）を提示し、手術試験（3860 試験）のデータは別途提示した。

死亡に至った有害事象は 2.7.4.2.1.3 に、その他の重篤な有害事象は 2.7.4.2.1.4 に記載した。治験中止に至った有害事象を含むその他の重要な有害事象は 2.7.4.2.1.5 に記載した。

特に注目すべき安全性領域については、器官別又は症候群別の有害事象の解析の項（2.7.4.2.1.6）に記載した。また、併合データ（3776、3859、4033 及び 3885 試験）を用いて MedDRA 検索を行った（詳細は後述）。

PEG に関する安全性評価の概要は 2.7.4.2.1.8 に、N8-GP の原薬製造工程別の安全性評価は 2.7.4.2.1.9 に記載した。

N8-GP の添付文書案に含める副作用の評価は、安全性データの医学的判断に基づくものである。N8-GP と有害事象の因果関係を示す根拠がある場合には、副作用として特定するための詳細な医学的評価を実施した。特定された副作用の一覧は 2.7.4.2.1.7 に提示した。また、添付文書案に含める副作用の根拠は付録 3 に示した。

死亡、重篤な有害事象、特に注目すべき医学的事象及びすべての中止例の叙述は、2.7.4.2.2 に記載した。

3776 及び 3859 試験の両方に参加した 10 例（図 2.7.4.1-1）は、各試験で異なる被験者番号が割り振られたが、付録 1 の併合データでは 1 つの識別コードで示している（付録 1、表 2.7.4.7.1-94 参照）。

MedDRA 検索式

安全性シグナルの検出を目的として、MedDRA 標準検索式（SMQ）を用いた（結果は 2.7.4.2.1.6 参照）。適切な SMQ がない場合は、関連する基本語に基づきノボ ノルディスク社が固有の MedDRA 検索式（以下、NNMQ）を作成した。SMQ 及び NNMQ の用語一覧を付録 1、表 2.7.4.7.1-86～93 及び 95 に示す。

2.7.4.2.1.2　比較的よく見られる有害事象

比較的よく見られる有害事象（3776、3859、4033 及び 3885 試験の併合データ）

全体的に N8-GP の忍容性は良好であり、予期されない安全性上の問題は認められなかった。

すべての有害事象の要約を表 2.7.4.2-1（治療法別）及び表 2.7.4.2-2（年齢グループ別）に示す。239 例（88.5%）で計 2,307 件の有害事象が報告され、単位時間あたりの発現件数は 2.6 件／人・年であった。年齢グループ別のすべての有害事象の要約を付録 1、表 2.7.4.7.1-38 に示す。

すべての有害事象の単位時間あたりの発現件数は、小児及び成人患者と比較して青年患者でわずかに高かった〔0～5 歳の年齢グループ：3.30 件／人・年、6～11 歳の年齢グループ：2.60 件／人・年、18 歳以上の年齢グループ：2.35 件／人・年に対し、12～17 歳の年齢グループ：3.64 件／人・年（表 2.7.4.2-2）〕。青年患者における有害事象の傾向からは、安全性上の懸念は認められなかった。すなわち、重篤な有害事象、重度の有害事象及び N8-GP との因果関係が「あり」又は「可能性あり」と判定された有害事象について、単位時間あたりの発現件数が他の年齢グループと比較して 12～17 歳の年齢グループで多い傾向はみられなかった。0～5 歳の年齢グループでは、6～11 歳の年齢グループと比較して有害事象の単位時間あたりの発現件数が多かった。この差は、主に幼児で一般的にみられる疾患（鼻咽頭炎及び咳嗽）が多く発現したことによるものであり、安全性上の懸念は認められなかった。

全体的に、有害事象の傾向は治験対象集団に典型的なものと考えられた。最も高頻度で報告された有害事象は、ウイルス性上気道感染〔78 例（28.9%）130 件〕、上気道感染〔57 例（21.1%）105 件〕、頭痛〔56 例（20.7%）118 件〕、関節炎〔43 例（15.9%）66 件〕、咳嗽〔37 例（13.7%）53 件〕、下痢〔31 例（11.5%）39 件〕及びインフルエンザ〔29 例（10.7%）42 件〕であった。5%超の被験者で報告

された有害事象の要約を表 2.7.4.2-3（全体）、付録 1、表 2.7.4.7.1-17（治療法別）及び表 2.7.4.7.1-39（年齢グループ別）に示す。

大部分（2,307 件中 2,240 件）の有害事象は非重篤であり、重症度は軽度又は中等度であった（表 2.7.4.2-1、付録 1、表 2.7.4.7.1-42 及び 43）。42 例（15.6%）で報告された 66 件の有害事象の重症度は重度であった付録 1、表 2.7.4.7.1-44）。このうち 4 件〔椎間板炎及び過敏症（重篤な有害事象）、ならびに胃炎及び筋肉内出血（非重篤な有害事象）〕は、治験責任医師により N8-GP との因果関係が「あり」又は「可能性あり」と判定された（付録 1、表 2.7.4.7.1-60）。その他の重度の有害事象は、N8-GP との因果関係は「なし」と判定された。

人種及び民族別の有害事象及び重篤な有害事象の概要及び要約を付録 1、表 2.7.4.7.1-45～47（人種別）及び表 2.7.4.7.1-48～50（民族別）に示す。すべての有害事象及び重篤な有害事象について、人種及び民族による明らかな違いはみられなかった。

40 例（14.8%）で報告された計 84 件の有害事象は、治験責任医師により N8-GP との因果関係が「あり」又は「可能性あり」と判定され、単位時間あたりの発現件数は 0.10 件／人・年であった〔付録 1、表 2.7.4.7.1-18（治療法別）及び表 2.7.4.7.1-40（年齢グループ別）〕。これらの有害事象の大部分は非重篤、かつ軽度又は中等度であり、大部分の被験者が回復した（付録 1、表 2.7.4.7.1-60）。

治験責任医師により N8-GP との因果関係が「あり」又は「可能性あり」と判定された有害事象（基本語別）のうち、6 例（2.2%）を超えて報告された事象はなかった。最も高頻度で報告された有害事象は、アスパラギン酸アミノトランスフェラーゼ増加（6 例 7 件）、アラニンアミノトランスフェラーゼ増加（4 例 5 件）、頭痛（4 例 4 件）、発疹（3 例 6 件）、関節痛（3 例 3 件）、γ－グルタミルトランスフェラーゼ増加（2 例 2 件）及び浮動性めまい（2 例 2 件）であった。その他の N8-GP との因果関係が「あり」又は「可能性あり」と判定された有害事象は、1 件のみの報告又は同一被験者における同一事象の複数の報告であり、様々な器官別大分類の事象であった。

表 2.7.4.2-1 有害事象の概要 – 治療法別（3776、3859、4033 及び 3885 試験）

	Phase 1 single dose N(%) E		Prophylaxis multiple dose N(%) E[R]		On-demand N(%) E[R,F]		Total N(%) E[R]	
Number of patients	26		245		12		270	
Patient years of exposure	1.77		846.92		33.44		882.13	
Exposure days	26		78015		1405		79446	
All adverse events	11(42.3)	17	226(92.2)	2174[2.57]	10(83.3)	116[3.47, 0.083]	239(88.5)	2307[2.62]
Serious adverse events	1(3.8)	1	43(17.6)	62[0.07]	3(25.0)	4[0.12, 0.003]	47(17.4)	67[0.08]
Non serious adverse events	11(42.3)	16	224(91.4)	2112[2.49]	10(83.3)	112[3.35, 0.080]	237(87.8)	2240[2.54]
Severity								
Mild	9(34.6)	13	211(86.1)	1725[2.04]	9(75.0)	76[2.27, 0.054]	221(81.9)	1814[2.06]
Moderate	4(15.4)	4	143(58.4)	387[0.46]	9(75.0)	35[1.05, 0.025]	154(57.0)	426[0.48]
Severe	-		41(16.7)	62[0.07]	2(16.7)	4[0.12, 0.003]	42(15.6)	66[0.07]
Missing	-			-	1(8.3)	1[0.03, 0.001]	1(0.4)	1[0.00]
Relationship								
Probably or possibly	1(3.8)	1	36(14.7)	74[0.09]	4(33.3)	9[0.27, 0.006]	40(14.8)	84[0.10]
Unlikely	10(38.5)	16	224(91.4)	2092[2.47]	10(83.3)	107[3.20, 0.076]	237(87.8)	2215[2.51]
Missing	-		4(1.6)	8[0.01]		-	4(1.5)	8[0.01]
Adverse events								
Leading to withdrawal	-		7(2.9)	7[0.01]		-	7(2.6)	7[0.01]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
[F]: Number of adverse events per exposure days (E/exposure days)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients might be included in multiple treatment types and therefore the number of patients in each row might not necessarily add up to the Total.

表 2.7.4.2-2　有害事象の概要 – 年齢グループ別（3776、3859、4033 及び 3885 試験）

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Number of patients	34		34		25		177		270	
Patient years of exposure	106.03		128.04		76.37		571.70		882.13	
Exposure days	11140		13481		6586		48239		79446	
All adverse events	32(94.1)	350[3.30]	33(97.1)	333[2.60]	25(100)	278[3.64]	149(84.2)	1346[2.35]	239(88.5)	2307[2.62]
Serious adverse events	10(29.4)	12[0.11]	5(14.7)	5[0.04]	5(20.0)	7[0.09]	27(15.3)	43[0.08]	47(17.4)	67[0.08]
Non serious adverse events	32(94.1)	338[3.19]	32(94.1)	328[2.56]	24(96.0)	271[3.55]	149(84.2)	1303[2.28]	237(87.8)	2240[2.54]
Severity										
Mild	27(79.4)	278[2.62]	31(91.2)	298[2.33]	22(88.0)	241[3.16]	141(79.7)	997[1.74]	221(81.9)	1814[2.06]
Moderate	25(73.5)	63[0.59]	17(50.0)	33[0.26]	13(52.0)	32[0.42]	99(55.9)	298[0.52]	154(57.0)	426[0.48]
Severe	7(20.6)	9[0.08]	2(5.9)	2[0.02]	5(20.0)	5[0.07]	28(15.8)	50[0.09]	42(15.6)	66[0.07]
Missing		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Relationship										
Probably or possibly	7(20.6)	12[0.11]	3(8.8)	3[0.02]	4(16.0)	8[0.10]	26(14.7)	61[0.11]	40(14.8)	84[0.10]
Unlikely	30(88.2)	333[3.14]	33(97.1)	330[2.58]	25(100)	269[3.52]	149(84.2)	1283[2.24]	237(87.8)	2215[2.51]
Missing	1(2.9)	5[0.05]		-	1(4.0)	1[0.01]	2(1.1)	2[0.00]	4(1.5)	8[0.01]
Adverse events										
Leading to withdrawal	2(5.9)	2[0.02]		-	1(4.0)	1[0.01]	4(2.3)	4[0.01]	7(2.6)	7[0.01]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.

表 2.7.4.2-3　高頻度（5%超）に報告された有害事象の要約 – 基本語別（3776、3859、4033 及び 3885 試験）

	Total N(%) E[R]
Number of patients	270
Patient years of exposure	882.13
Exposure days	79446
All adverse events	239(88.5) 2307[2.62]
感染症および寄生虫症	
ウイルス性上気道感染	78(28.9) 130[0.15]
上気道感染	57(21.1) 105[0.12]
インフルエンザ	29(10.7) 42[0.05]
胃腸炎	20(7.4) 28[0.03]
扁桃炎	18(6.7) 24[0.03]
鼻炎	15(5.6) 19[0.02]
気管支炎	15(5.6) 17[0.02]
筋骨格系および結合組織障害	
関節痛	43(15.9) 66[0.07]
四肢痛	22(8.1) 30[0.03]
筋骨格痛	17(6.3) 18[0.02]
背部痛	15(5.6) 18[0.02]
傷害、中毒および処置合併症	
挫傷	20(7.4) 32[0.04]
裂傷	19(7.0) 21[0.02]
転倒	17(6.3) 19[0.02]
四肢損傷	16(5.9) 26[0.03]
胃腸障害	
下痢	31(11.5) 39[0.04]
嘔吐	20(7.4) 24[0.03]
悪心	17(6.3) 22[0.02]
歯痛	15(5.6) 16[0.02]
呼吸器、胸郭および縦隔障害	
咳嗽	37(13.7) 53[0.06]
口腔咽頭痛	29(10.7) 35[0.04]
鼻漏	15(5.6) 20[0.02]
神経系障害	
頭痛	56(20.7) 118[0.13]
皮膚および皮下組織障害	
湿疹	15(5.6) 19[0.02]
発疹	14(5.2) 18[0.02]
一般・全身障害および投与部位の状態	
発熱	25(9.3) 41[0.05]
臨床検査	
アラニンアミノトランスフェラーゼ増加	14(5.2) 21[0.02]
血管障害	
高血圧	19(7.0) 20[0.02]
免疫系障害	
季節性アレルギー	14(5.2) 19[0.02]

N: Number of patients with adverse event. %: Percentage of patients with adverse event.
E: Number of adverse events.
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0.

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比較的よく見られる有害事象（3860 試験）

37 件（77%）の手術において計 118 件の有害事象が報告された。このうち 5 件は重篤な有害事象であった。大部分の有害事象は、基本語別で 1～2 件のみの報告であった。最も高頻度で報告された有害事象は便秘〔11 件（23%）の手術で 11 件〕及び悪心〔6 件（13%）の手術で 6 件〕であり、治験責任医師により N8-GP との因果関係があると判定された事象はなかった。

5 件（10%）の手術で報告された計 19 件の有害事象は、治験責任医師により N8-GP との因果関係が「あり」又は「可能性あり」と判定された。19 件中 17 件は非重篤な有害事象であり、転帰は「回復」又は「軽快」（18 件）、もしくは「回復したが後遺症あり」（1 件）であった。また、大部分の有害事象の重症度は軽度又は中等度であった。

手術中の死亡の報告はなかった。5 件の重篤な有害事象のうち、2 件（出血及び虚血：同一の手術における報告）は治験責任医師により N8-GP との因果関係が「可能性あり」と判定された（2.7.4.2.1.4）。有害事象により治験を中止した被験者はいなかった。特に注目すべき医学的事象として 2 件の有害事象（アレルギー性皮膚炎及び水疱）が報告されたが、いずれも治験薬との因果関係は「なし」と判定された。FVIII インヒビター発生及び血栓塞栓性事象は認められなかった。手術における有害事象の詳細は、3860 試験（Module 5.3.5.2, Section 12）を参照のこと。

全体的に、本試験における有害事象の傾向は、大手術において血友病 A 患者に典型的にみられるものと同じであると考えられた。

2.7.4.2.1.3　死亡

N8-GP の臨床試験では、1 例の死亡が報告された：

- 3859 試験の 1 例（被験者番号[redacted]、[redacted]歳）において、遠隔転移を伴う膵癌による死亡が報告された。当該事象は N8-GP の投与後 88 日に報告された。当該被験者は、過去数ヵ月間で原因不明の 10 kg の体重減少を経験し、かつ腹痛を訴えたため、悪性腫瘍が疑われたことから入院した。膵癌の肝転移又は胆管細胞癌に合致する所見がみられた。被験者は化学療法（ゲムシタビン）を開始し、約 6 ヵ月後に吐血により救急処置室へ搬送され、オメプラゾールマグネシウム及び晶質液（未特定）による治療を受けたが意識不明となり、酸素飽和度低下及び大量吐血が発現した。原疾患のため蘇生は実施されず、当該被験者は死亡した。当該事象は、治験責任医師及びノボ ノルディスク社により N8-GP との因果関係は「なし」と判定された。詳細は、3859 試験延長期間パート 2（Module 5.3.5.2, Section 14.3.3）の叙述を参照のこと。

N8-GP の臨床試験において、その他に死亡例の報告はない（付録 1、表 2.7.4.7.1-63）。

2.7.4.2.1.4　その他の重篤な有害事象

その他の重篤な有害事象（3776、3859、4033 及び 3885 試験の併合データ）

47 例（17%）で計 67 件の重篤な有害事象が報告され、単位時間あたりの発現件数は 0.08 件／人・年であった〔付録 1、表 2.7.4.7.1-19（治療法別）及び表 2.7.4.7.1-41（年齢グループ別）〕。

大部分の重篤な有害事象はそれぞれ 1 件のみの報告であり、様々な器官別大分類の事象であった。重篤な有害事象は 2～363 曝露日後の発現であり、曝露期間と発現頻度に相関はみられなかった（付録 1、表 2.7.4.7.1-61）。67 件中 4 件（椎間板炎、第 VIII 因子抑制、出血及び過敏症）は、治験責任医師により N8-GP との因果関係が「あり」又は「可能性あり」と判定された（表 2.7.4.2-4）。その他の重篤な有害事象は、治験責任医師により N8-GP との因果関係は「なし」と判定された。第 VIII 因子抑制及び過敏症の詳細は、それぞれ 2.7.4.2.1.6.1 及び 2.7.4.2.1.6.2 を参照のこと。

表 2.7.4.2-4　治験責任医師により N8-GP との因果関係が「あり」又は「可能性あり」と判定された重篤な有害事象（3776、3859、4033 及び 3885 試験）

被験者番号／試験 ID	年齢	基本語	曝露日数	因果関係	重症度	転帰
[redacted]／3859	[redacted]	椎間板炎	60	可能性あり	重度	回復
[redacted]／3859		第 VIII 因子抑制	97	あり	中等度	未回復
[redacted]／3885		出血	4	あり	中等度	回復
[redacted]／3885		過敏症	4	あり	重度	回復

本臨床概要の cut-off date までに、大部分の被験者は重篤な有害事象から回復したが、1 件の転帰は「死亡」（2.7.4.2.1.3）、11 件の転帰は「未回復」であった。

その他の重篤な有害事象（3860 試験）

4 件（8.3%）の手術において計 5 件の重篤な有害事象が報告された。このうち 2 件（出血及び虚血）は治験責任医師により N8-GP との因果関係が「可能性あり」と判定された（表 2.7.4.2-5）。両事象とも、同一被験者における膝関節全置換術中に報告された〔3860 試験（Module 5.3.5.2, Section 12.3.2）〕。これらの事象の転帰は、それぞれ「回復したが後遺症あり」及び「回復」であった（表 2.7.4.2-5）。

表 2.7.4.2-5　治験責任医師により N8-GP との因果関係が「あり」又は「可能性あり」と判定された重篤な有害事象（3860 試験）

被験者番号	年齢	MedDRA 基本語	発現日	因果関係	重症度	転帰
[redacted]	[redacted]	出血	手術後 1～6 日	可能性あり	重度	回復したが後遺症あり
		虚血	手術後 7～14 日	可能性あり	重度	回復

本試験で報告されたその他 3 件の重篤な有害事象（抜歯、運動性低下及び急性膵炎）は、治験責任医師により N8-GP との因果関係は「なし」と判定された。重症度はそれぞれ軽度、中等度及び重度であり、転帰はそれぞれ「回復」、「軽快」及び「回復」であった〔3860 試験（Module 5.3.5.2, Section 14.3.2.1）〕。

2.7.4.2.1.5　その他の重要な有害事象

2.7.4.2.1.5.1　治験中止に至った有害事象

3859 試験の 5 例（日本人患者 1 例を含む：2.7.4.5.1.2.1）及び 3885 試験の 2 例は、有害事象により治験を中止した（表 2.7.4.2-6）。さらに、2 例が安全性に関する中止・脱落基準に合致したため、治験を中止した〔3859 試験の 1 例は「中央検査機関による再検査で確認された FVIII インヒビター（5 BU 以上）」に合致したため、治験を中止した。また、3885 試験の 1 例は「治験薬に関連するアレルギー／アナフィラキシー反応」に合致したため、治験を中止した〕。両被験者とも有害事象による治験中止ではなかったが、表 2.7.4.2-6 に含めた。

7 件の治験中止に至った有害事象のうち、6 件は重篤な有害事象であった。このうち 3885 試験で報告された 1 件（出血）は、治験責任医師により N8-GP との因果関係が「あり」と判定された。その他の 6 件は、N8-GP との因果関係は「なし」と判定された。また、安全性に関する中止・脱落基準に合致したため治験を中止した 2 例で報告された有害事象（第 VIII 因子抑制及び過敏症）は、治験責任医師により N8-GP との因果関係が「あり」と判定された（2.7.4.2.1.6.1 及び 2.7.4.2.1.6.2）。

表 2.7.4.2-6　　治験中止に至った有害事象（3776、3859、4033 及び 3885 試験）

被験者番号／試験	年齢	MedDRA 基本語	曝露日数	因果関係[a]	重症度	重篤／非重篤	転帰
[redacted]/ 3859	[redacted]	遠隔転移を伴う膵癌	88	なし	中等度	重篤	死亡
[redacted]/ 3859		肝細胞癌	135	なし	中等度	重篤	未回復
[redacted]/ 3859		十二指腸潰瘍	94	なし	重度	重篤	回復
[redacted]/ 3859		交通事故	150	なし	中等度	重篤	回復
[redacted]/ 3859		足関節部骨折	156	なし	重度	重篤	回復
[redacted]/ 3859[b]		第 VIII 因子抑制	97	あり	中等度	重篤	未回復
[redacted]/ 3885		出血	4	あり	中等度	重篤	回復
[redacted]/ 3885		関節膨張	8	なし	軽度	非重篤	回復
[redacted]/ 3885[b]		過敏症	4	あり	重度	重篤	回復

a：N8-GP との因果関係は治験責任医師により判定された。
b：両被験者とも有害事象による治験中止ではなかったが、安全性に関する中止・脱落基準に合致したために治験を中止したことから、本表に含めた。1 例（被験者番号[redacted]）では、アレルギー反応に関する他の有害事象（非重篤）も報告された（付録 1、表 2.7.4.7.1-65）。

2.7.4.2.1.6　器官別又は症候群別の有害事象の解析

2.7.4.2.1.6.1　免疫原性

FVIII インヒビター

インヒビター発生は、血液凝固因子製剤における既知のクラス効果の 1 つである。多くの場合、インヒビターは小児期早期又は曝露日数が比較的少ないうちに発生する。その他の背景情報の詳細は、2.7.4.1.2.4.3 を参照のこと。

本臨床開発プログラムを通じて、FVIII インヒビター発生の評価を実施した。すべての N8-GP の臨床試験において、被験者は FVIII インヒビターの検査を受けた。FVIII インヒビター発生は、有害事象及び特に注目すべき医学的事象として記録された。

治療歴のある患者において、以下 1 件の FVIII インヒビター発生（0.6 BU 以上）が報告された：

- 3859 試験の主要期間で N8-GP の予防治療を受けた 1 例（被験者番号[redacted]、[redacted]歳）において、FVIII インヒビター発生が 1 件報告された。93 曝露日数時点で FVIII インヒビター陽性（1.3 BU）となり、その 14 日後に実施された 2 回目の検査結果（1.9 BU）で確定された。これは、治験実施計画書で規定した FVIII インヒビター発生の基準に合致した（2.7.4.1.2.4.3）。FVIII インヒビターの力価が低く、臨床的な影響も認められなかったことから、治験責任医師及びノボ ノルディスク社は当該被験者の治験を継続可能と判断した。約 2.5 ヵ月後に FVIII インヒビターの力価が 13.5 BU に増大し

たため、当該被験者は治験を中止した。治験期間を通じて、当該被験者の予防治療に対する臨床反応は良好であった。
その後の担当医師との連絡により、以下の情報が得られた：治験中止後、当該被験者の出血に対する治療には rFVIIa 製剤が使用された。治験中止から約 5 ヵ月後に FVIII インヒビターは消滅し、治験前の FVIII 製剤による治療が再開された。当該被験者の治験中止後、本申請の cut-off date まで（約 3.5 年間）に、FVIII インヒビターの再発は認められていない。
当該被験者の背景情報の詳細は、Integrated summary of immunogenicity（Module 5.3.5.3, Section 5.1.2）を参照のこと。

その他の治療歴のある患者において、FVIII インヒビター発生は認められていない。N8-GP の臨床試験で実施した FVIII インヒビター検査の詳細は、2.7.4.3.1 を参照のこと。

治療歴のある患者において FVIII インヒビター発生が 1 件報告されたことで、FVIII インヒビター発生率の推定値は 0.4%、片側 97.5%信頼区間の上限は 2.3%となった（付録 1、表 2.7.4.7.1-82、2.7.4.1.2.3.4 に記載した定義に基づく被験者数：235）。

治療歴のない患者を対象とした 3908 試験（実施中）では、32 例中 4 例で FVIII インヒビター発生が報告された（高力価 1 例及び低力価 3 例）。さらに、1 例では治験実施施設における 1 回の FVIII インヒビター検査が陽性であったが、直後に実施された中央検査機関における検査結果は陰性であった。治療歴のない患者における結果の詳細は、2.7.4.5.2 を参照のこと。

FVIII インヒビター発生は副作用と考えられる（2.7.4.2.1.7）。これまでに得られているデータからは、他の FVIII 製剤と比較して、N8-GP によるインヒビター発生のリスクの増加は示唆されなかった（2.7.4.1.2.3.4）。FVIII インヒビター発生については、通常の医薬品安全性監視活動によるモニターを継続する。本監視活動には、インヒビター発生に起因する可能性がある「有効性の欠如」の追跡も含める。

その他の抗体

抗 N8-GP 抗体、抗 PEG 抗体及び抗 CHO HCP 抗体の結果は、2.7.4.3.1 を参照のこと。

2.7.4.2.1.6.2　アレルギー反応

アナフィラキシーを含むアレルギー反応は、既存の FVIII 製剤で報告されている。その他の背景情報の詳細は、2.7.4.1.2.4.4 を参照のこと。

すべての N8-GP の臨床試験において、アレルギー反応は特に注目すべき医学的事象として報告された（2.7.4.2.1.1.1）。すべてのアレルギー反応を確実に特定するため、NNMQ「アレルギー反応」による検索（狭域及び広域）を行った。本 NNMQ に含まれる基本語は、付録 1、表 2.7.4.7.1-86（広域）及び表 2.7.4.7.1-95（狭域）に提示する。狭域検索の結果は、付録 1、表 2.7.4.7.1-23～25 を参照のこと。

狭域検索と広域検索の結果の傾向は一致していたが、予測された通り、特定された有害事象の発現頻度は広域検索に比べて狭域検索で大幅に低かった。以下のアレルギー反応に関する記述は、広域検索に基づくものである。

本 NNMQ 広域検索により、105 例（39%）217 件の有害事象が特定された（付録 1、表 2.7.4.7.1-20）。最も高頻度で報告された有害事象（基本語別）は、咳嗽〔37 例（14%）53 件〕、湿疹〔15 例（5.6%）19 件〕、季節性アレルギー〔14 例（5.2%）19 件〕及び発疹〔14 例（5.2%）18 件〕であった。

これらの有害事象の大部分は非重篤かつ軽度又は中等度であり、治験責任医師により N8-GP との因果関係は「なし」と判定された（付録 1、表 2.7.4.7.1-65）。3 件は重度であり、このうち 2 件は重篤な有害事象として報告された（付録 1、表 2.7.4.7.1-22）。

以下に 2 件の重篤な有害事象〔過敏症（N8-GP との因果関係が「あり」と判定された）及び循環虚脱（N8-GP との因果関係は「なし」と判定された）〕の詳細について記述する：

- 3885 試験の 1 例（被験者番号[redacted]、[redacted]歳）において過敏症が発現し、重篤な有害事象として報告された。当該被験者は、中止・脱落基準「治験薬に関連するアレルギー／アナフィラキシー反応」に合致したため、治験を中止した。N8-GP の初回投与後に軽度の I 型アレルギー反応が発現し、4 回目の投与後に重度のアレルギー反応が発現した。いずれの事象も治療を必要とせず、臨床症状は 2 時間後に消失した。治験中止までの N8-GP の曝露日数は 4 日であった。低力価の抗 PEG 抗体（ベースライン時に報告され、経時的に力価が低下した）を除き、N8-GP 及び HCP に対する IgM、IgG 又は IgE 抗体は検出されなかった。また、PEG に対する IgE 抗体も検出されなかった。その後、他の非 PEG 化 rFVIII 製剤へ切り替えられたが、同様の有害反応が認められたため、PEG が原因ではないことが示唆された。切り替え後の 2 回目の投与時には、治験中止に至った有害事象と同様の嘔吐が発現した。治験責任医師は胃腸障害を排除できなかった。最終フォローアップ時点で、当該被験者は上記 rFVIII 製剤の週 1〜3 回投与（自宅注射）を継続しており、治験中止後に複数回投与していた。当該被験者における抗体測定に関する詳細は、Integrated summary of immunogenicity（Module 5.3.5.3, Section 5.2）を参照のこと。
- 3859 試験の 1 例（被験者番号[redacted]、[redacted]歳）において循環虚脱が発現し、重篤な有害事象として報告された。治験責任医師の記述は「circulatory collapse relating to injection of 'resin bomb' of methylenedioxymethamphetamine (MDMA)」であった。治験責任医師により N8-GP との因果関係は「なし」と判定された。

7 例で報告された 13 件の有害事象は、治験責任医師により N8-GP との因果関係が「あり」又は「可能性あり」と判定された。上記の重篤な有害事象である過敏症を除き、これらの有害事象の重症度はすべて軽度又は中等度であった（表 2.7.4.2-7）。

表 2.7.4.2-7　治験責任医師により N8-GP との因果関係が「あり」又は「可能性あり」と判定されたアレルギー反応 – NNMQ 広域検索

被験者番号／試験	年齢	MedDRA 基本語	曝露日数	因果関係	重症度	重篤／非重篤	転帰
[redacted]/ 3859	[redacted]	発疹	1	あり	中等度	非重篤	回復
		発疹	123	あり	軽度	非重篤	回復
[redacted]/ 3859		紅斑	9	あり	軽度	非重篤	回復
		紅斑	10	あり	軽度	非重篤	回復
		紅斑	11	あり	軽度	非重篤	回復
[redacted]/ 3859		発疹	22	可能性あり	軽度	非重篤	回復
[redacted]/ 3859		そう痒症	14	可能性あり	軽度	非重篤	回復
[redacted]/ 3885		過敏症	1	あり	軽度	非重篤	回復
		過敏症	4	あり	重度	重篤	回復
[redacted]/ 3885		咳嗽	4	可能性あり	軽度	非重篤	回復
[redacted]/ 3885		発疹	68	可能性あり	軽度	非重篤	回復
		発疹	72	可能性あり	軽度	非重篤	回復
		発疹	79	あり	軽度	非重篤	回復

N8-GP との因果関係が「あり」又は「可能性あり」と判定された 13 件の有害事象（表 2.7.4.2-7）のうち、以下の 2 例で報告された 5 件は治験責任医師により特に注目すべき医学的事象として報告された（付録 1、表 2.7.4.7.1-64）：

- 3859 試験の 1 例（被験者番号[redacted]、[redacted]歳）において、2 件の発疹が発現した。1 件目の発疹は中等度であり、N8-GP の初回投与から 1 時間 30 分後に発現した。被験者は N8-GP による予防治療を継続し、その後の 3 週間で N8-GP 投与後に発疹症状が複数回みられた。その後、被験者は回復した。2 件目の発疹は軽度であり、123 曝露日数時点で発現した。痒みを伴う発疹が徐々に進展し、両腕、背部、腹部及び陰嚢に拡大した。いずれの事象も治療を必要とせず、被験者は回復した。これらの事象は、治験責任医師により N8-GP との因果関係が「あり」と判定された。
- 3859 試験の 1 例（被験者番号[redacted]、[redacted]歳）において、3 件の N8-GP 注射部位周辺における軽度の紅斑が発現した。3 件とも軽度であった。いずれの事象も治療を必要とせず、被験者は回復した。これらの事象は、治験責任医師により N8-GP との因果関係が「あり」と判定された。

ノボ ノルディスク社は、NNMQ「アレルギー反応」の広域検索により特定された有害事象の大部分は、他の病因により説明される、もしくは時期的な関連性は認められないと評価した。N8-GP との因

果関係が「あり」又は「可能性あり」と判定された事象はわずかであった。ノボ ノルディスク社の評価では、発疹、紅斑、そう痒症及び過敏症は副作用と考えられた（2.7.4.2.1.7 及び付録 3）。

2.7.4.2.1.6.3　血栓塞栓性事象

すべての N8-GP の臨床試験において、血栓塞栓性事象は特に注目すべき医学的事象として報告された。すべての血栓塞栓性事象を確実に特定するため、SMQ「塞栓および血栓」による検索を行った。本 SMQ に含まれる基本語は、付録 1、表 2.7.4.7.1-87 に提示する。

本臨床開発プログラムでは、確定診断された血栓塞栓性事象の報告はなかった。3859 試験において、以下 1 件の血栓塞栓性事象の疑いが報告された（付録 1、表 2.7.4.7.1-26 及び 66）：

- 3859 試験の 1 例（被験者番号 [redacted][i]、[redacted]歳）において、頭部 MRI 実施後に微小脳梗塞の疑い（基本語「脳梗塞」に分類）が認められ、重篤な有害事象として報告された。しかしながら、確定診断はされず、治験責任医師及びノボ ノルディスク社により N8-GP との因果関係は「なし」と判定された。本事象は 168 曝露日後に発現した。当該被験者は N8-GP の投与を継続し、転帰は未回復であった。同時に脳微小出血の疑いが報告された。これら 2 件の病因として、原疾患（血友病）、血管炎及び感染後が治験責任医師により報告された。

非臨床及び臨床試験で得られた広範なデータに基づき、血栓塞栓性事象は N8-GP の安全性上の懸念には含まれないとノボ ノルディスク社は評価した。このことは、血友病 A 患者では血栓症のリスクが高いにも関わらず、血栓塞栓性合併症は非常に稀であることを示した公表文献からも支持される[17]。また、N8-GP のような高純度の FVIII 製剤では、血栓塞栓性合併症のリスクは低いと考えられている[18]。投与後の FVIII 活性ピーク時における N8-GP の安全性プロファイルは、他の FVIII 製剤での報告と同様と考えられた。

2.7.4.2.1.6.4　投薬過誤

すべての N8-GP の臨床試験において、投薬過誤は特に注目すべき医学的事象として報告された。すべての潜在的な投薬過誤を確実に特定するため、SMQ「投薬過誤」による検索を行った。本 SMQ に含まれる基本語は、付録 1、表 2.7.4.7.1-89 に提示する。

本 SMQ 検索により、6 例 6 件の有害事象（3859 試験：製品調製過誤、過量投与及び偶発的過量投与、3885 試験：偶発的過量投与、薬剤誤投与及び投薬過誤）が特定された（付録 1、表 2.7.4.7.1-28）。これらの事象はすべて軽度であり、転帰は「回復」であった（付録 1、表 2.7.4.7.1-68）。いずれの投薬過誤についても、それに関連する有害事象は報告されなかった。

[i] 注：当該被験者の 3859 試験における被験者番号は [redacted] であったが、併合データにおける識別コードは NN7088_3776/[redacted] である（2.7.4.2.1.1.2 及び付録 1、表 2.7.4.7.1-94）。

以下の小児患者において最も高い用量が投与された：

- 3885 試験の 1 例（被験者番号[redacted]）は N8-GP の 2000 IU バイアル 4mL を処方されたが、誤って 8mL（114 IU/kg に相当）を投与した。被験者は過量投与後 1 時間に渡って観察されたが、臨床症状は認められなかった。過量投与後の FVIII 活性は 285%であった〔3885 試験（Module 5.3.5.2, Appendix 16.2.6, Listing 16.2.6.7）〕。当日中に被験者は回復した。N8-GP の過量投与に関連する症状は認められなかった。

2.7.4.2.1.6.5　治験薬による病原体感染の疑い

治験薬が滅菌条件下で製造されていない等の理由によって治験薬が病原体感染の原因となる場合、当該治験薬の使用は安全ではなく、重大な事態を引き起こす可能性がある。N8-GP によるウイルス及びその他の血行性感染因子の感染リスクは、実質的に排除されている。N8-GP の原薬は、特性が十分に解明されており、既知の感染因子のない哺乳類の CHO 細胞株内で、細胞培養培地において血清又は他の動物由来成分を使用せずに産生される。

現在、ノボ ノルディスク社が実施する臨床試験では、病原体感染の生じた場合には重篤な有害事象として報告することを標準としている。しかしながら、N8-GP の臨床試験の治験実施計画書作成時点では、病原体感染は特に注目すべき医学的事象として報告する手順であった。すべての病原体感染を確実に特定するため、NNMQ 検索「病原体感染」による検索を行った。本 NNMQ 検索に含まれる基本語は、付録 1、表 2.7.4.7.1-92 に提示する。

N8-GP の臨床試験において、治験薬による病原体感染の疑いがある事象は認められなかった（付録 1、表 2.7.4.7.1-35 及び 71）。

2.7.4.2.1.6.6　注射部位反応

注射部位反応は、FVIII 製剤の注射における既知の事象である。潜在的な注射部位反応を特定するため、NNMQ「注射部位反応」による検索を行った。本 NNMQ に含まれる基本語は、付録 1、表 2.7.4.7.1-93 に提示する。

本 NNMQ 検索により、7 例 7 件の有害事象（3859 試験：注入部位反応、注射部位反応、注射部位紅斑、注射部位発疹、血管穿刺部位血腫及び血管穿刺部位疼痛、3885 試験：注射部位腫脹）が特定された（付録 1、表 2.7.4.7.1-36）。これらの事象はすべて軽度又は中等度であり、大部分の被験者が回復した（付録 1、表 2.7.4.7.1-72）。

注射部位反応は、静脈内投与の薬剤に固有の潜在リスクであり、一般的に注射手技にも関連する。N8-GP の臨床試験で報告された注射部位反応の大部分は、治験責任医師により N8-GP との因果関係は「なし」と判定された。2 件（3859 試験の注射部位反応及び 3885 試験の注射部位膨張）は、治験責任

医師により N8-GP との因果関係が「あり」又は「可能性あり」と判定された（付録 1、表 2.7.4.7.1-72）。

NNMQ 検索により特定された注射部位反応は、副作用と考えられた（詳細は、付録 3 を参照のこと）。

2.7.4.2.1.6.7　薬剤性肝障害

SMQ「薬剤性肝障害」による検索を行った。本 SMQ に含まれる基本語は、付録 1、表 2.7.4.7.1-90 に提示する。

1970 年代から 1980 年代初期にかけて、多くの血友病 A 患者が血漿由来製剤、クリオ製剤又は新鮮凍結血漿製剤の投与を介して C 型肝炎に感染した。本臨床開発プログラムでは、120 例（44%）がベースライン時に C 型肝炎に感染していた（付録 1、表 2.7.4.7.1-55）。また、6 例（2%）がベースライン時に B 型肝炎に感染しており、その半数は C 型肝炎についても陽性であった。

本 SMQ 検索により、34 例（13%）74 件の有害事象が特定された（付録 1、表 2.7.4.7.1-29）。これらの事象が発現した被験者の大部分（34 例中 22 例）は C 型肝炎及び／又は B 型肝炎陽性であり、それが原因と考えられた（付録 1、表 2.7.4.7.1-69）。74 件中 2 件（肝腫大及び血中アルカリホスファターゼ増加）は小児患者で報告されたが、いずれの事象も転帰は回復であり、安全性上の懸念は認められなかった。

78 件中 58 件は治験責任医師により N8-GP との因果関係は「なし」と判定された。また、大部分の有害事象は非重篤、かつ軽度又は中等度であった。

2 例では重度の有害事象として報告された〔重篤な有害事象として報告された胃静脈瘤出血（下記参照）、ならびに 3859 試験の 1 例（被験者番号[redacted]）で同時に発現した 3 件の事象（γ－グルタミルトランスフェラーゼ増加、アラニンアミノトランスフェラーゼ増加及びアスパラギン酸アミノトランスフェラーゼ増加）〕。すべての事象が治験責任医師により N8-GP との因果関係は「なし」と判定され、両被験者ともに回復した。

以下 3 件は重篤な有害事象として報告されたが、いずれも治験責任医師により N8-GP との因果関係は「なし」と判定された（付録 1、表 2.7.4.7.1-69）：

- 3859 試験の 1 例（被験者番号[redacted]、[redacted]歳）において、肝細胞癌が重篤な有害事象として報告された。本事象は 135 曝露日後に発現し、重症度は中等度であった。当該被験者は C 型肝炎陽性であった。治験責任医師により N8-GP との因果関係は「なし」と判定された。当該被験者は治験を中止した（2.7.4.2.1.5.1）。
- 3859 試験の 1 例（被験者番号[redacted]、[redacted]歳）において、胃静脈瘤が重篤な有害事象として報告された。本事象は 2 曝露日後に発現し、重症度は中等度であった。当該被験者は C 型肝炎陽性であった。被験者は本事象から回復した。治験責任医師により N8-GP との因果関係は「なし」と判定された。

- 3859 試験の 1 例（被験者番号[redacted]、[redacted]歳）において、胃静脈瘤出血が重篤な有害事象として報告された。本事象は 117 曝露日後に発現し、重症度は重度であった。当該被験者は C 型肝炎陽性であった。被験者は本事象から回復した。治験責任医師により N8-GP との因果関係は「なし」と判定された。

20 件の有害事象は治験責任医師により N8-GP との因果関係が「あり」又は「可能性あり」と判定されたが、これらの事象はすべて非重篤、かつ軽度（19 件）又は中等度（1 件）であり、大部分の転帰は「回復」であった（付録 1、表 2.7.4.7.1-69）。

全体的に、肝酵素上昇に関連する有害事象は一過性であり、異常値の経時的な分布に明らかな傾向は認められなかった。肝酵素の評価の概要は、2.7.4.2.1.8 を参照のこと。

肝障害を有する患者における N8-GP の安全性プロファイルは、正常な肝機能を有する患者と同様であると考えられる。

結論として、これまでに得られているデータからは、N8-GP の長期曝露による血友病患者の肝機能に対する悪影響は示唆されていない。N8-GP の投与に関連する肝障害に関する有害事象の全体的なリスクは、非常に低いと考えられる。

2.7.4.2.1.6.8　腎障害

SMQ「急性腎不全」による検索を行った。本 SMQ に含まれる基本語は、付録 1、表 2.7.4.7.1-91 に提示する。

本 SMQ 検索により、4 例（1.5%）6 件の有害事象が特定された（付録 1、表 2.7.4.7.1-32）。3 例で 5 件の血清クレアチニン増加が報告されたが、これらの事象はすべて非重篤、かつ軽度又は中等度であり、転帰は「回復」であった（付録 1、表 2.7.4.7.1-33 及び 70）。また、治験責任医師により N8-GP との因果関係は「なし」と判定された。上記 4 例における血清クレアチニンのすべての結果は、付録 1、表 2.7.4.7.1-70 を参照のこと。

重篤な有害事象として、以下 1 件の尿細管間質性腎炎が報告された（付録 1、表 2.7.4.7.1-34）：

- 3859 試験の 1 例（被験者番号[redacted]、[redacted]歳）は 110 曝露日後に尿細管間質性腎炎と診断され、重篤な有害事象として報告された。当該被験者の関連する既往歴には、慢性 C 型肝炎、肝細胞癌手術及び糖尿病が含まれた。N8-GP の 109 曝露日後に、治験責任医師により尿路感染によるグラム陰性桿菌敗血症と診断された。敗血症に関連する徴候として、腎障害により引き起こされる播種性血管内凝固が発現した。治験責任医師により N8-GP との因果関係は「なし」と判定された。当該被験者はコルチコステロイドによる治療を拒否し、2015 年 9 月 8 日に転帰は「軽快」と報告された。ステロイド療法なしではそれ以上の症状の改善が期待されないため、転帰は「軽快」と判断された。

結論として、これまでに得られているデータからは、N8-GP の長期曝露による血友病患者の腎機能に対する悪影響は示唆されていない。N8-GP の投与に関連する腎障害に関する有害事象の全体的なリスクは、非常に低いと考えられる。

2.7.4.2.1.6.9　稀な有害事象

NNMQ「稀な有害事象」による検索を行った。本 NNMQ に含まれる基本語は、付録 1、表 2.7.4.7.1-88 に提示する。

本 NNMQ 検索において、安全性上の懸念は認められなかった。本 NNMQ 検索により、31 例（11.5%）37 件の有害事象が特定された。これらの有害事象は 9 種類の器官別大分類に渡っており、クラスターはみられなかった（付録 1、表 2.7.4.7.1-27 及び 67）。心室性期外収縮、ジルベール症候群、胃静脈瘤、好中球減少症及び血小板減少症（各 2 件）、ならびに肝線維症（3 件）を除き、すべての有害事象（基本語別）は 1 件のみの報告であった。

2.7.4.2.1.7　副作用

累積データに基づき、ノボ ノルディスク社はすべての有害事象について N8-GP との因果関係を評価した。本評価は医学的判断に基づいて行った（付録 3 参照）。本評価に基づき、治療歴のある患者に対して N8-GP を投与したときに予期される副作用を表 2.7.4.2-8 に示す。

表 2.7.4.2-8　治療歴のある患者における副作用

MedDRA 器官別大分類	MedDRA 基本語	発現頻度（%）	発現頻度分類
皮膚および皮下組織障害	発疹	14/270 (5.2%)	一般的
皮膚および皮下組織障害	紅斑	5/270 (1.9%)	一般的
皮膚および皮下組織障害	そう痒症	4/270 (1.5%)	一般的
一般・全身障害および投与部位の状態	注射部位反応 [a]	7/270 (2.6%)	一般的
免疫系障害	過敏症	2/270 (0.7%)	一般的でない
血液およびリンパ系障害	第ＶＩＩＩ因子抑制 [b]	1/235[c] (0.4%)	一般的でない

a：注射部位反応には以下の基本語が含まれる：注入部位反応、注射部位反応、注射部位紅斑、注射部位発疹、血管穿刺部位血腫、血管穿刺部位疼痛及び注射部位膨張。

b：FVIII インヒビターを発生した被験者の定義は、最初の検査結果が 0.6 BU 以上であり、2 週間以内に採取した 2 回目の検体で確定された被験者である（2.7.4.1.2.4.3）。

c：分母の被験者数は、N8-GP の曝露日数が 50 日以上である被験者及び曝露日数に関わらず FVIII インヒビターが発生した被験者の合計である（2.7.4.1.2.3.4）。

2.7.4.2.1.8　PEG に関する安全性評価

背景情報

PEG 化は薬剤の循環血中半減期の延長に広く用いられている確立された技法である[19]。PEG は添加剤又は薬物付加体として、食品、化粧品及び医薬品において広く使用されている。多くの PEG 化製剤が既承認又は開発中であり、PEG の非臨床プロファイルが十分に明らかにされている [19,20,21,22,23,24,25,26,27,28]。他の PEG 化タンパクを用いた長期非臨床試験の公表文献では、マクロファージ内、ならびに腎臓、肝臓及び脈絡叢といった排出器官の細胞内における空胞形成が認められている [26]。PEG に関連した空胞形成による細胞反応（炎症、変性又は壊死等）は認められておらず、動物における有害作用及び *in vivo* での機能変化も生じなかった。公表文献では、臨床用量の PEG は活性がなく、機能的変化及び毒性変化を起こさないと結論付けられた [20,21,22,23,24,25]。PEG を結合させたタンパクは、その薬理作用及び毒性作用に影響することなく、作用の延長を除いて PEG の影響は全く又はほぼ受けないと考えられる。

N8-GP の 40 kDa PEG の曝露により生じる可能性がある安全性シグナルは、N8-GP の安全性評価において特に注視し、非臨床試験及び臨床試験の両方で検討した。理論上、PEG との関連が疑われる、腎臓、肝臓及び脈絡叢の機能に関する有害所見を特定することに留意した。N8-GP 投与後の PEG の潜在的な臨床上の影響を評価した結果、安全性上の懸念は認められなかった（詳細は下記参照）。

非臨床データ

N8-GP の非臨床安全性評価では、最長 52 週間の長期投与試験を実施し、頑健な非臨床安全性の評価が可能であった。N8-GP の長期毒性試験において、PEG との関連が疑われる安全性上の懸念は認められなかった。

N8-GP の PEG 部分は広範囲に分布し、経時的に血漿中及び組織中から消失し、その後、尿及び糞便中に排泄されることが示された。

N8-GP の長期毒性試験では、PEG の脳への局在を評価するため、高感度の免疫組織染色を用いて脳組織（脈絡叢を含む）を検討した。ラットに N8-GP を 52 週間反復投与（最大 1,200 IU/kg を 4 日に 1 回投与）したが、脳組織又は脈絡叢のいずれからも N8-GP の PEG は検出されなかった。

詳細は、Module 2.4.5 及び Module 2.4.6 を参照のこと。

臨床データ

ノボ ノルディスク社は、N8-GP の長期投与後の PEG による臨床的影響について検討するため、本臨床開発プログラムから得られたすべての安全性データを評価し、特に神経系、腎臓及び肝臓に関連する所見を注視した。臨床試験で N8-GP の投与を受けた被験者において、PEG に関連する安全性上の懸念は認められなかった。N8-GP の投与を受けた被験者（計 270 例）の曝露期間は、192 例（63 例の小児患者を含む）で 3 年以上、139 例（15 例の小児患者を含む）で 4 年以上、18 例（小児患者を含まない）

で 5 年以上であった（表 2.7.4.1-3）。これらの評価は、臨床試験における通常の安全性評価の方法で得られるデータに基づいて行った（評価の詳細は下記参照）。

神経系障害及び精神障害に関する評価

臨床試験では身体所見の一部として神経学的評価を実施し、中枢及び末梢神経系の一般的評価、筋骨格系の機能評価、ならびに全身の外観を含めた。これらの評価は、治験実施機関の手順に従って実施した。臨床試験を通じてこれらの有害事象を収集し、身体所見に関する臨床的に問題となる変化について記録した。器官別大分類「神経系障害」及び「精神障害」に分類された有害事象を慎重に評価した結果、安全性上の懸念は認められなかった。これらの有害事象の要約は、付録 1、表 2.7.4.7.1-38 を参照のこと。被験者ごとの有害事象の詳細な記述は、個々の治験総括報告書（Module 5）を参照のこと。

器官別大分類「神経系障害」に含まれた有害事象のうち、最も高頻度に報告された事象（基本語）は、頭痛〔56（21%）例 118 件〕であった（付録 1、表 2.7.4.7.1-38）。これらの頭痛はすべて非重篤、かつ軽度又は中等度であり、特定の異常傾向は認められなかった。特筆すべきことは、個々の被験者における頭痛の臨床症状は、N8-GP の投与期間中と投与前で同様であった。

数例の被験者では有害事象として頭痛が複数回発現したが、概して持続期間は短かった。ごく一部の被験者における頭痛は、未回復の長期に渡る事象として誤って解釈される可能性があるが、治験責任医師が個々の頭痛を遡及的に報告することの事務的な負荷により有害事象報告を完了しなかった（すなわち、未回復）ことが原因であり、報告形式における偶発的なものといえる。

全体的に、いずれの被験者においても、頭痛の発現、持続期間及び時期について、N8-GP の投与との関連は認められなかった。同様に、N8-GP の投与期間及び総曝露量との関連もみられなかった。

器官別大分類「神経系障害」及び「精神障害」に分類されたその他の有害事象は、様々な基本語の事象であり、数例でのみ報告された（付録 1、表 2.7.4.7.1-38）。

器官別大分類「神経系障害」に含まれた事象のうち、3 例で報告された 4 件は重篤な有害事象として報告された〔同一被験者における脳微小出血の疑い及び脳梗塞（2.7.4.2.1.6.3）、ならびに失神及び痙攣発作〕（付録 1、表 2.7.4.7.1-61）。また、器官別大分類「精神障害」に含まれた 1 件のうつ病が重篤な有害事象として報告された。これらの重篤な有害事象はすべて成人患者での報告であり、治験責任医師により N8-GP との因果関係は「なし」と判定された。

以上のように、神経系障害及び精神障害に関連する副作用は特定されず、N8-GP の PEG 部分に起因すると考えられる事象は認められなかった。

腎機能に関する評価

3859 及び 3885 試験では、腎機能パラメータとして血清クレアチニンの測定を定期的に行った。いずれの年齢グループにおいても、N8-GP の投与期間中（最長 48 ヵ月）に血清クレアチニンが異常値へ変

動する傾向は認められなかった（付録 1、図 2.7.4.7.1-83～85）。特筆すべきことは、多くの成人患者は腎機能及びクレアチニンに影響を及ぼすことが知られている併発疾患[29,30]を有していた。48 ヵ月の N8-GP の投与期間中に血清クレアチニンの異常値（1 時点のみでの観察）が認められたのは数例のみであり、5 件の血清クレアチニン増加が有害事象として報告された。腎障害に関連する有害事象が報告された 4 例における血清クレアチニンのすべての結果は、付録 1、表 2.7.4.7.1-70 を参照のこと。上記 5 件の血清クレアチニン増加は、すべて非重篤、かつ軽度又は中等度であり、転帰は「回復」であった。また、治験責任医師により N8-GP との因果関係は「なし」と判定された。以上のことから、N8-GP の投与に関連する腎障害に関する有害事象の全体的なリスクは、非常に低いと考えられる（2.7.4.2.1.6.8）。

結論として、N8-GP の投与期間中に安全性上の懸念は認められておらず、これまでに得られているデータからは、いずれの年齢グループにおいても、N8-GP の長期曝露による血友病患者の腎機能に対する悪影響は示唆されていない。

肝機能に関する評価

肝障害に関連する有害事象を発現したすべての被験者のデータについて、詳細な医学的検討を行った〔SMQ 検索により特定（2.7.4.2.1.6.7）〕。また、肝酵素の経時的変化についても詳細に評価した。その結果、安全性上の懸念は認められなかった。

3859 及び 3885 試験では、主要な肝機能パラメータとして、総ビリルビン、アスパラギン酸アミノトランスフェラーゼ（ASAT）、アラニンアミノトランスフェラーゼ（ALAT）、γ-グルタミルトランスフェラーゼ（GGT）の測定を定期的に行った。すべての生化学的検査項目及びそれらの採血頻度は、3859 試験延長期間パート 2（Module 5.3.5.2, Section 9.5.5.3）及び 3885 試験延長期間（Module 5.3.5.2, Section 9.5.5.3）を参照のこと。

数例の成人患者において、肝酵素上昇がみられた。これらの異常値の一部は、有害事象として報告された（2.7.4.2.1.6.7）。これらの肝機能パラメータについて、いずれの年齢グループにおいても、試験期間を通じてベースラインからの系統的な変化及び異常傾向はみられず、N8-GP の曝露との経時的な関連も示唆されなかった。試験期間中に肝機能パラメータが正常範囲を超えた成人患者は、概してベースライン時に C 型肝炎陽性であり、異常値が認められた（3859 試験の 161 例中 109 例）。C 型肝炎陰性の被験者における肝酵素上昇の所見はすべて一過性であり（大部分は 1 時点のみでの観察）、異常値の経時的分布に明らかな傾向は認められなかったことから、健康被験者における一般的な変動と同様であることが示唆された[31,32]。

結論として、N8-GP の投与期間中に安全性上の懸念は認められておらず、これまでに得られているデータからは、いずれの年齢グループにおいても、N8-GP の長期曝露による血友病患者の肝機能に対する悪影響は示唆されていない。

2.7.4.2.1.9　N8-GP の原薬製造工程別の安全性

本臨床開発プログラムの期間中に、N8-GP 原薬の製造を[redacted]し、原薬製造工程を最適化した。2 つの原薬製造工程による N8-GP は、物理的・化学的特性、非臨床薬物動態／薬力学的特性及び免疫原性の点において同等であることが示された（Module 3.2.S.2.6.1 及び 2.4.4.8）。4033 試験では、2 つの原薬製造工程による N8-GP の薬物動態は同様であることが示唆された（Module 2.7.1.2.2）。

4033 試験において、2 つの原薬製造工程による N8-GP の単回投与後の安全性を検討した。FVIII インヒビターが発生した被験者はいなかった。また、抗体、有害事象、バイタルサイン、身体所見及び臨床検査の結果について、安全性シグナルは認められなかった。全体的に、2 つの原薬製造工程による N8-GP の単回投与時の安全性プロファイルは同様であった〔4033 試験（Module 5.3.5.2, Section 12）〕。

第 3 相試験（青年及び成人患者を対象とした 3859 試験、ならびに小児患者を対象とした 3885 試験）では、N8-GP（[redacted]実生産工程）及び N8-GP（[redacted]実生産工程）の反復投与時の安全性を評価した。Cut-off date までに、2 試験の 254 例中 92 例が N8-GP（[redacted]実生産工程）へ切り替えた（表 2.7.4.1-4）。総曝露日数は、N8-GP（[redacted]実生産工程）（5,217 日）よりも N8-GP（[redacted]実生産工程）（74,076 日）の方が多かった（表 2.7.4.2-9）。

第 3 相試験において、N8-GP（[redacted]実生産工程）投与後の安全性プロファイルに新たな傾向は認められなかった。本評価は、有害事象、重篤な有害事象、死亡及び抗体発生（FVIII インヒビター、抗 N8-GP 抗体、抗 PEG 抗体及び抗 CHO HCP 抗体）に基づいている。N8-GP の原薬製造工程別の有害事象の要約を表 2.7.4.2-9 に示す。有害事象の単位時間あたりの発現件数及び種類は、原薬製造工程変更前後の N8-GP 間で同様であった〔付録 1、表 2.7.4.7.1-52（すべての有害事象）、付録 1、表 2.7.4.7.1-53 及び 54（重篤な有害事象）〕。N8-GP（[redacted]実生産工程）投与後に、死亡、インヒビター発生、重度のアレルギー反応の報告はなかった（付録 1、表 2.7.4.7.1-63～65）。また、抗 N8-GP 抗体、抗 PEG 抗体及び抗 CHO HCP 抗体の発生についても、原薬製造工程変更前後の N8-GP 間で違いはみられなかった〔Integrated summary of immunogenicity（Module 5.3.5.3, Section 5.3）〕。

有害事象発現時に被験者が投与していた製剤〔N8-GP（[redacted]実生産工程）又は N8-GP（[redacted]実生産工程）〕に関する情報は、すべての有害事象一覧（付録 1）に記載している。

表 2.7.4.2-9　　N8-GP の原薬製造工程別の有害事象の要約（3859 及び 3885 試験）

	Pivotal process N(%) E[R]		Commercial process N(%) E[R]	
Number of patients	254		92	
Patient years of exposure	824.02		54.40	
Exposure days	74076		5217	
All adverse events	233(91.7)	2186[2.65]	48(52.2)	98[1.80]
Serious adverse events	45(17.7)	65[0.08]	1(1.1)	1[0.02]
Non serious adverse events	231(90.9)	2121[2.57]	48(52.2)	97[1.78]
Severity				
Mild	217(85.4)	1714[2.08]	42(45.7)	82[1.51]
Moderate	147(57.9)	405[0.49]	14(15.2)	16[0.29]
Severe	42(16.5)	66[0.08]		-
Missing	1(0.4)	1[0.00]		-
Relationship				
Probably or possibly	39(15.4)	82[0.10]		-
Unlikely	230(90.6)	2096[2.54]	48(52.2)	98[1.80]
Missing	4(1.6)	8[0.01]		-
Adverse events				
Leading to withdrawal	7(2.8)	7[0.01]		-

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Exposure to N8-GP from the different production methods is accounted from the scheduled visit where product was first dispensed.

nn7088/nn7088-filing/sum_20171208_er
09DEC2017:10:49:15 - t_teae_ov.sas/t_274200350_teae_ov_pmethod.txt

2.7.4.2.2　　個別有害事象の文章による説明

3776、3859、4033、3885 及び 3860 試験における、死亡、重篤の有害事象、特に注目すべき医学的事象及び治験中止の叙述は、個々の治験総括報告書〔3776 試験（Module 5.3.5.2, Section 14.3.3）、3859 試験延長期間パート 2（Module 5.3.5.2, Section 14.3.3）、3885 試験延長期間（Module 5.3.5.2, Section 14.3.3）、3860 試験（Module 5.3.5.2, Section 14.3.3）及び 4033 試験（Module 5.3.5.2, Section 14.3.3）〕を参照のこと。治療歴のない患者を対象とした実施中の試験（3908 試験）における、死亡（該当なし）、重篤な有害事象及び特に注目すべき医学的事象の叙述は、付録 2 を参照のこと。

2.7.4.3 臨床検査値の評価

2.7.4.3.1　　免疫原性

FVIII インヒビター

すべての被験者において FVIII インヒビター検査を実施し、検出されたすべてのインヒビターは、有害事象及び特に注目すべき医学的事象として記録された。治療歴のある患者で 1 件の FVIII インヒビター発生が報告された。本事象の概要及び詳細は、2.7.4.2.1.6.1 及び Integrated summary of immunogenicity（Module 5.3.5.3, Section 5.1.2）を参照のこと。

3885 試験の 2 例（被験者番号[redacted]及び[redacted]）において、それぞれ 1 回の来院で 1 件の FVIII インヒビター検査陽性が報告されたが、2 回目の検査では陰性であった。そのため、治験実施計画書で規定した FVIII インヒビター発生の基準に合致しなかった（2.7.4.1.2.4.3）。詳細は、Integrated summary of immunogenicity（Module 5.3.5.3, Section 5.1.2）を参照のこと。

別の 2 例（3885 試験の被験者番号[redacted]及び 3776 試験の被験者番号[redacted]）では、N8-GP 初回投与前のインヒビター検査が陽性であった〔3885 試験（Module 5.3.5.2, Table 10-2）及び 3776 試験（Module 5.3.5.2, Section 10.1）〕。いずれの被験者も、後にスクリーニング不適格と考えられた。

治療歴のない患者を対象とした 3908 試験（実施中）において FVIII インヒビター発生が認められた 4 例の詳細は、2.7.4.2.1.6.1 及び 2.7.4.5.2 を参照のこと。

その他の抗体

すべての臨床試験において、抗 N8-GP 非中和抗体及び抗 PEG 抗体の評価を行った。また、重度のアレルギー／アナフィラキシー反応の発現時には、抗 CHO HCP 抗体の評価を実施した。3859 及び 3885 試験では、抗 N8-GP 抗体評価のために十分な量の血液検体を採取している場合、当該検体を用いて抗 CHO HCP 抗体についての定期的な分析も実施する旨を治験実施計画書に追記した。本改訂は、N8-GP 原薬の製造施設及び工程の変更後の検体を収集する目的で行った。以下に結果の概要を示す。詳細は、Integrated summary of immunogenicity（Module 5.3.5.3）及び付録 2 を参照のこと。

3859 及び 3885 試験の計 6 例において抗 N8-GP 抗体が検出され、このうち 2 例は N8-GP 投与開始前に陽性であった。他の 4 例では N8-GP 投与後に発生した。3 例では一過性であったが、1 例〔FVIII インヒビターが発生した被験者（2.7.4.2.1.6.1）と同一〕では持続性であった。1 例では回収率への影響がみられたが、陽性となった前後の時期に関連する有害事象は認められなかった。3860 試験で大手術を受けた被験者については、潜在的なインヒビター発生について評価するため、術後数ヵ月にわたり慎重なモニタリングを実施した。これら N8-GP の頻回投与を受けた被験者において、手術後に抗 N8-GP 抗体の発生は認められなかった。詳細は、Integrated summary of immunogenicity（Module 5.3.5.3, Section 5.1.3）を参照のこと。

3859 及び 3885 試験の計 32 例（12.6%）において、N8-GP 投与開始前に抗 PEG 抗体が検出され、その頻度は 0～5 歳の年齢グループで最も高かった（48.5%）。N8-GP 投与後に、11 例で一過性の低力価抗 PEG 抗体の発生が報告された。このうち 1 例は、最終来院でのみ陽性であった。N8-GP 投与開始前に抗 PEG 抗体を有していた 32 例中 20 例では、N8-GP 投与後に測定可能な抗 PEG 抗体は検出されなかった。抗 PEG 抗体による回収率への影響はみられず、出血頻度の増加及び陽性となった前後の時期に関連する有害事象は認められなかった。さらに、薬物動態プロファイルについて、抗 PEG 抗体陽性の被験者と陰性の被験者の間で明らかな違いはみられなかった。3860 試験で大手術を受けた被験者において、手術後に抗 PEG 抗体の発生は認められなかった。詳細は、Integrated summary of immunogenicity（Module 5.3.5.3, Section 5.1.4）を参照のこと。

3859 及び 3885 試験の計 11 例において抗 CHO HCP 抗体が検出され、このうち 2 例は N8-GP 投与開始前に陽性であった。N8-GP 投与後に 9 例で低力価の抗 CHO HCP 抗体が発生し、このうち 3 例では持続性であった。陽性となった前後の時期に、関連する有害事象は認められなかった。3860 試験で大手術を受けた被験者において、手術後に抗 CHO HCP 抗体発生は認められなかった。詳細は、Integrated summary of immunogenicity（Module 5.3.5.3, Section 5.1.5）を参照のこと。

2.7.4.3.2　血液学的検査、血液生化学的検査、凝固関連パラメータ及び尿検査

2.7.4.3.2.1　臨床検査値に関連した有害事象

臨床検査値の臨床的に問題となる変化はすべて有害事象として報告され、有害事象一覧（付録 1、表 2.7.4.7.1-38）の器官別大分類「臨床検査」及び「血液およびリンパ系障害」に含め、全体的な有害事象の解析にも含めた（2.7.4.2.1）。

2.7.4.3.2.2　血液学的検査

すべての N8-GP の臨床試験において、標準的な血液学的検査項目〔各施設で測定したヘモグロビン、赤血球数、血小板、白血球数及び白血球分画（リンパ球、単球、好中球、好酸球及び好塩基球）を含む〕について定期的に評価した〔3776 試験（Module 5.3.5.2, Section 12.4）、3859 試験（Module 5.3.5.2, Section 12.5.1）、3859 試験延長期間パート 2（Module 5.3.5.2, Sections 12.6.2 and 12.6.3）、3885 試験延長期間（Module 5.3.5.2, Sections 12.5.1 to 12.5.3）、3860 試験（Module 5.3.5.2, Section 12.5.1.2）及び 4033 試験（Module 5.3.5.2, Sections 12.5.1 to 12.5.3）〕。

これらの血液学的検査項目について、いずれの年齢グループにおいても、系統的な変化及び異常傾向はみられず、N8-GP の曝露との経時的な関連も示唆されなかった。

3860 試験（手術試験）では、予測された通りベースラインと比べて試験終了時（手術後）に赤血球数、ヘモグロビン及びヘマトクリットの減少、ならびに血小板数の増加が認められた（平均値）。そ

の他の項目についても手術中及び手術後の変動がみられたが、いずれも予測されたものであり、試験終了時には概ねベースライン値まで戻った〔3860 試験（Module 5.3.5.2, Section 12.5.1.2）〕。

2.7.4.3.2.3　血液生化学的検査

すべての N8-GP の臨床試験において、標準的な血液生化学的検査項目について評価した。全体的に、N8-GP の投与と関連すると考えられる臨床的に問題となる変化はみられなかった。認められた異常値は、治験対象集団において予想されるものであった〔3776 試験（Module 5.3.5.2, Section 12.4）、3859 試験（Module 5.3.5.2, Section 12.5.1）、3859 試験延長期間パート 2（Module 5.3.5.2, Sections 12.6.2 and 12.6.3）、3885 試験延長期間（Module 5.3.5.2, Sections 12.5.1 to 12.5.3）、3860 試験（Module 5.3.5.2, Section 12.5.1.1）及び 4033 試験（Module 5.3.5.2, Sections 12.5.1 to 12.5.3）〕。

肝臓及び腎臓関連の臨床検査項目の評価は、N8-GP の安全性評価において PEG に関連する項目として特に注視された（2.7.4.2.1.8）。

複数の被験者で肝酵素上昇が認められ、そのうち数件は有害事象として報告されたが、これらの所見からは安全性上の懸念は生じなかった。詳細は、2.7.4.2.1.6.7 及び 2.7.4.2.1.8 を参照のこと。

3 例で 5 件の血清クレアチニン増加が有害事象として報告されたが、これらの所見からは安全性上の懸念は生じなかった（2.7.4.2.1.6.8）。

3860 試験（手術試験）では、予測された通り手術後に一定の変動がみられたが、試験終了時には概ねベースライン値まで戻った〔3860 試験（Module 5.3.5.2, Section 12.5.1.1）〕。

2.7.4.3.2.4　凝固関連パラメータ

3885 及び 4033 試験を除くすべての N8-GP の臨床試験において、凝固関連パラメータについて評価した。

予測された通り、すべての試験で N8-GP 投与後の aPTT 低下が認められた。凝固関連パラメータについて、その他に臨床的に問題となる変化はみられなかった〔3776 試験（Module 5.3.5.2, Section 12.4）、3859 試験（Module 5.3.5.2, Sections 12.5.1 to 12.5.3）及び 3860 試験（Module 5.3.5.2, Section 12.5.1.3）〕。

2.7.4.3.2.5　尿検査

3776 試験において尿検査を実施したが、臨床的に問題となる変化はみられなかった〔3776 試験（Module 5.3.5.2, Section 12.4）〕。3859 試験ではベースライン時にのみ尿検査を実施した〔3859 試験（Module 5.3.5.2, Section 10.2.4）〕。

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、身体所見及び心電図検査

2.7.4.4.1.1 バイタルサイン

すべての N8-GP の臨床試験において、バイタルサインの変化を評価した。試験期間中に、特記すべき変化はみられなかった。

詳細は、3776 試験（Module 5.3.5.2, Section 12.5.1）、3859 試験延長期間パート 2（Module 5.3.5.2, Section 12.7.1）、3885 試験（Module 5.3.5.2, Section 12.6.1）、3860 試験（Module 5.3.5.2, Section 12.6.1）及び 4033 試験（Module 5.3.5.2, Section 12.6.1）を参照のこと。

3860 試験（手術試験）では、予測された通り一定の変化がみられたが、これらは手術に関連したものであり、N8-GP の投与との関連はないと考えられた〔3860 試験（Module 5.3.5.2, Section 12.6.1）〕。

2.7.4.4.1.2 身体所見

すべての N8-GP の臨床試験において、身体所見の評価を行った。多くの被験者におけるベースライン時の身体所見の異常は、被験者の原疾患及びその影響を反映したものであった。

試験期間中、新たな異常所見及び既存の異常所見の悪化について評価した。いずれの試験においても、臨床的に問題となる変化はみられなかった。また、異常所見がみられた被験者の割合に、明らかな経時変化もみられなかった。

詳細は、3776 試験（Module 5.3.5.2, Section 12.5.2）、3859 試験延長期間パート 2（Module 5.3.5.2, Section 12.7.2）、3885 試験（Module 5.3.5.2, Section 12.6.2）、3860 試験（Module 5.3.5.2, Section 12.6.2）及び 4033 試験（Module 5.3.5.2, Section 12.6.2）を参照のこと。

2.7.4.4.1.3 心電図

3776、3859、4033 及び 3860 試験において、心電図の評価を行った。全体的に、心電図所見の異常について、経時的な傾向はみられなかった。

3776 試験では、N8-GP 投与後の新たな心電図異常及び既存の異常の悪化はみられなかった〔3776 試験（Module 5.3.5.2, Section 12.5.3）〕。

3859 試験の 6 例において、「臨床的に問題となる異常」に分類された心電図所見が報告された。このうち 4 例における所見は有害事象として報告され、重篤な有害事象として報告された 1 件の肥大型心筋症（158 曝露日数時点での発現、治験責任医師により N8-GP との因果関係は「なし」と判定された）、ならびに別の青年被験者で報告された 1 件の心電図ＳＴ部分上昇（治験責任医師により N8-GP との因果関係が「可能性あり」と判定された）が含まれた。このうち後者では、治験責任医師により N8-GP との因果関係が「可能性あり」と判定された洞性不整脈及び洞性徐脈（57 曝露日数時点での発

現）も同時に報告された。これらの 3 件の重症度は軽度又は中等度であった〔3859 試験延長期間パート 2（Module 5.3.5.2, Section 12.7.3 及び Listing 16.2.7.2）〕。

3860 試験では、心電図について臨床的に問題となる所見は認められなかった〔3860 試験（Module 5.3.5.2, Section 12.6.3）〕。

4033 試験では、心電図検査はスクリーニング時にのみ実施された〔4033 試験（Module 5.3.5.2, Section 10.2）〕。

2.7.4.5 特別な患者集団及び状況下における安全性

2.7.4.5.1 内因性要因

2.7.4.5.1.1 年齢

2.7.4.5.1.1.1 2 歳未満の患者における安全性

3885 試験（小児試験）への組み入れ時点で、6 例は 2 歳未満であった（付録 1、表 2.7.4.7.1-58）。Cut-off date 時点で、これらの被験者における N8-GP の曝露日数は 337～391 日間であった（付録 1、表 2.7.4.7.1-78）。

これらの被験者において安全性上の懸念は示唆されなかった。有害事象の要約及び一覧表を付録 1、表 2.7.4.7.1-59 及び 79 に示す。報告された 53 件の有害事象のうち、2 件は重篤な有害事象として報告された〔1 件の転倒（被験者番号 [redacted]）及び 1 件の敗血症症候群（被験者番号 [redacted]）〕。いずれの事象も治験責任医師により N8-GP との因果関係は「なし」と判定された。両被験者ともに回復した。

上記 2 件の重篤かつ重度の有害事象を除き、すべての有害事象は軽度又は中等度であった。

2 例で報告された 4 件の有害事象は、治験責任医師により N8-GP との因果関係が「あり」又は「可能性あり」と判定された〔1 件の処置後合併症（被験者番号 [redacted]）及び 3 件の発疹（被験者番号 [redacted]）〕。両被験者ともに、これらの事象から回復した。その他の 49 件は、治験責任医師により N8-GP との因果関係は「なし」と判定された。

2 歳未満の年齢グループ及び 2～5 歳の年齢グループで報告されたすべての有害事象の概要及び要約は、それぞれ付録 1、表 2.7.4.7.1-58 及び 59 を参照のこと。

2.7.4.5.1.1.2 65 歳以上の患者における安全性

N8-GP の臨床試験への組み入れ時点で、3 例は 65 歳以上であった。Cut-off date 時点で、これらの被験者における N8-GP の曝露日数は 162～342 日であった（付録 1、表 2.7.4.7.1-80）。

3 例の組み入れ時点での年齢は 65～66 歳であった。これらの被験者における有害事象の一覧を付録 1、表 2.7.4.7.1-81 に示す。報告された 26 件の有害事象のうち、1 件は重篤な有害事象であった〔遠隔転移を伴う膵癌による死亡（2.7.4.2.1.3）〕。これらの被験者において安全性上の懸念は示唆されなかった。全体的に、N8-GP について加齢に伴う安全性上の懸念は認められていない。

2.7.4.5.1.2 人種

2.7.4.5.1.2.1 日本人患者における安全性

本申請の cut-off date までに、計 19 例の日本人患者が N8-GP の投与を受け、曝露量の平均は 2.18 人・年、曝露日数の中央値は 141 日（範囲：1～459 日）であった（付録 1、表 2.7.4.7.1-13 及び 77）。

日本人患者の総曝露量 41 人・年において、19 例中 15 例で計 210 件の有害事象が報告された（付録 1、表 2.7.4.7.1-56）。5 例で報告された計 12 件の有害事象は重篤な有害事象であった（付録 1、表 2.7.4.7.1-57）。これらの重篤な有害事象は、1 件のみの報告又は同一被験者における同一事象の複数の報告であり、様々な器官別大分類の事象であった。N8-GP との因果関係が「可能性あり」と判定された 1 件の椎間板炎（3859 試験の被験者番号[redacted]）を除き、すべての重篤な有害事象は治験責任医師により N8-GP との因果関係は「なし」と判定された（表 2.7.4.2-4 及び付録 1、表 2.7.4.7.1-74）。

5 例で報告された計 7 件の有害事象（椎間板炎、肝機能異常、肝機能検査異常、発疹、紫斑、発熱及びC－反応性蛋白増加）は、治験責任医師により N8-GP との因果関係が「可能性あり」と判定された。その他の 203 件の有害事象は、N8-GP との因果関係は「なし」と判定された（付録 1、表 2.7.4.7.1-73）。N8-GP との因果関係が「可能性あり」と判定された有害事象について、上記の椎間板炎（重篤かつ重度）を除き、重症度はすべて軽度であった。すべての被験者が回復した。

3859 試験の 1 例（被験者番号[redacted]）は、重篤な有害事象（肝細胞癌）により治験を中止した。本事象は、治験責任医師により N8-GP との因果関係は「なし」と判定された（付録 1、表 2.7.4.7.1-75、2.7.4.2.1.5.1 及び 2.7.4.2.1.6.7）。

全体的に、日本人と全集団の間で安全性プロファイルに違いはみられなかった。

2.7.4.5.2　外因性要因

治験対象集団の数が限られており、また、すべての N8-GP の臨床試験において対照群を設定していないため、有害事象の単位時間あたりの発現件数について、異なる外因性要因〔HIV の有無、C 型肝炎の有無、併用薬剤及び薬物相互作用等〕を有する被験者集団間で、意味のある比較及び解析を行うことはできなかった。

治療歴のない患者における安全性

実施中の 3908 試験では、治療歴のない〔凝固製剤を含む精製 FVIII 製剤による治療歴がない（血液製剤 5 曝露日数までは可）〕小児患者（年齢：6 歳未満）を対象としている。

Cut-off date までに、治療歴のない患者 32 例に対して N8-GP が投与された（総曝露日数：2,901 日、各被験者における曝露日数：1～354 日）（社内資料）。本試験は実施中であるため、データは予備的なものである。

5 例が治験を中止したが、いずれも有害事象による中止ではなかった。本試験における重篤な有害事象及び特に注目すべき医学的事象の叙述は、付録 2 を参照のこと。9 例で計 14 件の重篤な有害事象が報告された。

4 例で FVIII インヒビター発生が認められ、このうち 1 例では高力価（6.1 BU）、その他 3 例では低力価（1.0、1.6 及び 4.9 BU）であった。低力価（4.9 BU）の 1 例は同意撤回により治験を中止し、その他 3 例は治験を継続した。さらに、1 例では治験実施施設における 1 回の FVIII インヒビター検査が陽

性（1.0 BU）であったが、直後に実施された中央検査機関における検査結果は陰性であった（社内資料）。

本試験で発現したその他の重篤な有害事象には、頭部損傷、治療ノンレスポンダー、脊髄硬膜外血腫、舌損傷及び挫傷（各 1 件）、ならびに 1 例で報告された 3 件の肺炎及び同一被験者における 1 件のヘモフィルス性肺炎が含まれた。治験責任医師により N8-GP との因果関係が「あり」と判定された治療ノンレスポンダーを除き、すべての重篤な有害事象は治験責任医師により N8-GP との因果関係は「なし」と判定された。治療ノンレスポンダーは、予定されていた中心静脈アクセス機器移植後に出血過多を経験した被験者において報告された。当該被験者はバイパス製剤により治療されたが、14 曝露日数時点で有効性の欠如により治験を中止した。当該被験者は最終来院においてインヒビター陰性であったが、抗 N8-GP 抗体陽性であった。

2.7.4.5.3 薬物相互作用

薬物相互作用試験は実施していない。これまでに、N8-GP と他の医薬品との薬物相互作用は報告されていない。

2.7.4.5.4 妊娠及び授乳時の使用

動物における生殖毒性試験は実施していない。血友病 A が女性で発症することは稀であり、妊娠中及び授乳中の FVIII 製剤使用経験に関するデータは得られていない。N8-GP がヒト乳汁中に移行するかは不明である。

2.7.4.5.5 過量投与

本臨床開発プログラムにおいて、最高で 114 IU/kg の過量投与による FVIII 活性 285%への上昇が報告された（2.7.4.2.1.6.4）。過量投与に関連する症状は認められなかったため、安全性上の懸念はないものと考えられる。

2.7.4.5.6 薬物乱用

薬物乱用を検討する試験は実施していないが、N8-GP の薬物乱用の潜在性は予期されない。これまでに、薬物乱用は報告されていない。

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情報は得られていない。

2.7.4.5.8　　自動車運転及び機械操作に対する影響又は精神機能の障害

自動車運転及び機械操作に対する影響を検討した試験は実施していないが、N8-GP の投与による自動車運転及び機械操作の能力低下、ならびに精神機能の低下は示唆されていない。

2.7.4.6 市販後データ

N8-GP の製造販売後の使用経験はない。

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ツロクトコグ アルファ ペゴル（遺伝子組換え）

2.7.4.7 付録 1

ノボ ノルディスク ファーマ株式会社

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Trial Treatment	Number of patients	Patient years of exposure	Exposure days
Trial 3776			
N8-GP 25 IU/kg single dose	7	0.50	7
N8-GP 50 IU/kg single dose	9	0.60	9
N8-GP 75 IU/kg single dose	10	0.68	10
Total	26	1.77	26
Trial 3859			
N8-GP 50 IU/kg prophylaxis	177	503.65	47484
N8-GP 75 IU/kg prophylaxis	61	107.27	5783
N8-GP 20-75 IU/kg on-demand	12	33.44	1405
Total	186	644.36	54672
Trial 4033			
N8-GP 50 IU/kg single dose	19	0.42	47
N8-GP 75 IU/kg single dose	2	0.04	6
N8-GP 50 IU/kg prophylaxis	15	0.97	53
N8-GP 75 IU/kg prophylaxis	6	0.50	21
Total	21	1.93	127
Trial 3885			
N8-GP 50-75 IU/kg prophylaxi	68	234.07	24621
Total	68	234.07	24621
All Trials			
N8-GP 25 IU/kg single dose	7	0.50	7
N8-GP 50 IU/kg single dose	25	1.02	56
N8-GP 75 IU/kg single dose	12	0.72	16
N8-GP 50 IU/kg prophylaxis	177	504.62	47537
N8-GP 75 IU/kg prophylaxis	61	107.78	5804
N8-GP 50-75 IU/kg prophylaxi	68	234.07	24621
N8-GP 20-75 IU/kg on-demand	12	33.44	1405
Total	270	882.13	79446

An exposure day is a day when the patient received at least one dose of N8-GP.
Patients might be included in multiple trials or treated with multiple dose regimens within a trial and therefore the Total row might not necessarily add up to the sum of the individual rows.

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2. N8-GP の累積曝露 – 試験別及び年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Trial Age group	Number of patients	Patient years of exposure	Exposure days
Trial 3776			
>=18 years	26	1.77	26
Total	26	1.77	26
Trial 3859			
12-17 years	25	76.37	6586
>=18 years	161	567.99	48086
Total	186	644.36	54672
Trial 4033			
>=18 years	21	1.93	127
Total	21	1.93	127
Trial 3885			
0-5 years	34	106.03	11140
6-11 years	34	128.04	13481
Total	68	234.07	24621
All Trials			
0-5 years	34	106.03	11140
6-11 years	34	128.04	13481
12-17 years	25	76.37	6586
>=18 years	177	571.70	48239
Total	270	882.13	79446

An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.

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3. N8-GP の累積曝露 – 試験別及び人種別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Trial Race	Number of patients	Patient years of exposure	Exposure days
Trial 3776			
Asian	3	0.21	3
Black or African American	1	0.08	1
White	21	1.42	21
Other	1	0.07	1
Total	26	1.77	26
Trial 3859			
Asian	35	104.48	9357
Black or African American	11	20.15	1248
White	137	510.26	43324
Other	2	5.33	484
NA	1	4.14	259
Total	186	644.36	54672
Trial 4033			
Black or African American	1	0.06	3
White	19	1.79	119
NA	1	0.09	5
Total	21	1.93	127
Trial 3885			
Asian	5	18.36	1951
Black or African American	3	11.42	1187
White	55	189.27	19898
Other	2	3.85	399
NA	3	11.16	1186
Total	68	234.07	24621
All Trials			
Asian	43	123.05	11311
Black or African American	15	31.71	2439
White	203	702.74	63362
Other	5	9.24	884
NA	4	15.39	1450
Total	270	882.13	79446

Other: algerian, caucasian/ black carribean, parent stated other (latin decent), puerto rican (multi-racial), unknown
An exposure day is a day when the patient received at least one dose of N8-GP.

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4. N8-GP の累積曝露 – 試験別及び民族別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Trial Ethnicity	Number of patients	Patient years of exposure	Exposure days
Trial 3776			
Not Hispanic or Latino	26	1.77	26
Total	26	1.77	26
Trial 3859			
Hispanic or Latino	13	41.71	3747
Not Hispanic or Latino	172	598.51	50666
NA	1	4.14	259
Total	186	644.36	54672
Trial 4033			
Hispanic or Latino	3	0.28	19
Not Hispanic or Latino	17	1.56	103
NA	1	0.09	5
Total	21	1.93	127
Trial 3885			
Hispanic or Latino	3	11.69	1218
Not Hispanic or Latino	64	218.70	23017
NA	1	3.68	386
Total	68	234.07	24621
All Trials			
Hispanic or Latino	16	53.68	4984
Not Hispanic or Latino	252	820.54	73812
NA	2	7.91	650
Total	270	882.13	79446

An exposure day is a day when the patient received at least one dose of N8-GP.

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10SEP2018:16:57:02 - t_exp_cum.sas/t_274100130_exp_cum_aethnic.txt

5. N8-GP の累積曝露 – 試験別及び治療法別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Trial Treatment type	Number of patients	Patient years of exposure	Exposure days
Trial 3776			
Phase 1 single dose	26	1.77	26
Total	26	1.77	26
Trial 3859			
Prophylaxis multiple dose	177	610.92	53267
On-demand	12	33.44	1405
Total	186	644.36	54672
Trial 4033			
Prophylaxis multiple dose	21	1.93	127
Total	21	1.93	127
Trial 3885			
Prophylaxis multiple dose	68	234.07	24621
Total	68	234.07	24621
All Trials			
Phase 1 single dose	26	1.77	26
Prophylaxis multiple dose	245	846.92	78015
On-demand	12	33.44	1405
Total	270	882.13	79446

An exposure day is a day when the patient received at least one dose of N8-GP.
Patients in trial 4033 were recruited from 3859 and returned to 3859 after completion of the trial. Prophylaxis treatment was allowed in between visits in 4033. Therefore exposure for 4033 is summarised under prophylaxis.
Patients might be included in multiple treatment types and therefore the number of patients in the rows might not necessarily add up to the Totals.

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6. N8-GP の曝露期間 – 期間別及び年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Duration interval	0-5 years N	6-11 years N	12-17 years N	>=18 years N	Total N
0 - <3months	4	-	1	23	28
3 - <6months	1	-	-	3	4
6 - <12months	-	-	4	6	10
12 - <18months	-	-	1	12	13
18 - <24months	-	-	3	11	14
24 - <30months	-	-	1	1	2
30 - <36months	-	-	1	6	7
36 - <42months	6	-	1	2	9
42 - <48months	16	26	-	2	44
48 - <54months	7	8	6	52	73
54 - <60months	-	-	6	42	48
60 - <66months	-	-	1	17	18

Duration intervals are based on patient years of exposure.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.

nn7088/nn7088-filing/sum_20180910_er
10SEP2018:16:57:05 - t_exp_int.sas/t_274100150_exp_int_pye_agegr1.txt

7. N8-GP の曝露日数 – 期間別及び年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Duration interval	0-5 years N	6-11 years N	12-17 years N	>=18 years N	Total N
1 - 24 EDs	4	-	1	24	29
25 - 49 EDs	1	-	1	4	6
50 - 74 EDs	-	-	2	8	10
75 - 99 EDs	-	-	1	7	8
100 - 124 EDs	-	-	1	6	7
125 - 149 EDs	-	-	-	4	4
150 - 174 EDs	-	-	3	3	6
175 - 199 EDs	-	-	1	3	4
200 - 224 EDs	-	-	-	2	2
225 - 249 EDs	-	-	-	6	6
250 - 274 EDs	-	-	-	10	10
275 - 299 EDs	-	-	2	6	8
300 - 324 EDs	-	-	3	6	9
325 - 349 EDs	4	-	-	6	10
350 - 374 EDs	9	3	2	14	28
375 - 399 EDs	7	18	4	17	46
400 - 424 EDs	5	11	-	15	31
425 - 449 EDs	4	2	3	18	27
450 - 474 EDs	-	-	1	7	8
475 - 499 EDs	-	-	-	3	3
500 - 524 EDs	-	-	-	4	4
525 - 549 EDs	-	-	-	3	3
550 - 574 EDs	-	-	-	1	1

An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.

nn7088/nn7088-filing/sum_20180910_er
10SEP2018:16:57:05 - t_exp_int.sas/t_274100160_exp_int_ed_agegr1.txt

8. N8-GP の曝露期間 – 期間別及び治療法別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

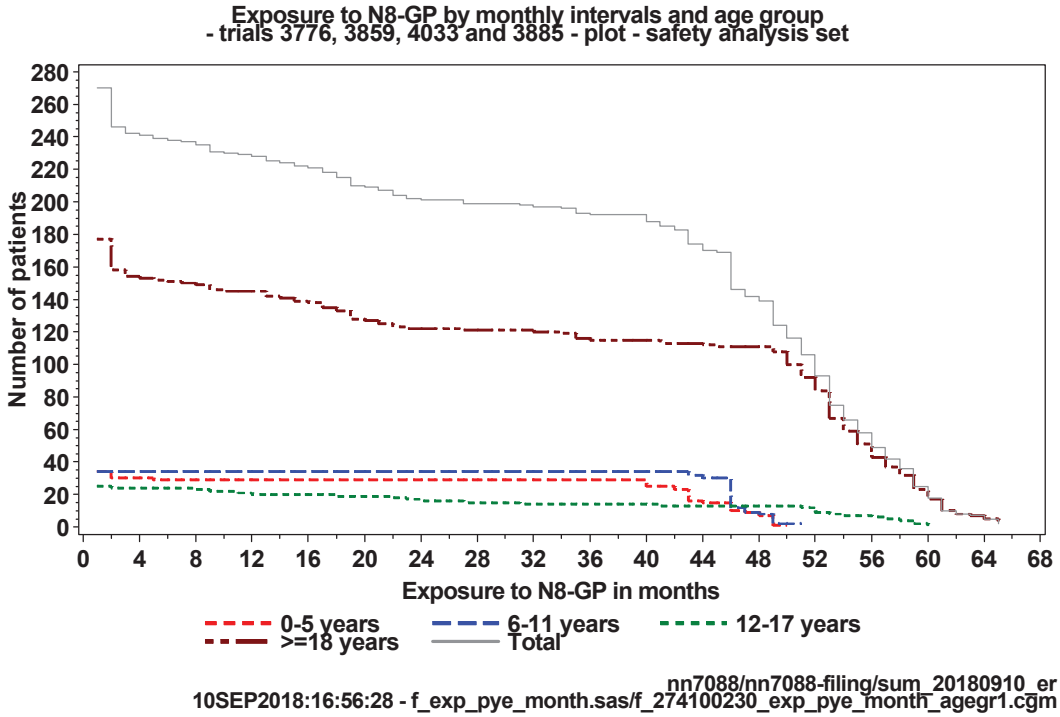
Duration interval	Phase 1 single dose N	Prophylaxis Multiple Dose N	On-demand N	Total N
0 - <3months	26	12	-	28
3 - <6months	-	4	1	4
6 - <12months	-	10	-	10
12 - <18months	-	12	1	13
18 - <24months	-	11	3	14
24 - <30months	-	2	2	2
30 - <36months	-	8	-	7
36 - <42months	-	9	1	9
42 - <48months	-	45	-	44
48 - <54months	-	72	-	73
54 - <60months	-	46	3	48
60 - <66months	-	14	1	18

Duration intervals are based on patient years of exposure.
Patients might be included in multiple treatment types and therefore the number of patients in each row might not necessarily add up to the Total.

9. N8-GP の曝露日数 – 期間別及び治療法別– 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Duration interval	Phase 1 single dose N	Prophylaxis Multiple Dose N	On-demand N	Total N
1 - 24 EDs	26	13	1	29
25 - 49 EDs	-	5	1	6
50 - 74 EDs	-	7	4	10
75 - 99 EDs	-	6	2	8
100 - 124 EDs	-	7	1	7
125 - 149 EDs	-	4	-	4
150 - 174 EDs	-	6	-	6
175 - 199 EDs	-	2	2	4
200 - 224 EDs	-	2	-	2
225 - 249 EDs	-	6	-	6
250 - 274 EDs	-	10	-	10
275 - 299 EDs	-	11	-	8
300 - 324 EDs	-	8	-	9
325 - 349 EDs	-	9	-	10
350 - 374 EDs	-	28	-	28
375 - 399 EDs	-	45	-	46
400 - 424 EDs	-	31	-	31
425 - 449 EDs	-	26	1	27
450 - 474 EDs	-	8	-	8
475 - 499 EDs	-	3	-	3
500 - 524 EDs	-	4	-	4
525 - 549 EDs	-	3	-	3
550 - 574 EDs	-	1	-	1

An exposure day is a day when the patient received at least one dose of N8-GP.
Patients might be included in multiple treatment types and therefore the number of patients in each row might not necessarily add up to the Total.



10. N8-GP の曝露期間 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

11. N8-GP の曝露 – 試験別、年齢グループ別及び原薬製造工程別 – 安全性解析対象集団（3859 及び 3885 試験）

	Pivotal process			Commercial process			Total		
Age group	Number of patients	PYE	ED	Number of patients	PYE	ED	Number of patients	PYE	ED
Trial 3859									
12-17 years	25	72.10	6189	6	4.27	397	25	76.37	6586
>=18 years	161	543.60	45954	43	24.39	2132	161	567.99	48086
Total	186	615.70	52143	49	28.66	2529	186	644.36	54672
Trial 3885									
0-5 years	34	93.07	9791	21	12.96	1349	34	106.03	11140
6-11 years	34	115.25	12142	22	12.79	1339	34	128.04	13481
Total	68	208.33	21933	43	25.74	2688	68	234.07	24621
All Trials									
0-5 years	34	93.07	9791	21	12.96	1349	34	106.03	11140
6-11 years	34	115.25	12142	22	12.79	1339	34	128.04	13481
12-17 years	25	72.10	6189	6	4.27	397	25	76.37	6586
>=18 years	161	543.60	45954	43	24.39	2132	161	567.99	48086
Total	254	824.02	74076	92	54.40	5217	254	878.43	79293

ED: exposure days
PYE: Patient years of exposure
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
Exposure to N8-GP from the different production methods is accounted from the scheduled visit where product was first dispensed.

12. N8-GP の曝露 – 年齢グループ別及び試験別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Age group	Trial	Number of patients	Patient years of exposure				Exposure days			
			Sum	Mean (SD)	Median	min ; max	Sum	Mean (SD)	Median	min ; max
0-5 years	Trial 3885	34	106.03	3.12 (1.30)	3.48	0.04 ; 4.16	11140	327.65 (137.06)	366	2 ; 440
	Total	34	106.03	3.12 (1.30)	3.48	0.04 ; 4.16	11140	327.65 (137.06)	366	2 ; 440
6-11 years	Trial 3885	34	128.04	3.77 (0.17)	3.73	3.49 ; 4.20	13481	396.50 (17.54)	395	361 ; 442
	Total	34	128.04	3.77 (0.17)	3.73	3.49 ; 4.20	13481	396.50 (17.54)	395	361 ; 442
12-17 years	Trial 3859	25	76.37	3.05 (1.70)	4.16	0.08 ; 4.92	6586	263.44 (144.40)	306	10 ; 465
	Total	25	76.37	3.05 (1.70)	4.16	0.08 ; 4.92	6586	263.44 (144.40)	306	10 ; 465
>=18 years	Trial 3776	26	1.77	0.07 (0.01)	0.07	0.02 ; 0.09	26	1.00 (0.00)	1	1 ; 1
	Trial 3859	161	567.99	3.53 (1.58)	4.27	0.01 ; 5.41	48086	298.67 (150.09)	354	1 ; 556
	Trial 4033	21	1.93	0.09 (0.03)	0.09	0.05 ; 0.16	127	6.05 (2.18)	6	2 ; 10
	Total	177	571.70	3.23 (1.82)	4.21	0.01 ; 5.41	48239	272.54 (167.26)	322	1 ; 556
Total	Trial 3776	26	1.77	0.07 (0.01)	0.07	0.02 ; 0.09	26	1.00 (0.00)	1	1 ; 1
	Trial 3859	186	644.36	3.46 (1.60)	4.24	0.01 ; 5.41	54672	293.94 (149.44)	342	1 ; 556
	Trial 4033	21	1.93	0.09 (0.03)	0.09	0.05 ; 0.16	127	6.05 (2.18)	6	2 ; 10
	Trial 3885	68	234.07	3.44 (0.98)	3.70	0.04 ; 4.20	24621	362.07 (102.99)	388	2 ; 442
	Total	270	882.13	3.27 (1.63)	3.94	0.01 ; 5.41	79446	294.24 (156.10)	363	1 ; 556

An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.

13. N8-GP の曝露 – 日本人 – 年齢グループ別及び試験別– 安全性解析対象集団（3776、3859 及び 3885 試験）

Age group	Trial	Number of patients	Patient years of exposure				Exposure days			
			Sum	Mean (SD)	Median	min ; max	Sum	Mean (SD)	Median	min ; max
6-11 years	Trial 3885	2	7.42	3.71 (0.02)	3.71	3.70 ; 3.72	794	397.00 (11.31)	397	389 ; 405
	Total	2	7.42	3.71 (0.02)	3.71	3.70 ; 3.72	794	397.00 (11.31)	397	389 ; 405
12-17 years	Trial 3859	1	0.62	0.62 (-)	0.62	0.62 ; 0.62	62	62.00 (-)	62	62 ; 62
	Total	1	0.62	0.62 (-)	0.62	0.62 ; 0.62	62	62.00 (-)	62	62 ; 62
>=18 years	Trial 3776	2	0.12	0.06 (0.02)	0.06	0.04 ; 0.08	2	1.00 (0.00)	1	1 ; 1
	Trial 3859	14	33.25	2.37 (1.87)	1.61	0.05 ; 5.41	2979	212.79 (170.58)	151	5 ; 459
	Total	16	33.37	2.09 (1.91)	1.49	0.04 ; 5.41	2981	186.31 (174.50)	141	1 ; 459
Total	Trial 3776	2	0.12	0.06 (0.02)	0.06	0.04 ; 0.08	2	1.00 (0.00)	1	1 ; 1
	Trial 3859	15	33.86	2.26 (1.86)	1.52	0.05 ; 5.41	3041	202.73 (168.92)	141	5 ; 459
	Trial 3885	2	7.42	3.71 (0.02)	3.71	3.70 ; 3.72	794	397.00 (11.31)	397	389 ; 405
	Total	19	41.40	2.18 (1.86)	1.52	0.04 ; 5.41	3837	201.95 (175.82)	141	1 ; 459

An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.

14. N8-GP の曝露 – 大手術を受けた被験者 – 年齢グループ別 – 安全性解析対象集団（3860 試験）

Age group	Trial	Number of patients	Patient years of exposure				Exposure days			
			Sum	Mean (SD)	Median	min ; max	Sum	Mean (SD)	Median	min ; max
12-17 years	Trial 3860	1	0.07	0.07 (-)	0.07	0.07 ; 0.07	12	12.00 (-)	12	12 ; 12
>=18 years	Trial 3860	33	6.33	0.19 (0.14)	0.15	0.04 ; 0.59	967	29.30 (22.34)	24	3 ; 101
Total	Trial 3860	34	6.40	0.19 (0.14)	0.15	0.04 ; 0.59	979	28.79 (22.20)	24	3 ; 101

An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.

15. N8-GP の曝露 – 原薬製造工程別及び試験別 – 安全性解析対象集団（3859 及び 3885 試験）

Production method	Trial	Number of patients	Patient years of exposure				Exposure days			
			Sum	Mean (SD)	Median	min ; max	Sum	Mean (SD)	Median	min ; max
Pivotal process	Trial 3859	186	615.70	3.31 (1.53)	3.97	0.01 ; 5.37	52143	280.34 (142.06)	315	1 ; 556
	Trial 3885	68	208.33	3.06 (0.91)	3.22	0.04 ; 4.19	21933	322.54 (96.82)	339	2 ; 442
	Total	254	824.02	3.24 (1.39)	3.57	0.01 ; 5.37	74076	291.64 (132.62)	331	1 ; 556
Commercial process	Trial 3859	49	28.66	0.58 (0.19)	0.65	0.01 ; 0.87	2529	51.61 (18.69)	56	1 ; 78
	Trial 3885	43	25.74	0.60 (0.11)	0.55	0.48 ; 0.78	2688	62.51 (11.92)	57	49 ; 81
	Total	92	54.40	0.59 (0.16)	0.61	0.01 ; 0.87	5217	56.71 (16.72)	57	1 ; 81
Total	Trial 3859	186	644.36	3.46 (1.60)	4.24	0.01 ; 5.41	54672	293.94 (149.44)	342	1 ; 556
	Trial 3885	68	234.07	3.44 (0.98)	3.70	0.04 ; 4.20	24621	362.07 (102.99)	388	2 ; 442
	Total	254	878.43	3.46 (1.46)	3.99	0.01 ; 5.41	79293	312.18 (141.61)	371	1 ; 556

An exposure day is a day when the patient received at least one dose of N8-GP.
Exposure to N8-GP from the different production methods is accounted from the scheduled visit where product was first dispensed.

16. 有害事象の概要 – 治療法別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	Phase 1 single dose N(%) E		Prophylaxis multiple dose N(%) E[R]		On-demand N(%) E[R,F]		Total N(%) E[R]	
Number of patients	26		245		12		270	
Patient years of exposure	1.77		846.92		33.44		882.13	
Exposure days	26		78015		1405		79446	
All adverse events	11(42.3)	17	226(92.2)	2174[2.57]	10(83.3)	116[3.47, 0.083]	239(88.5)	2307[2.62]
Serious adverse events	1(3.8)	1	43(17.6)	62[0.07]	3(25.0)	4[0.12, 0.003]	47(17.4)	67[0.08]
Non serious adverse events	11(42.3)	16	224(91.4)	2112[2.49]	10(83.3)	112[3.35, 0.080]	237(87.8)	2240[2.54]
Severity								
Mild	9(34.6)	13	211(86.1)	1725[2.04]	9(75.0)	76[2.27, 0.054]	221(81.9)	1814[2.06]
Moderate	4(15.4)	4	143(58.4)	387[0.46]	9(75.0)	35[1.05, 0.025]	154(57.0)	426[0.48]
Severe	-		41(16.7)	62[0.07]	2(16.7)	4[0.12, 0.003]	42(15.6)	66[0.07]
Missing	-			-	1(8.3)	1[0.03, 0.001]	1(0.4)	1[0.00]
Relationship								
Probably or possibly	1(3.8)	1	36(14.7)	74[0.09]	4(33.3)	9[0.27, 0.006]	40(14.8)	84[0.10]
Unlikely	10(38.5)	16	224(91.4)	2092[2.47]	10(83.3)	107[3.20, 0.076]	237(87.8)	2215[2.51]
Missing	-		4(1.6)	8[0.01]		-	4(1.5)	8[0.01]
Adverse events								
Leading to withdrawal	-		7(2.9)	7[0.01]		-	7(2.6)	7[0.01]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
[F]: Number of adverse events per exposure days (E/exposure days)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients might be included in multiple treatment types and therefore the number of patients in each row might not necessarily add up to the Total.

17. 5%超の被験者（基本語別）で報告された有害事象の要約 – 治療法別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	Phase 1 single dose N(%) E		Prophylaxis multiple dose N(%) E[R]		On-demand N(%) E[R,F]		Total N(%) E[R]	
Number of patients	26		245		12		270	
Patient years of exposure	1.77		846.92		33.44		882.13	
Exposure days	26		78015		1405		79446	
All adverse events	11(42.3)	17	226(92.2)	2174[2.57]	10(83.3)	116[3.47, 0.083]	239(88.5)	2307[2.62]
Infections and infestations								
Viral upper respiratory tract infection	1(3.8)	1	72(29.4)	119[0.14]	5(41.7)	10[0.30, 0.007]	78(28.9)	130[0.15]
Upper respiratory tract infection	-		57(23.3)	105[0.12]	-		57(21.1)	105[0.12]
Influenza	-		27(11.0)	40[0.05]	2(16.7)	2[0.06, 0.001]	29(10.7)	42[0.05]
Gastroenteritis	-		19(7.8)	27[0.03]	1(8.3)	1[0.03, 0.001]	20(7.4)	28[0.03]
Tonsillitis	-		17(6.9)	23[0.03]	1(8.3)	1[0.03, 0.001]	18(6.7)	24[0.03]
Rhinitis	-		15(6.1)	19[0.02]	-		15(5.6)	19[0.02]
Bronchitis	-		14(5.7)	16[0.02]	1(8.3)	1[0.03, 0.001]	15(5.6)	17[0.02]
Musculoskeletal and connective tissue disorders								
Arthralgia	-		40(16.3)	63[0.07]	3(25.0)	3[0.09, 0.002]	43(15.9)	66[0.07]
Pain in extremity	-		22(9.0)	30[0.04]	-		22(8.1)	30[0.03]
Musculoskeletal pain	-		17(6.9)	18[0.02]	-		17(6.3)	18[0.02]
Back pain	1(3.8)	1	11(4.5)	14[0.02]	3(25.0)	3[0.09, 0.002]	15(5.6)	18[0.02]
Injury, poisoning and procedural complications								
Contusion	-		19(7.8)	23[0.03]	1(8.3)	9[0.27, 0.006]	20(7.4)	32[0.04]
Laceration	-		19(7.8)	21[0.02]	-		19(7.0)	21[0.02]
Fall	-		16(6.5)	18[0.02]	1(8.3)	1[0.03, 0.001]	17(6.3)	19[0.02]
Limb injury	-		16(6.5)	26[0.03]	-		16(5.9)	26[0.03]
Gastrointestinal disorders								
Diarrhoea	-		29(11.8)	37[0.04]	2(16.7)	2[0.06, 0.001]	31(11.5)	39[0.04]
Vomiting	-		19(7.8)	23[0.03]	1(8.3)	1[0.03, 0.001]	20(7.4)	24[0.03]
Nausea	1(3.8)	1	16(6.5)	20[0.02]	1(8.3)	1[0.03, 0.001]	17(6.3)	22[0.02]
Toothache	-		14(5.7)	15[0.02]	1(8.3)	1[0.03, 0.001]	15(5.6)	16[0.02]
Respiratory, thoracic and mediastinal disorders								

Summary of adverse events (preferred term > 5%) by treatment type - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Phase 1 single dose N(%)	E	Prophylaxis multiple dose N(%)	E[R]	On-demand N(%)	E[R,F]	Total N(%)	E[R]
Cough	1(3.8)	1	35(14.3)	50[0.06]	1(8.3)	2[0.06, 0.001]	37(13.7)	53[0.06]
Oropharyngeal pain	1(3.8)	1	27(11.0)	33[0.04]	1(8.3)	1[0.03, 0.001]	29(10.7)	35[0.04]
Rhinorrhoea	-		15(6.1)	20[0.02]	-		15(5.6)	20[0.02]
Nervous system disorders								
Headache	2(7.7)	2	51(20.8)	112[0.13]	3(25.0)	4[0.12, 0.003]	56(20.7)	118[0.13]
Skin and subcutaneous tissue disorders								
Eczema	-		14(5.7)	17[0.02]	1(8.3)	2[0.06, 0.001]	15(5.6)	19[0.02]
Rash	-		14(5.7)	18[0.02]	-		14(5.2)	18[0.02]
General disorders and administration site conditions								
Pyrexia	-		24(9.8)	39[0.05]	2(16.7)	2[0.06, 0.001]	25(9.3)	41[0.05]
Investigations								
Alanine aminotransferase increased	-		11(4.5)	16[0.02]	3(25.0)	5[0.15, 0.004]	14(5.2)	21[0.02]
Vascular disorders								
Hypertension	1(3.8)	1	18(7.3)	19[0.02]	-		19(7.0)	20[0.02]
Immune system disorders								
Seasonal allergy	-		14(5.7)	19[0.02]	-		14(5.2)	19[0.02]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
[F]: Number of adverse events per exposure days (E/exposure days)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients might be included in multiple treatment types and therefore the number of patients in each row might not necessarily add up to the Total.
MedDRA version: 20.0

18. 治験薬との因果関係が「あり」又は「可能性あり」と判定された有害事象の要約 – 治療法別 – 安全性解析対象集団（3776、3859、4033及び 3885 試験）

	Phase 1 single dose N(%) E		Prophylaxis multiple dose N(%) E[R]		On-demand N(%) E[R,F]		Total N(%) E[R]	
Number of patients	26		245		12		270	
Patient years of exposure	1.77		846.92		33.44		882.13	
Exposure days	26		78015		1405		79446	
All adverse events	1(3.8)	1	36(14.7)	74[0.09]	4(33.3)	9[0.27, 0.006]	40(14.8)	84[0.10]
Investigations	-		12(4.9)	28[0.03]	2(16.7)	4[0.12, 0.003]	14(5.2)	32[0.04]
Aspartate aminotransferase increased	-		5(2.0)	6[0.01]	1(8.3)	1[0.03, 0.001]	6(2.2)	7[0.01]
Alanine aminotransferase increased	-		3(1.2)	4[0.00]	1(8.3)	1[0.03, 0.001]	4(1.5)	5[0.01]
Gamma-glutamyltransferase increased	-		1(0.4)	1[0.00]	1(8.3)	1[0.03, 0.001]	2(0.7)	2[0.00]
Coagulation factor VIII level increased	-		1(0.4)	7[0.01]		-	1(0.4)	7[0.01]
Anti factor VIII antibody test	-		1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Aspartate aminotransferase abnormal	-		1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Blood bilirubin increased	-		1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
C-reactive protein increased	-		1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Electrocardiogram ST segment elevation	-		1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Liver function test abnormal	-			-	1(8.3)	1[0.03, 0.001]	1(0.4)	1[0.00]
Mean cell haemoglobin decreased	-		1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Mean cell volume decreased	-		1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Serum ferritin decreased	-		1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Transaminases abnormal	-		1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Transaminases increased	-		1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Nervous system disorders	1(3.8)	1	6(2.4)	6[0.01]		-	7(2.6)	7[0.01]
Headache	1(3.8)	1	3(1.2)	3[0.00]		-	4(1.5)	4[0.00]
Dizziness	-		2(0.8)	2[0.00]		-	2(0.7)	2[0.00]
Presyncope	-		1(0.4)	1[0.00]		-	1(0.4)	1[0.00]

Summary of adverse events possibly or probably related to trial product by treatment type - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Phase 1 single dose N(%) E	Prophylaxis multiple dose N(%) E[R]		On-demand N(%) E[R,F]		Total N(%) E[R]	
Skin and subcutaneous tissue disorders	-	6(2.4)	11[0.01]	-		6(2.2)	11[0.01]
Rash	-	3(1.2)	6[0.01]	-		3(1.1)	6[0.01]
Erythema	-	1(0.4)	3[0.00]	-		1(0.4)	3[0.00]
Pruritus	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Purpura	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Injury, poisoning and procedural complications	-	6(2.4)	6[0.01]	-		6(2.2)	6[0.01]
Accidental overdose	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Contusion	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Drug administration error	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Overdose	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Post procedural complication	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Product preparation error	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Musculoskeletal and connective tissue disorders	-	4(1.6)	4[0.00]	1(8.3)	1[0.03, 0.001]	5(1.9)	5[0.01]
Arthralgia	-	2(0.8)	2[0.00]	1(8.3)	1[0.03, 0.001]	3(1.1)	3[0.00]
Joint range of motion decreased	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Muscle haemorrhage	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Gastrointestinal disorders	-	2(0.8)	4[0.00]	1(8.3)	2[0.06, 0.001]	3(1.1)	6[0.01]
Nausea	-	1(0.4)	3[0.00]	-		1(0.4)	3[0.00]
Flatulence	-	-		1(8.3)	2[0.06, 0.001]	1(0.4)	2[0.00]
Gastritis	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Blood and lymphatic system disorders	-	3(1.2)	3[0.00]	-		3(1.1)	3[0.00]
Factor VIII inhibition	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Neutropenia	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Thrombocytopenia	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
General disorders and administration site conditions	-	3(1.2)	3[0.00]	-		3(1.1)	3[0.00]
Injection site reaction	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Injection site swelling	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

Summary of adverse events possibly or probably related to trial product by treatment type - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Phase 1 single dose N(%) E	Prophylaxis multiple dose N(%) E[R]		On-demand N(%) E[R,F]		Total N(%) E[R]	
Pyrexia	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Infections and infestations	-	1(0.4)	1[0.00]	1(8.3)	1[0.03, 0.001]	2(0.7)	2[0.00]
Intervertebral discitis	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Tinea infection	-	-		1(8.3)	1[0.03, 0.001]	1(0.4)	1[0.00]
Vascular disorders	-	2(0.8)	2[0.00]	-		2(0.7)	2[0.00]
Haematoma	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Haemorrhage	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Cardiac disorders	-	1(0.4)	2[0.00]	-		1(0.4)	2[0.00]
Sinus arrhythmia	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Sinus bradycardia	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Immune system disorders	-	1(0.4)	2[0.00]	-		1(0.4)	2[0.00]
Hypersensitivity	-	1(0.4)	2[0.00]	-		1(0.4)	2[0.00]
Hepatobiliary disorders	-	-		1(8.3)	1[0.03, 0.001]	1(0.4)	1[0.00]
Hepatic function abnormal	-	-		1(8.3)	1[0.03, 0.001]	1(0.4)	1[0.00]
Metabolism and nutrition disorders	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Iron deficiency	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Cough	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
[F]: Number of adverse events per exposure days (E/exposure days)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients might be included in multiple treatment types and therefore the number of patients in each row might not necessarily add up to the Total.
MedDRA version: 20.0

19. 重篤な有害事象の要約 – 治療法別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	Phase 1 single dose N(%) E		Prophylaxis multiple dose N(%) E[R]		On-demand N(%) E[R,F]		Total N(%) E[R]	
Number of patients	26		245		12		270	
Patient years of exposure	1.77		846.92		33.44		882.13	
Exposure days	26		78015		1405		79446	
All adverse events	1(3.8)	1	43(17.6)	62[0.07]	3(25.0)	4[0.12, 0.003]	47(17.4)	67[0.08]
Infections and infestations	1(3.8)	1	13(5.3)	19[0.02]	-		14(5.2)	20[0.02]
Cellulitis	-		2(0.8)	3[0.00]	-		2(0.7)	3[0.00]
Device related infection	-		2(0.8)	3[0.00]	-		2(0.7)	3[0.00]
Bacterial sepsis	-		2(0.8)	2[0.00]	-		2(0.7)	2[0.00]
Anal abscess	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Catheter site infection	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Encephalitis	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Enteritis infectious	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Infective spondylitis	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Intervertebral discitis	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Osteomyelitis	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pneumonia	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Sepsis syndrome	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Tonsillitis	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Tuberculosis	1(3.8)	1	-		-		1(0.4)	1[0.00]
Viral infection	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Injury, poisoning and procedural complications	-		9(3.7)	9[0.01]	2(16.7)	2[0.06, 0.001]	11(4.1)	11[0.01]
Fall	-		1(0.4)	1[0.00]	1(8.3)	1[0.03, 0.001]	2(0.7)	2[0.00]
Ankle fracture	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Extradural haematoma	-		-		1(8.3)	1[0.03, 0.001]	1(0.4)	1[0.00]
Face injury	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Femoral neck fracture	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Forearm fracture	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Head injury	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Injury	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Road traffic accident	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Toxicity to various agents	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Gastrointestinal disorders	-		7(2.9)	7[0.01]	-		7(2.6)	7[0.01]
Duodenal ulcer	-		2(0.8)	2[0.00]	-		2(0.7)	2[0.00]
Abdominal hernia	-		1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

Summary of serious adverse events by treatment type - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Phase 1 single dose N(%) E	Prophylaxis multiple dose N(%) E[R]		On-demand N(%) E[R,F]		Total N(%) E[R]	
Gastric varices	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Gastric varices haemorrhage	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Gastritis	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pancreatitis acute	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Nervous system disorders	-	3(1.2)	4[0.00]	-		3(1.1)	4[0.00]
Cerebral infarction	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Cerebral microhaemorrhage	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Seizure	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Syncope	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Musculoskeletal and connective tissue disorders	-	3(1.2)	3[0.00]	-		3(1.1)	3[0.00]
Muscle haemorrhage	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pathological fracture	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Synovitis	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	3(1.2)	3[0.00]	-		3(1.1)	3[0.00]
Hepatocellular carcinoma	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Neuroma	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pancreatic carcinoma metastatic	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Renal and urinary disorders	-	2(0.8)	2[0.00]	1(8.3)	1[0.03, 0.001]	3(1.1)	3[0.00]
Calculus urinary	-	-		1(8.3)	1[0.03, 0.001]	1(0.4)	1[0.00]
IgA nephropathy	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Tubulointerstitial nephritis	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Congenital, familial and genetic disorders	-	2(0.8)	2[0.00]	-		2(0.7)	2[0.00]
Hydrocele	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hypertrophic cardiomyopathy	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
General disorders and administration site conditions	-	2(0.8)	2[0.00]	-		2(0.7)	2[0.00]

Summary of serious adverse events by treatment type - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Phase 1 single dose N(%) E	Prophylaxis multiple dose N(%) E[R]		On-demand N(%) E[R,F]		Total N(%) E[R]	
Complication associated with device	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pyrexia	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	-	2(0.8)	2[0.00]	-		2(0.7)	2[0.00]
Adenoidal hypertrophy	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hypoxia	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Vascular disorders	-	2(0.8)	2[0.00]	-		2(0.7)	2[0.00]
Circulatory collapse	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Haemorrhage	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Blood and lymphatic system disorders	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Factor VIII inhibition	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Cardiac disorders	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Aortic valve stenosis	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Eye disorders	-	-		1(8.3)	1[0.03, 0.001]	1(0.4)	1[0.00]
Cataract	-	-		1(8.3)	1[0.03, 0.001]	1(0.4)	1[0.00]
Hepatobiliary disorders	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Cholecystitis	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Immune system disorders	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hypersensitivity	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Product issues	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Device dislocation	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Psychiatric disorders	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Depression	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Reproductive system and breast disorders	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Acquired phimosis	-	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
[F]: Number of adverse events per exposure days (E/exposure days)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients might be included in multiple treatment types and therefore the number of patients in each row might not necessarily add up to the Total.
MedDRA version: 20.0

20. アレルギー反応（広域検索）に関連する有害事象の要約 – 年齢グループ別– 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Number of patients	34		34		25		177		270	
Patient years of exposure	106.03		128.04		76.37		571.70		882.13	
Exposure days	11140		13481		6586		48239		79446	
All adverse events	22(64.7)	58[0.55]	19(55.9)	32[0.25]	10(40.0)	20[0.26]	54(30.5)	107[0.19]	105(38.9)	217[0.25]
Skin and subcutaneous tissue disorders	10(29.4)	17[0.16]	9(26.5)	10[0.08]	3(12.0)	3[0.04]	30(16.9)	50[0.09]	52(19.3)	80[0.09]
Eczema	2(5.9)	2[0.02]	5(14.7)	5[0.04]	-		8(4.5)	12[0.02]	15(5.6)	19[0.02]
Rash	5(14.7)	7[0.07]	-		1(4.0)	1[0.01]	8(4.5)	10[0.02]	14(5.2)	18[0.02]
Urticaria	1(2.9)	1[0.01]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	4(2.3)	4[0.01]	7(2.6)	7[0.01]
Erythema	3(8.8)	5[0.05]	1(2.9)	1[0.01]	-		1(0.6)	3[0.01]	5(1.9)	9[0.01]
Dermatitis contact	1(2.9)	1[0.01]	2(5.9)	2[0.02]	-		1(0.6)	1[0.00]	4(1.5)	4[0.00]
Pruritus	-		-		-		4(2.3)	4[0.01]	4(1.5)	4[0.00]
Blister	-		-		-		3(1.7)	5[0.01]	3(1.1)	5[0.01]
Skin erosion	-		-		-		2(1.1)	4[0.01]	2(0.7)	4[0.00]
Dermatitis	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Photosensitivity reaction	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Rash pruritic	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Drug eruption	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Mechanical urticaria	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pruritus allergic	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Pruritus generalised	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	16(47.1)	30[0.28]	7(20.6)	8[0.06]	7(28.0)	11[0.14]	16(9.0)	21[0.04]	46(17.0)	70[0.08]
Cough	14(41.2)	23[0.22]	5(14.7)	5[0.04]	7(28.0)	11[0.14]	11(6.2)	14[0.02]	37(13.7)	53[0.06]
Asthma	1(2.9)	3[0.03]	1(2.9)	1[0.01]	-		2(1.1)	2[0.00]	4(1.5)	6[0.01]
Rhinitis allergic	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	3(1.1)	3[0.00]
Sneezing	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Allergic respiratory disease	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Asthmatic crisis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Bronchial hyperreactivity	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Dyspnoea	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nasal obstruction	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Wheezing	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Immune system disorders	4(11.8)	6[0.06]	1(2.9)	1[0.01]	1(4.0)	2[0.03]	13(7.3)	17[0.03]	19(7.0)	26[0.03]

Summary of adverse events by age group - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set
Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Seasonal allergy	2(5.9)	2[0.02]	1(2.9)	1[0.01]	1(4.0)	2[0.03]	10(5.6)	14[0.02]	14(5.2)	19[0.02]
Hypersensitivity	1(2.9)	2[0.02]	-	-	-	-	1(0.6)	1[0.00]	2(0.7)	3[0.00]
Allergic oedema	1(2.9)	2[0.02]	-	-	-	-	-	-	1(0.4)	2[0.00]
Allergy to chemicals	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Drug hypersensitivity	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
General disorders and administration site conditions	-	-	4(11.8)	4[0.03]	2(8.0)	3[0.04]	8(4.5)	8[0.01]	14(5.2)	15[0.02]
Oedema peripheral	-	-	1(2.9)	1[0.01]	-	-	4(2.3)	4[0.01]	5(1.9)	5[0.01]
Peripheral swelling	-	-	2(5.9)	2[0.02]	1(4.0)	1[0.01]	1(0.6)	1[0.00]	4(1.5)	4[0.00]
Local swelling	-	-	1(2.9)	1[0.01]	1(4.0)	1[0.01]	1(0.6)	1[0.00]	3(1.1)	3[0.00]
Injection site rash	-	-	-	-	1(4.0)	1[0.01]	-	-	1(0.4)	1[0.00]
Localised oedema	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Oedema	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Infections and infestations	2(5.9)	2[0.02]	2(5.9)	2[0.02]	1(4.0)	1[0.01]	4(2.3)	4[0.01]	9(3.3)	9[0.01]
Conjunctivitis	2(5.9)	2[0.02]	2(5.9)	2[0.02]	1(4.0)	1[0.01]	4(2.3)	4[0.01]	9(3.3)	9[0.01]
Eye disorders	2(5.9)	2[0.02]	4(11.8)	5[0.04]	-	-	1(0.6)	1[0.00]	7(2.6)	8[0.01]
Conjunctivitis allergic	-	-	3(8.8)	4[0.03]	-	-	-	-	3(1.1)	4[0.00]
Eye pruritus	1(2.9)	1[0.01]	-	-	-	-	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Eye allergy	-	-	1(2.9)	1[0.01]	-	-	-	-	1(0.4)	1[0.00]
Eye swelling	1(2.9)	1[0.01]	-	-	-	-	-	-	1(0.4)	1[0.00]
Gastrointestinal disorders	-	-	1(2.9)	1[0.01]	-	-	5(2.8)	5[0.01]	6(2.2)	6[0.01]
Stomatitis	-	-	-	-	-	-	3(1.7)	3[0.01]	3(1.1)	3[0.00]
Gingival swelling	-	-	1(2.9)	1[0.01]	-	-	-	-	1(0.4)	1[0.00]
Mouth ulceration	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Swollen tongue	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vascular disorders	1(2.9)	1[0.01]	-	-	-	-	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Circulatory collapse	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Flushing	1(2.9)	1[0.01]	-	-	-	-	-	-	1(0.4)	1[0.00]
Blood and lymphatic system disorders	-	-	1(2.9)	1[0.01]	-	-	-	-	1(0.4)	1[0.00]
Eosinophilia	-	-	1(2.9)	1[0.01]	-	-	-	-	1(0.4)	1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

21. アレルギー反応（広域検索）に関連する治験薬との因果関係が「あり」又は「可能性あり」と判定された有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	3(8.8) 6[0.06]	-	-	4(2.3) 7[0.01]	7(2.6) 13[0.01]
Skin and subcutaneous tissue disorders	1(2.9) 3[0.03]	-	-	4(2.3) 7[0.01]	5(1.9) 10[0.01]
Rash	1(2.9) 3[0.03]	-	-	2(1.1) 3[0.01]	3(1.1) 6[0.01]
Erythema	-	-	-	1(0.6) 3[0.01]	1(0.4) 3[0.00]
Pruritus	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Immune system disorders	1(2.9) 2[0.02]	-	-	-	1(0.4) 2[0.00]
Hypersensitivity	1(2.9) 2[0.02]	-	-	-	1(0.4) 2[0.00]
Respiratory, thoracic and mediastinal disorders	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Cough	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

22. アレルギー反応（広域検索）に関連する重篤な有害事象の要約 – 年齢グループ別 - 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	1(2.9) 1[0.01]	-	-	1(0.6) 1[0.00]	2(0.7) 2[0.00]
Immune system disorders	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Hypersensitivity	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Vascular disorders	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Circulatory collapse	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

23. アレルギー反応（狭域検索）に関連する有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%)	0-5 years E[R]	6-11 years N(%)	6-11 years E[R]	12-17 years N(%)	12-17 years E[R]	>=18 years N(%)	>=18 years E[R]	Total N(%)	Total E[R]
Number of patients	34		34		25		177		270	
Patient years of exposure	106.03		128.04		76.37		571.70		882.13	
Exposure days	11140		13481		6586		48239		79446	
All adverse events	10(29.4)	17[0.16]	12(35.3)	16[0.12]	4(16.0)	4[0.05]	28(15.8)	37[0.06]	54(20.0)	74[0.08]
Skin and subcutaneous tissue disorders	8(23.5)	11[0.10]	8(23.5)	9[0.07]	3(12.0)	3[0.04]	22(12.4)	31[0.05]	41(15.2)	54[0.06]
Eczema	2(5.9)	2[0.02]	5(14.7)	5[0.04]	-		8(4.5)	12[0.02]	15(5.6)	19[0.02]
Rash	5(14.7)	7[0.07]	-		1(4.0)	1[0.01]	8(4.5)	10[0.02]	14(5.2)	18[0.02]
Urticaria	1(2.9)	1[0.01]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	4(2.3)	4[0.01]	7(2.6)	7[0.01]
Dermatitis contact	1(2.9)	1[0.01]	2(5.9)	2[0.02]	-		1(0.6)	1[0.00]	4(1.5)	4[0.00]
Dermatitis	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Rash pruritic	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Drug eruption	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pruritus allergic	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Eye disorders	1(2.9)	1[0.01]	4(11.8)	5[0.04]	-		-		5(1.9)	6[0.01]
Conjunctivitis allergic	-		3(8.8)	4[0.03]	-		-		3(1.1)	4[0.00]
Eye allergy	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Eye swelling	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Immune system disorders	2(5.9)	4[0.04]	-		-		2(1.1)	2[0.00]	4(1.5)	6[0.01]
Hypersensitivity	1(2.9)	2[0.02]	-		-		1(0.6)	1[0.00]	2(0.7)	3[0.00]
Allergic oedema	1(2.9)	2[0.02]	-		-		-		1(0.4)	2[0.00]
Drug hypersensitivity	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		2(1.1)	2[0.00]	4(1.5)	4[0.00]
Rhinitis allergic	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	3(1.1)	3[0.00]
Allergic respiratory disease	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gastrointestinal disorders	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Gingival swelling	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Swollen tongue	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by age group - allergic reactions (narrow scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
General disorders and administration site conditions	-	-	1(4.0) 1[0.01]	-	1(0.4) 1[0.00]
Injection site rash	-	-	1(4.0) 1[0.01]	-	1(0.4) 1[0.00]
Vascular disorders	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Circulatory collapse	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

24. アレルギー反応（狭域検索）に関連する治験薬との因果関係が「あり」又は「可能性あり」と判定された有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	2(5.9) 5[0.05]	-	-	2(1.1) 3[0.01]	4(1.5) 8[0.01]
Skin and subcutaneous tissue disorders	1(2.9) 3[0.03]	-	-	2(1.1) 3[0.01]	3(1.1) 6[0.01]
Rash	1(2.9) 3[0.03]	-	-	2(1.1) 3[0.01]	3(1.1) 6[0.01]
Immune system disorders	1(2.9) 2[0.02]	-	-	-	1(0.4) 2[0.00]
Hypersensitivity	1(2.9) 2[0.02]	-	-	-	1(0.4) 2[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

25. アレルギー反応（狭域検索）に関連する重篤な有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	1(2.9) 1[0.01]	-	-	1(0.6) 1[0.00]	2(0.7) 2[0.00]
Immune system disorders	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Hypersensitivity	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Vascular disorders	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Circulatory collapse	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

26. 血栓塞栓性事象（SMQ 検索）の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Nervous system disorders	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Cerebral infarction	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

27. 稀な有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	-	1(2.9) 1[0.01]	5(20.0) 7[0.09]	25(14.1) 29[0.05]	31(11.5) 37[0.04]
Congenital, familial and genetic disorders	-	1(2.9) 1[0.01]	2(8.0) 2[0.03]	5(2.8) 5[0.01]	8(3.0) 8[0.01]
Gilbert's syndrome	-	-	2(8.0) 2[0.03]	-	2(0.7) 2[0.00]
Dermoid cyst	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Hydrocele	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Hypertrophic cardiomyopathy	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Odontogenic cyst	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Pectus carinatum	-	1(2.9) 1[0.01]	-	-	1(0.4) 1[0.00]
Thalassaemia alpha	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Cardiac disorders	-	-	2(8.0) 3[0.04]	5(2.8) 5[0.01]	7(2.6) 8[0.01]
Ventricular extrasystoles	-	-	1(4.0) 1[0.01]	1(0.6) 1[0.00]	2(0.7) 2[0.00]
Atrial fibrillation	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Atrioventricular block first degree	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Extrasystoles	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Palpitations	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Sinus arrhythmia	-	-	1(4.0) 1[0.01]	-	1(0.4) 1[0.00]
Sinus bradycardia	-	-	1(4.0) 1[0.01]	-	1(0.4) 1[0.00]
Gastrointestinal disorders	-	-	1(4.0) 1[0.01]	4(2.3) 5[0.01]	5(1.9) 6[0.01]
Gastric varices	-	-	-	1(0.6) 2[0.00]	1(0.4) 2[0.00]
Gastric varices haemorrhage	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Pancreatitis	-	-	1(4.0) 1[0.01]	-	1(0.4) 1[0.00]
Pancreatitis acute	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Swollen tongue	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Blood and lymphatic system disorders	-	-	1(4.0) 1[0.01]	4(2.3) 4[0.01]	5(1.9) 5[0.01]
Neutropenia	-	-	1(4.0) 1[0.01]	1(0.6) 1[0.00]	2(0.7) 2[0.00]
Thrombocytopenia	-	-	-	2(1.1) 2[0.00]	2(0.7) 2[0.00]

Summary of adverse events by age group - rare events - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Pancytopenia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatobiliary disorders	-		-		-		5(2.8)	5[0.01]	5(1.9)	5[0.01]
Hepatic fibrosis	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Hepatic cirrhosis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatic steatosis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Renal and urinary disorders	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
IgA nephropathy	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Tubulointerstitial nephritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Investigations	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Platelet count decreased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nervous system disorders	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Syncope	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vascular disorders	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Circulatory collapse	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

28. 投薬過誤（SMQ 検索）に関連する有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	1(2.9) 1[0.01]	2(5.9) 2[0.02]	1(4.0) 1[0.01]	2(1.1) 2[0.00]	6(2.2) 6[0.01]
Injury, poisoning and procedural complications	1(2.9) 1[0.01]	2(5.9) 2[0.02]	1(4.0) 1[0.01]	2(1.1) 2[0.00]	6(2.2) 6[0.01]
Accidental overdose	-	1(2.9) 1[0.01]	-	1(0.6) 1[0.00]	2(0.7) 2[0.00]
Drug administration error	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Medication error	-	1(2.9) 1[0.01]	-	-	1(0.4) 1[0.00]
Overdose	-	-	1(4.0) 1[0.01]	-	1(0.4) 1[0.00]
Product preparation error	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

29. 薬剤性肝障害（SMQ 検索）に関連する有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	2(5.9) 2[0.02]	-	1(4.0) 2[0.03]	31(17.5) 70[0.12]	34(12.6) 74[0.08]
Investigations	1(2.9) 1[0.01]	-	1(4.0) 2[0.03]	23(13.0) 60[0.10]	25(9.3) 63[0.07]
Alanine aminotransferase increased	-	-	1(4.0) 1[0.01]	13(7.3) 20[0.03]	14(5.2) 21[0.02]
Aspartate aminotransferase increased	-	-	1(4.0) 1[0.01]	11(6.2) 17[0.03]	12(4.4) 18[0.02]
Gamma-glutamyltransferase increased	-	-	-	9(5.1) 15[0.03]	9(3.3) 15[0.02]
Blood bilirubin increased	-	-	-	3(1.7) 3[0.01]	3(1.1) 3[0.00]
Aspartate aminotransferase abnormal	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Blood alkaline phosphatase increased	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Hepatic enzyme increased	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Liver function test abnormal	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Transaminases abnormal	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Transaminases increased	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Hepatobiliary disorders	1(2.9) 1[0.01]	-	-	6(3.4) 6[0.01]	7(2.6) 7[0.01]
Hepatic fibrosis	-	-	-	3(1.7) 3[0.01]	3(1.1) 3[0.00]
Hepatic cirrhosis	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Hepatic function abnormal	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Hepatic steatosis	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Hepatomegaly	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Gastrointestinal disorders	-	-	-	2(1.1) 3[0.01]	2(0.7) 3[0.00]
Gastric varices	-	-	-	1(0.6) 2[0.00]	1(0.4) 2[0.00]
Gastric varices haemorrhage	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]

Summary of adverse events by age group - drug related hepatic disorders (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Hepatocellular carcinoma	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

30. 薬剤性肝障害（SMQ 検索）に関連する治験薬との因果関係が「あり」又は「可能性あり」と判定された有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	-	-	1(4.0) 2[0.03]	10(5.6) 18[0.03]	11(4.1) 20[0.02]
Investigations	-	-	1(4.0) 2[0.03]	9(5.1) 17[0.03]	10(3.7) 19[0.02]
Aspartate aminotransferase increased	-	-	1(4.0) 1[0.01]	5(2.8) 6[0.01]	6(2.2) 7[0.01]
Alanine aminotransferase increased	-	-	1(4.0) 1[0.01]	3(1.7) 4[0.01]	4(1.5) 5[0.01]
Gamma-glutamyltransferase increased	-	-	-	2(1.1) 2[0.00]	2(0.7) 2[0.00]
Aspartate aminotransferase abnormal	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Blood bilirubin increased	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Liver function test abnormal	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Transaminases abnormal	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Transaminases increased	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Hepatobiliary disorders	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Hepatic function abnormal	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

31. 薬剤性肝障害（SMQ 検索）に関連する重篤な有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	-	-	-	3(1.7) 3[0.01]	3(1.1) 3[0.00]
Gastrointestinal disorders	-	-	-	2(1.1) 2[0.00]	2(0.7) 2[0.00]
Gastric varices	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Gastric varices haemorrhage	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Hepatocellular carcinoma	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

32. 急性腎不全（SMQ 検索）に関連する有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	1(2.9) 1[0.01]	-	-	3(1.7) 5[0.01]	4(1.5) 6[0.01]
Investigations	1(2.9) 1[0.01]	-	-	2(1.1) 4[0.01]	3(1.1) 5[0.01]
Blood creatinine increased	1(2.9) 1[0.01]	-	-	2(1.1) 4[0.01]	3(1.1) 5[0.01]
Renal and urinary disorders	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Tubulointerstitial nephritis	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

nn7088/nn7088-filing/sum_20180910_er
10SEP2018:16:57:42 - t_teae.sas/t_274200211_teae_agegr1_smq04_re.txt

33. 急性腎不全（SMQ 検索）に関連する治験薬との因果関係が「あり」又は「可能性あり」と判定された有害事象の要約 – 年齢グループ別（3776、3859、4033 及び 3885 試験） – 安全性解析対象集団

There is no data to display

nn7088/nn7088-filing/sum_20180910_er
10SEP2018:16:57:42 - t_teae.sas/t_274200212_teae_agegr1_re_pp.txt

34. 急性腎不全（SMQ 検索）に関連する重篤な有害事象の要約 – 年齢グループ別– 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Renal and urinary disorders	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Tubulointerstitial nephritis	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

nn7088/nn7088-filing/sum_20180910_er
10SEP2018:16:57:43 - t_teae.sas/t_274200213_teae_agegr1_re_sae.txt

35. 治験薬による病原体感染の疑いに関連する有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

There is no data to display

nn7088/nn7088-filing/sum_20180910_er
10SEP2018:16:57:43 - t_teae.sas/t_274200221_teae_agegr1_cq04_ti.txt

36. 注射部位反応に関連する有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	1(2.9) 1[0.01]	-	2(8.0) 2[0.03]	4(2.3) 4[0.01]	7(2.6) 7[0.01]
General disorders and administration site conditions	1(2.9) 1[0.01]	-	2(8.0) 2[0.03]	4(2.3) 4[0.01]	7(2.6) 7[0.01]
Infusion site reaction	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Injection site erythema	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Injection site rash	-	-	1(4.0) 1[0.01]	-	1(0.4) 1[0.00]
Injection site reaction	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Injection site swelling	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Vessel puncture site haematoma	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Vessel puncture site pain	-	-	1(4.0) 1[0.01]	-	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

37. 有害事象の概要 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%)	0-5 years E[R]	6-11 years N(%)	6-11 years E[R]	12-17 years N(%)	12-17 years E[R]	>=18 years N(%)	>=18 years E[R]	Total N(%)	Total E[R]
Number of patients	34		34		25		177		270	
Patient years of exposure	106.03		128.04		76.37		571.70		882.13	
Exposure days	11140		13481		6586		48239		79446	
All adverse events	32(94.1)	350[3.30]	33(97.1)	333[2.60]	25(100)	278[3.64]	149(84.2)	1346[2.35]	239(88.5)	2307[2.62]
Serious adverse events	10(29.4)	12[0.11]	5(14.7)	5[0.04]	5(20.0)	7[0.09]	27(15.3)	43[0.08]	47(17.4)	67[0.08]
Non serious adverse events	32(94.1)	338[3.19]	32(94.1)	328[2.56]	24(96.0)	271[3.55]	149(84.2)	1303[2.28]	237(87.8)	2240[2.54]
Severity										
Mild	27(79.4)	278[2.62]	31(91.2)	298[2.33]	22(88.0)	241[3.16]	141(79.7)	997[1.74]	221(81.9)	1814[2.06]
Moderate	25(73.5)	63[0.59]	17(50.0)	33[0.26]	13(52.0)	32[0.42]	99(55.9)	298[0.52]	154(57.0)	426[0.48]
Severe	7(20.6)	9[0.08]	2(5.9)	2[0.02]	5(20.0)	5[0.07]	28(15.8)	50[0.09]	42(15.6)	66[0.07]
Missing		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Relationship										
Probably or possibly	7(20.6)	12[0.11]	3(8.8)	3[0.02]	4(16.0)	8[0.10]	26(14.7)	61[0.11]	40(14.8)	84[0.10]
Unlikely	30(88.2)	333[3.14]	33(97.1)	330[2.58]	25(100)	269[3.52]	149(84.2)	1283[2.24]	237(87.8)	2215[2.51]
Missing	1(2.9)	5[0.05]		-	1(4.0)	1[0.01]	2(1.1)	2[0.00]	4(1.5)	8[0.01]
Adverse events										
Leading to withdrawal	2(5.9)	2[0.02]		-	1(4.0)	1[0.01]	4(2.3)	4[0.01]	7(2.6)	7[0.01]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.

38. 有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%)	0-5 years E[R]	6-11 years N(%)	6-11 years E[R]	12-17 years N(%)	12-17 years E[R]	>=18 years N(%)	>=18 years E[R]	Total N(%)	Total E[R]
Number of patients	34		34		25		177		270	
Patient years of exposure	106.03		128.04		76.37		571.70		882.13	
Exposure days	11140		13481		6586		48239		79446	
All adverse events	32(94.1)	350[3.30]	33(97.1)	333[2.60]	25(100)	278[3.64]	149(84.2)	1346[2.35]	239(88.5)	2307[2.62]
Infections and infestations	26(76.5)	113[1.07]	27(79.4)	129[1.01]	13(52.0)	60[0.79]	107(60.5)	316[0.55]	173(64.1)	618[0.70]
Viral upper respiratory tract infection	11(32.4)	22[0.21]	10(29.4)	18[0.14]	7(28.0)	15[0.20]	50(28.2)	75[0.13]	78(28.9)	130[0.15]
Upper respiratory tract infection	10(29.4)	16[0.15]	12(35.3)	26[0.20]	5(20.0)	11[0.14]	30(16.9)	52[0.09]	57(21.1)	105[0.12]
Influenza	3(8.8)	5[0.05]	6(17.6)	10[0.08]	2(8.0)	3[0.04]	18(10.2)	24[0.04]	29(10.7)	42[0.05]
Gastroenteritis	5(14.7)	8[0.08]	8(23.5)	11[0.09]	-	-	7(4.0)	9[0.02]	20(7.4)	28[0.03]
Tonsillitis	1(2.9)	1[0.01]	3(8.8)	6[0.05]	1(4.0)	1[0.01]	13(7.3)	16[0.03]	18(6.7)	24[0.03]
Rhinitis	7(20.6)	7[0.07]	4(11.8)	7[0.05]	-	-	4(2.3)	5[0.01]	15(5.6)	19[0.02]
Bronchitis	3(8.8)	5[0.05]	3(8.8)	3[0.02]	1(4.0)	1[0.01]	8(4.5)	8[0.01]	15(5.6)	17[0.02]
Ear infection	5(14.7)	5[0.05]	3(8.8)	5[0.04]	3(12.0)	4[0.05]	2(1.1)	2[0.00]	13(4.8)	16[0.02]
Viral infection	2(5.9)	2[0.02]	2(5.9)	2[0.02]	6(24.0)	7[0.09]	3(1.7)	4[0.01]	13(4.8)	15[0.02]
Otitis media	3(8.8)	3[0.03]	4(11.8)	4[0.03]	-	-	2(1.1)	3[0.01]	9(3.3)	10[0.01]
Conjunctivitis	2(5.9)	2[0.02]	2(5.9)	2[0.02]	1(4.0)	1[0.01]	4(2.3)	4[0.01]	9(3.3)	9[0.01]
Sinusitis	1(2.9)	1[0.01]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	6(3.4)	6[0.01]	9(3.3)	9[0.01]
Pharyngitis	1(2.9)	1[0.01]	1(2.9)	2[0.02]	1(4.0)	1[0.01]	5(2.8)	6[0.01]	8(3.0)	10[0.01]
Pharyngitis streptococcal	2(5.9)	2[0.02]	1(2.9)	2[0.02]	1(4.0)	1[0.01]	2(1.1)	2[0.00]	6(2.2)	7[0.01]
Tooth abscess	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-	-	3(1.7)	6[0.01]	5(1.9)	8[0.01]
Eye infection	-	-	1(2.9)	2[0.02]	2(8.0)	2[0.03]	2(1.1)	2[0.00]	5(1.9)	6[0.01]
Pneumonia	1(2.9)	1[0.01]	2(5.9)	2[0.02]	-	-	2(1.1)	2[0.00]	5(1.9)	5[0.01]
Nasopharyngitis	1(2.9)	1[0.01]	-	-	-	-	3(1.7)	5[0.01]	4(1.5)	6[0.01]
Device related infection	2(5.9)	3[0.03]	-	-	1(4.0)	1[0.01]	1(0.6)	1[0.00]	4(1.5)	5[0.01]
Periodontitis	-	-	1(2.9)	1[0.01]	-	-	3(1.7)	4[0.01]	4(1.5)	5[0.01]
Fungal skin infection	-	-	-	-	1(4.0)	1[0.01]	3(1.7)	3[0.01]	4(1.5)	4[0.00]
Gastroenteritis viral	-	-	2(5.9)	2[0.02]	-	-	2(1.1)	2[0.00]	4(1.5)	4[0.00]
Pulpitis dental	-	-	-	-	-	-	4(2.3)	4[0.01]	4(1.5)	4[0.00]
Varicella	3(8.8)	3[0.03]	1(2.9)	1[0.01]	-	-	-	-	4(1.5)	4[0.00]
Cellulitis	1(2.9)	1[0.01]	-	-	-	-	2(1.1)	5[0.01]	3(1.1)	6[0.01]
Urinary tract infection	-	-	-	-	-	-	3(1.7)	6[0.01]	3(1.1)	6[0.01]
Lower respiratory tract infection	-	-	-	-	1(4.0)	2[0.03]	2(1.1)	3[0.01]	3(1.1)	5[0.01]
Tooth infection	-	-	1(2.9)	2[0.02]	2(8.0)	3[0.04]	-	-	3(1.1)	5[0.01]
Folliculitis	-	-	-	-	-	-	3(1.7)	4[0.01]	3(1.1)	4[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Acute sinusitis	-		2(5.9)	2[0.02]	-		1(0.6)	1[0.00]	3(1.1)	3[0.00]
Localised infection	-		1(2.9)	1[0.01]	-		2(1.1)	2[0.00]	3(1.1)	3[0.00]
Molluscum contagiosum	2(5.9)	2[0.02]	1(2.9)	1[0.01]	-		-		3(1.1)	3[0.00]
Otitis externa	1(2.9)	1[0.01]	-		-		2(1.1)	2[0.00]	3(1.1)	3[0.00]
Respiratory tract infection	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Tinea pedis	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Enterobiasis	1(2.9)	5[0.05]	1(2.9)	1[0.01]	-		-		2(0.7)	6[0.01]
Hordeolum	-		-		1(4.0)	1[0.01]	1(0.6)	2[0.00]	2(0.7)	3[0.00]
Tinea infection	-		-		-		2(1.1)	3[0.01]	2(0.7)	3[0.00]
Bacterial sepsis	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Cystitis	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Gastrointestinal infection	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Herpes zoster	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Impetigo	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		-		2(0.7)	2[0.00]
Onychomycosis	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Pharyngotonsillitis	-		2(5.9)	2[0.02]	-		-		2(0.7)	2[0.00]
Scarlet fever	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Streptococcal infection	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		-		2(0.7)	2[0.00]
Upper respiratory tract infection bacterial	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		-		2(0.7)	2[0.00]
Viral pharyngitis	2(5.9)	2[0.02]	-		-		-		2(0.7)	2[0.00]
Otitis media acute	-		1(2.9)	3[0.02]	-		-		1(0.4)	3[0.00]
Paronychia	-		1(2.9)	3[0.02]	-		-		1(0.4)	3[0.00]
Genital herpes	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Helminthic infection	1(2.9)	2[0.02]	-		-		-		1(0.4)	2[0.00]
Abscess neck	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Anal abscess	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Body tinea	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Catheter site infection	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Chlamydial infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Citrobacter infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Conjunctivitis bacterial	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Encephalitis	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Enteritis infectious	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Epididymitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Fungal infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Genital infection bacterial	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
H1N1 influenza	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Helicobacter gastritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Helicobacter infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatitis C	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Infectious mononucleosis	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Infective spondylitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Intervertebral discitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Labyrinthitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Laryngitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Mumps	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Oral herpes	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Orchitis	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Osteomyelitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Postoperative wound infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sepsis syndrome	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Sinusitis bacterial	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Skin infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Subcutaneous abscess	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Tonsillitis streptococcal	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Tracheitis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Tuberculosis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Urethritis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Vestibular neuronitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Viral diarrhoea	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Viral parotitis	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Wound infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Musculoskeletal and connective tissue disorders	8(23.5)	18[0.17]	14(41.2)	22[0.17]	11(44.0)	37[0.48]	80(45.2)	172[0.30]	113(41.9)	249[0.28]
Arthralgia	2(5.9)	3[0.03]	4(11.8)	4[0.03]	5(20.0)	17[0.22]	32(18.1)	42[0.07]	43(15.9)	66[0.07]
Pain in extremity	3(8.8)	9[0.08]	6(17.6)	7[0.05]	3(12.0)	3[0.04]	10(5.6)	11[0.02]	22(8.1)	30[0.03]
Musculoskeletal pain	-		1(2.9)	1[0.01]	1(4.0)	1[0.01]	15(8.5)	16[0.03]	17(6.3)	18[0.02]
Back pain	-		1(2.9)	1[0.01]	2(8.0)	3[0.04]	12(6.8)	14[0.02]	15(5.6)	18[0.02]
Arthropathy	-		1(2.9)	1[0.01]	-		8(4.5)	10[0.02]	9(3.3)	11[0.01]
Haemophilic arthropathy	-		1(2.9)	1[0.01]	-		8(4.5)	8[0.01]	9(3.3)	9[0.01]
Myalgia	1(2.9)	1[0.01]	-		3(12.0)	5[0.07]	3(1.7)	3[0.01]	7(2.6)	9[0.01]
Tendonitis	-		1(2.9)	1[0.01]	-		6(3.4)	6[0.01]	7(2.6)	7[0.01]
Synovitis	-		-		-		6(3.4)	8[0.01]	6(2.2)	8[0.01]
Joint swelling	2(5.9)	2[0.02]	-		-		4(2.3)	5[0.01]	6(2.2)	7[0.01]
Musculoskeletal stiffness	-		1(2.9)	1[0.01]	-		4(2.3)	4[0.01]	5(1.9)	5[0.01]
Joint range of motion decreased	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		2(1.1)	2[0.00]	4(1.5)	4[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Neck pain	-		-		1(4.0)	3[0.04]	2(1.1)	3[0.01]	3(1.1)	6[0.01]
Pain in jaw	-		-		2(8.0)	3[0.04]	1(0.6)	1[0.00]	3(1.1)	4[0.00]
Bursitis	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Joint lock	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Musculoskeletal chest pain	-		-		1(4.0)	1[0.01]	2(1.1)	2[0.00]	3(1.1)	3[0.00]
Osteoarthritis	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Flank pain	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Muscle haemorrhage	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Muscle spasms	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Plantar fasciitis	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Rotator cuff syndrome	-		-		-		1(0.6)	3[0.01]	1(0.4)	3[0.00]
Tenosynovitis	-		-		-		1(0.6)	3[0.01]	1(0.4)	3[0.00]
Rheumatic disorder	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Arthritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Bone pain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Chondropathy	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Costochondritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Groin pain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Growing pains	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Joint effusion	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Limb discomfort	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Muscle tightness	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Musculoskeletal discomfort	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Myositis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pathological fracture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Periostitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Rhabdomyolysis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Scoliosis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Spinal osteoarthritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Synovial disorder	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Tendon pain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Torticollis	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Injury, poisoning and procedural complications	14(41.2)	34[0.32]	22(64.7)	55[0.43]	14(56.0)	33[0.43]	56(31.6)	115[0.20]	106(39.3)	237[0.27]
Contusion	2(5.9)	2[0.02]	4(11.8)	4[0.03]	1(4.0)	1[0.01]	13(7.3)	25[0.04]	20(7.4)	32[0.04]
Laceration	1(2.9)	1[0.01]	3(8.8)	3[0.02]	2(8.0)	2[0.03]	13(7.3)	15[0.03]	19(7.0)	21[0.02]
Fall	5(14.7)	7[0.07]	2(5.9)	2[0.02]	3(12.0)	3[0.04]	7(4.0)	7[0.01]	17(6.3)	19[0.02]
Limb injury	4(11.8)	4[0.04]	4(11.8)	12[0.09]	4(16.0)	5[0.07]	4(2.3)	5[0.01]	16(5.9)	26[0.03]
Ligament sprain	-		5(14.7)	5[0.04]	1(4.0)	1[0.01]	7(4.0)	8[0.01]	13(4.8)	14[0.02]
Joint injury	2(5.9)	2[0.02]	3(8.8)	4[0.03]	-		6(3.4)	6[0.01]	11(4.1)	12[0.01]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Head injury	2(5.9)	3[0.03]	3(8.8)	4[0.03]	4(16.0)	5[0.07]	-		9(3.3)	12[0.01]
Muscle strain	-		1(2.9)	1[0.01]	2(8.0)	3[0.04]	4(2.3)	5[0.01]	7(2.6)	9[0.01]
Arthropod bite	1(2.9)	2[0.02]	2(5.9)	2[0.02]	2(8.0)	2[0.03]	2(1.1)	2[0.00]	7(2.6)	8[0.01]
Skin abrasion	-		1(2.9)	2[0.02]	1(4.0)	1[0.01]	5(2.8)	5[0.01]	7(2.6)	8[0.01]
Arthropod sting	1(2.9)	3[0.03]	3(8.8)	3[0.02]	-		-		4(1.5)	6[0.01]
Face injury	1(2.9)	1[0.01]	2(5.9)	2[0.02]	-		1(0.6)	1[0.00]	4(1.5)	4[0.00]
Hand fracture	1(2.9)	1[0.01]	-		-		2(1.1)	3[0.01]	3(1.1)	4[0.00]
Excoriation	1(2.9)	1[0.01]	2(5.9)	2[0.02]	-		-		3(1.1)	3[0.00]
Post-traumatic pain	-		1(2.9)	1[0.01]	1(4.0)	1[0.01]	1(0.6)	1[0.00]	3(1.1)	3[0.00]
Road traffic accident	-		1(2.9)	1[0.01]	-		2(1.1)	2[0.00]	3(1.1)	3[0.00]
Scratch	-		-		1(4.0)	1[0.01]	2(1.1)	2[0.00]	3(1.1)	3[0.00]
Wound	1(2.9)	1[0.01]	-		-		2(1.1)	2[0.00]	3(1.1)	3[0.00]
Accidental overdose	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Chest injury	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Foot fracture	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Procedural pain	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Tendon injury	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Thermal burn	1(2.9)	1[0.01]	-		1(4.0)	1[0.01]	-		2(0.7)	2[0.00]
Traumatic haemorrhage	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Injury	-		-		1(4.0)	2[0.03]	-		1(0.4)	2[0.00]
Abdominal injury	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Alcohol poisoning	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Animal bite	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Ankle fracture	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Back injury	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Compression fracture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Concussion	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Corneal abrasion	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Drug administration error	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Electric shock	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Epicondylitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Epiphyseal injury	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Extradural haematoma	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Femoral neck fracture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Forearm fracture	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Foreign body in eye	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Lower limb fracture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Medication error	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Mouth injury	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Muscle rupture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Overdose	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	0-5 years E[R]	6-11 years N(%)	6-11 years E[R]	12-17 years N(%)	12-17 years E[R]	>=18 years N(%)	>=18 years E[R]	Total N(%)	Total E[R]
Post procedural complication	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Product preparation error	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Radius fracture	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Rib fracture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Splinter	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sunburn	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Tooth injury	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Toxicity to various agents	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Traumatic haematoma	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Vaccination complication	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Gastrointestinal disorders	14(41.2)	35[0.33]	15(44.1)	26[0.20]	11(44.0)	19[0.25]	65(36.7)	150[0.26]	105(38.9)	230[0.26]
Diarrhoea	5(14.7)	7[0.07]	3(8.8)	4[0.03]	3(12.0)	3[0.04]	20(11.3)	25[0.04]	31(11.5)	39[0.04]
Vomiting	8(23.5)	9[0.08]	1(2.9)	3[0.02]	1(4.0)	1[0.01]	10(5.6)	11[0.02]	20(7.4)	24[0.03]
Nausea	-		-		5(20.0)	5[0.07]	12(6.8)	17[0.03]	17(6.3)	22[0.02]
Toothache	-		1(2.9)	1[0.01]	-		14(7.9)	15[0.03]	15(5.6)	16[0.02]
Abdominal pain	5(14.7)	6[0.06]	1(2.9)	1[0.01]	-		7(4.0)	7[0.01]	13(4.8)	14[0.02]
Abdominal pain upper	1(2.9)	1[0.01]	1(2.9)	1[0.01]	1(4.0)	2[0.03]	8(4.5)	9[0.02]	11(4.1)	13[0.01]
Dental caries	1(2.9)	3[0.03]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	7(4.0)	8[0.01]	10(3.7)	13[0.01]
Constipation	2(5.9)	2[0.02]	3(8.8)	4[0.03]	2(8.0)	2[0.03]	2(1.1)	3[0.01]	9(3.3)	11[0.01]
Gastritis	1(2.9)	1[0.01]	2(5.9)	2[0.02]	-		4(2.3)	4[0.01]	7(2.6)	7[0.01]
Gastrooesophageal reflux disease	1(2.9)	1[0.01]	-		-		5(2.8)	6[0.01]	6(2.2)	7[0.01]
Dyspepsia	-		-		-		5(2.8)	5[0.01]	5(1.9)	5[0.01]
Abdominal discomfort	-		-		1(4.0)	1[0.01]	2(1.1)	2[0.00]	3(1.1)	3[0.00]
Stomatitis	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Irritable bowel syndrome	-		-		-		2(1.1)	3[0.01]	2(0.7)	3[0.00]
Aphthous ulcer	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Chapped lips	-		2(5.9)	2[0.02]	-		-		2(0.7)	2[0.00]
Duodenal ulcer	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Gastrointestinal disorder	1(2.9)	1[0.01]	-		1(4.0)	1[0.01]	-		2(0.7)	2[0.00]
Haemorrhoids	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Perianal erythema	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Dysphagia	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Flatulence	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Food poisoning	-		-		1(4.0)	2[0.03]	-		1(0.4)	2[0.00]
Gastric varices	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Abdominal hernia	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Anal fissure	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Barrett's oesophagus	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Chronic gastritis		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Dental discomfort		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Dental necrosis	1(2.9)	1[0.01]		-		-		-	1(0.4)	1[0.00]
Diaphragmatic hernia		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Duodenitis		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Enterocolitis		-	1(2.9)	1[0.01]		-		-	1(0.4)	1[0.00]
Faeces soft	1(2.9)	1[0.01]		-		-		-	1(0.4)	1[0.00]
Gastric varices haemorrhage		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gastritis erosive		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gingival bleeding		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gingival swelling		-	1(2.9)	1[0.01]		-		-	1(0.4)	1[0.00]
Glossodynia		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Haematochezia		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hiatus hernia		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Inguinal hernia		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Lip ulceration		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Loose tooth		-	1(2.9)	1[0.01]		-		-	1(0.4)	1[0.00]
Mouth haemorrhage	1(2.9)	1[0.01]		-		-		-	1(0.4)	1[0.00]
Mouth ulceration		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Noninfective gingivitis	1(2.9)	1[0.01]		-		-		-	1(0.4)	1[0.00]
Oral pain		-	1(2.9)	1[0.01]		-		-	1(0.4)	1[0.00]
Pancreatitis		-		-	1(4.0)	1[0.01]		-	1(0.4)	1[0.00]
Pancreatitis acute		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Rectal haemorrhage		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Retching		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Swollen tongue		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Uvulitis		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	16(47.1)	57[0.54]	16(47.1)	28[0.22]	11(44.0)	33[0.43]	46(26.0)	77[0.13]	89(33.0)	195[0.22]
Cough	14(41.2)	23[0.22]	5(14.7)	5[0.04]	7(28.0)	11[0.14]	11(6.2)	14[0.02]	37(13.7)	53[0.06]
Oropharyngeal pain	2(5.9)	2[0.02]	7(20.6)	9[0.07]	2(8.0)	4[0.05]	18(10.2)	20[0.03]	29(10.7)	35[0.04]
Rhinorrhoea	4(11.8)	4[0.04]	3(8.8)	4[0.03]	2(8.0)	5[0.07]	6(3.4)	7[0.01]	15(5.6)	20[0.02]
Epistaxis	4(11.8)	17[0.16]	1(2.9)	3[0.02]	4(16.0)	6[0.08]	4(2.3)	4[0.01]	13(4.8)	30[0.03]
Nasal congestion	2(5.9)	3[0.03]	2(5.9)	2[0.02]	2(8.0)	4[0.05]	1(0.6)	1[0.00]	7(2.6)	10[0.01]
Respiratory disorder		-		-		-	5(2.8)	14[0.02]	5(1.9)	14[0.02]
Asthma	1(2.9)	3[0.03]	1(2.9)	1[0.01]		-	2(1.1)	2[0.00]	4(1.5)	6[0.01]
Rhinitis allergic	1(2.9)	1[0.01]	1(2.9)	1[0.01]		-	1(0.6)	1[0.00]	3(1.1)	3[0.00]
Productive cough		-		-		-	2(1.1)	2[0.00]	2(0.7)	2[0.00]
Sneezing	1(2.9)	1[0.01]		-		-	1(0.6)	1[0.00]	2(0.7)	2[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Haemoptysis	-		-		-		1(0.6)	3[0.01]	1(0.4)	3[0.00]
Dysphonia	-		-		1(4.0)	2[0.03]	-		1(0.4)	2[0.00]
Adenoidal hypertrophy	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Allergic respiratory disease	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Asthma exercise induced	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Asthmatic crisis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Bronchial hyperreactivity	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Dyspnoea	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Dyspnoea exertional	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hypoxia	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Middle lobe syndrome	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nasal obstruction	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sinus congestion	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sleep apnoea syndrome	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Upper respiratory tract congestion	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Upper respiratory tract inflammation	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Wheezing	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Nervous system disorders	5(14.7)	7[0.07]	12(35.3)	16[0.12]	11(44.0)	32[0.42]	51(28.8)	108[0.19]	79(29.3)	163[0.18]
Headache	5(14.7)	6[0.06]	8(23.5)	12[0.09]	9(36.0)	29[0.38]	34(19.2)	71[0.12]	56(20.7)	118[0.13]
Dizziness	-		1(2.9)	1[0.01]	1(4.0)	1[0.01]	6(3.4)	7[0.01]	8(3.0)	9[0.01]
Paraesthesia	-		-		-		7(4.0)	7[0.01]	7(2.6)	7[0.01]
Carpal tunnel syndrome	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Post-traumatic headache	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		-		2(0.7)	2[0.00]
Presyncope	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Sciatica	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Seizure	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Altered state of consciousness	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Cerebral infarction	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Cerebral microhaemorrhage	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Cognitive disorder	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Dizziness exertional	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Dizziness postural	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Epilepsy	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Facial paralysis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hypoaesthesia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Lethargy	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Migraine	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nerve compression	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nervous system disorder	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Neuropathy peripheral	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Restless legs syndrome	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sensory loss	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sinus headache	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Syncope	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Tongue biting	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Skin and subcutaneous tissue disorders	11(32.4)	25[0.24]	13(38.2)	18[0.14]	8(32.0)	12[0.16]	43(24.3)	76[0.13]	75(27.8)	131[0.15]
Eczema	2(5.9)	2[0.02]	5(14.7)	5[0.04]	-		8(4.5)	12[0.02]	15(5.6)	19[0.02]
Rash	5(14.7)	7[0.07]	-		1(4.0)	1[0.01]	8(4.5)	10[0.02]	14(5.2)	18[0.02]
Acne	-		1(2.9)	1[0.01]	5(20.0)	6[0.08]	2(1.1)	2[0.00]	8(3.0)	9[0.01]
Urticaria	1(2.9)	1[0.01]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	4(2.3)	4[0.01]	7(2.6)	7[0.01]
Erythema	3(8.8)	5[0.05]	1(2.9)	1[0.01]	-		1(0.6)	3[0.01]	5(1.9)	9[0.01]
Dermatitis contact	1(2.9)	1[0.01]	2(5.9)	2[0.02]	-		1(0.6)	1[0.00]	4(1.5)	4[0.00]
Dry skin	-		1(2.9)	1[0.01]	-		3(1.7)	3[0.01]	4(1.5)	4[0.00]
Pruritus	-		-		-		4(2.3)	4[0.01]	4(1.5)	4[0.00]
Blister	-		-		-		3(1.7)	5[0.01]	3(1.1)	5[0.01]
Hyperhidrosis	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Skin lesion	1(2.9)	1[0.01]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	-		3(1.1)	3[0.00]
Skin erosion	-		-		-		2(1.1)	4[0.01]	2(0.7)	4[0.00]
Alopecia	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Dermal cyst	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Dermatitis	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Ingrowing nail	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Photosensitivity reaction	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Purpura	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Rash pruritic	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Miliaria	1(2.9)	3[0.03]	-		-		-		1(0.4)	3[0.00]
Papule	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Petechiae	-		-		1(4.0)	2[0.03]	-		1(0.4)	2[0.00]
Alopecia areata	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Blood blister	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Dermatitis diaper	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Drug eruption	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Eczema asteatotic	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hangnail	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Mechanical urticaria	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Nail disorder	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Onychalgia	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Pigmentation disorder	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pruritus allergic	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Pruritus generalised	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Psoriasis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Rash papular	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Scab	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sebaceous gland disorder	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Skin disorder	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Skin irritation	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Skin ulcer	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Telangiectasia	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Vitiligo	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
General disorders and administration site conditions	8(23.5)	19[0.18]	12(35.3)	17[0.13]	9(36.0)	17[0.22]	34(19.2)	47[0.08]	63(23.3)	100[0.11]
Pyrexia	7(20.6)	16[0.15]	5(14.7)	8[0.06]	1(4.0)	3[0.04]	12(6.8)	14[0.02]	25(9.3)	41[0.05]
Fatigue	-		1(2.9)	1[0.01]	1(4.0)	2[0.03]	6(3.4)	6[0.01]	8(3.0)	9[0.01]
Influenza like illness	-		1(2.9)	2[0.02]	4(16.0)	4[0.05]	2(1.1)	5[0.01]	7(2.6)	11[0.01]
Chest pain	-		-		-		5(2.8)	5[0.01]	5(1.9)	5[0.01]
Oedema peripheral	-		1(2.9)	1[0.01]	-		4(2.3)	4[0.01]	5(1.9)	5[0.01]
Peripheral swelling	-		2(5.9)	2[0.02]	1(4.0)	1[0.01]	1(0.6)	1[0.00]	4(1.5)	4[0.00]
Hyperthermia	2(5.9)	2[0.02]	1(2.9)	1[0.01]	-		-		3(1.1)	3[0.00]
Local swelling	-		1(2.9)	1[0.01]	1(4.0)	1[0.01]	1(0.6)	1[0.00]	3(1.1)	3[0.00]
Chills	-		-		1(4.0)	2[0.03]	1(0.6)	1[0.00]	2(0.7)	3[0.00]
Adverse drug reaction	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Complication associated with device	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
General physical health deterioration	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Infusion site reaction	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Injection site erythema	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Injection site rash	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Injection site reaction	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Injection site swelling	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Localised oedema	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Oedema	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pain	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Tenderness	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Ulcer	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vessel puncture site haematoma	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vessel puncture site pain	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Investigations	2(5.9)	3[0.03]	1(2.9)	1[0.01]	6(24.0)	9[0.12]	41(23.2)	109[0.19]	50(18.5)	122[0.14]
Alanine aminotransferase increased	-		-		1(4.0)	1[0.01]	13(7.3)	20[0.03]	14(5.2)	21[0.02]
Aspartate aminotransferase increased	-		-		1(4.0)	1[0.01]	11(6.2)	17[0.03]	12(4.4)	18[0.02]
Gamma-glutamyltransferase increased	-		-		-		9(5.1)	15[0.03]	9(3.3)	15[0.02]
C-reactive protein increased	-		-		1(4.0)	1[0.01]	7(4.0)	9[0.02]	8(3.0)	10[0.01]
Blood cholesterol increased	-		-		-		5(2.8)	5[0.01]	5(1.9)	5[0.01]
Blood creatinine increased	1(2.9)	1[0.01]	-		-		2(1.1)	4[0.01]	3(1.1)	5[0.01]
Blood bilirubin increased	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Red blood cell count increased	-		-		3(12.0)	3[0.04]	-		3(1.1)	3[0.00]
Blood pressure increased	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Haemoglobin increased	-		-		2(8.0)	2[0.03]	-		2(0.7)	2[0.00]
Weight decreased	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Coagulation factor VIII level increased	-		-		-		1(0.6)	7[0.01]	1(0.4)	7[0.01]
Haemoglobin decreased	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Anti factor VIII antibody test	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Aspartate aminotransferase abnormal	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Blood HIV RNA increased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Blood alkaline phosphatase increased	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Blood creatine phosphokinase increased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Blood sodium increased	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Blood triglycerides increased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
C-reactive protein abnormal	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Electrocardiogram ST segment elevation	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Electrocardiogram T wave inversion	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatic enzyme increased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Intraocular pressure test	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Laboratory test abnormal	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Liver function test abnormal	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Mean cell haemoglobin decreased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Mean cell volume decreased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Monocyte count increased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Neutrophil count increased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Platelet count decreased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Prostatic specific antigen abnormal	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Serum ferritin decreased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sputum abnormal	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Transaminases abnormal	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Transaminases increased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vitamin D decreased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
White blood cell count increased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
White blood cells urine positive	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vascular disorders	5(14.7)	5[0.05]	-		-		24(13.6)	25[0.04]	29(10.7)	30[0.03]
Hypertension	-		-		-		19(10.7)	20[0.03]	19(7.0)	20[0.02]
Haematoma	2(5.9)	2[0.02]	-		-		1(0.6)	1[0.00]	3(1.1)	3[0.00]
Circulatory collapse	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Essential hypertension	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Flushing	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Haemorrhage	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Peripheral venous disease	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vein disorder	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Vein rupture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Immune system disorders	6(17.6)	13[0.12]	4(11.8)	5[0.04]	1(4.0)	3[0.04]	16(9.0)	21[0.04]	27(10.0)	42[0.05]
Seasonal allergy	2(5.9)	2[0.02]	1(2.9)	1[0.01]	1(4.0)	2[0.03]	10(5.6)	14[0.02]	14(5.2)	19[0.02]
Food allergy	1(2.9)	2[0.02]	2(5.9)	3[0.02]	-		1(0.6)	1[0.00]	4(1.5)	6[0.01]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Hypersensitivity	1(2.9)	2[0.02]	-		-		1(0.6)	1[0.00]	2(0.7)	3[0.00]
Allergy to arthropod sting	1(2.9)	1[0.01]	-		1(4.0)	1[0.01]	-		2(0.7)	2[0.00]
Allergic oedema	1(2.9)	2[0.02]	-		-		-		1(0.4)	2[0.00]
Allergy to animal	1(2.9)	2[0.02]	-		-		-		1(0.4)	2[0.00]
Allergy to arthropod bite	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Allergy to chemicals	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Allergy to metals	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Allergy to plants	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Drug hypersensitivity	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Mite allergy	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Mycotic allergy	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Rubber sensitivity	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Psychiatric disorders	-		1(2.9)	1[0.01]	5(20.0)	5[0.07]	18(10.2)	19[0.03]	24(8.9)	25[0.03]
Depression	-		-		2(8.0)	2[0.03]	6(3.4)	6[0.01]	8(3.0)	8[0.01]
Insomnia	-		-		1(4.0)	1[0.01]	4(2.3)	4[0.01]	5(1.9)	5[0.01]
Anxiety	-		-		1(4.0)	1[0.01]	2(1.1)	2[0.00]	3(1.1)	3[0.00]
Attention deficit/hyperactivity disorder	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Adjustment disorder with depressed mood	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Alcohol abuse	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Depressed mood	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Illusion	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Mental status changes	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sleep disorder	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Stress	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Blood and lymphatic system disorders	3(8.8)	3[0.03]	3(8.8)	3[0.02]	4(16.0)	4[0.05]	11(6.2)	15[0.03]	21(7.8)	25[0.03]
Anaemia	2(5.9)	2[0.02]	1(2.9)	1[0.01]	-		4(2.3)	5[0.01]	7(2.6)	8[0.01]
Lymphadenopathy	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Leukocytosis	1(2.9)	1[0.01]	-		-		1(0.6)	3[0.01]	2(0.7)	4[0.00]
Neutropenia	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Thrombocytopenia	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Eosinophilia	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Factor VIII inhibition	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Iron deficiency anaemia	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Lymphadenitis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Monocytosis	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Pancytopenia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Metabolism and nutrition disorders	1(2.9)	1[0.01]	-		2(8.0)	2[0.03]	18(10.2)	19[0.03]	21(7.8)	22[0.02]
Vitamin D deficiency	-		-		2(8.0)	2[0.03]	5(2.8)	5[0.01]	7(2.6)	7[0.01]
Hyperlipidaemia	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Iron deficiency	1(2.9)	1[0.01]	-		-		2(1.1)	2[0.00]	3(1.1)	3[0.00]
Gout	-		-		-		2(1.1)	3[0.01]	2(0.7)	3[0.00]
Diabetes mellitus	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Hypercholesterolaemia	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Decreased appetite	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hyperuricaemia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Eye disorders	3(8.8)	3[0.03]	5(14.7)	6[0.05]	1(4.0)	1[0.01]	11(6.2)	22[0.04]	20(7.4)	32[0.04]
Cataract	-		-		-		3(1.7)	4[0.01]	3(1.1)	4[0.00]
Conjunctivitis allergic	-		3(8.8)	4[0.03]	-		-		3(1.1)	4[0.00]
Diplopia	-		-		-		2(1.1)	4[0.01]	2(0.7)	4[0.00]
Dry eye	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Eye pruritus	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Glaucoma	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Myopia	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		-		2(0.7)	2[0.00]
Blepharospasm	-		-		-		1(0.6)	4[0.01]	1(0.4)	4[0.00]
Ocular myasthenia	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Blepharitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Conjunctival haemorrhage	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Corneal disorder	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Eye allergy	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Eye irritation	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Eye swelling	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Renal and urinary disorders	1(2.9)	1[0.01]	-		1(4.0)	1[0.01]	12(6.8)	12[0.02]	14(5.2)	14[0.02]
Dysuria	-		-		1(4.0)	1[0.01]	5(2.8)	5[0.01]	6(2.2)	6[0.01]
Calculus urinary	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Haematuria	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
IgA nephropathy	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nephrolithiasis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pollakiuria	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Renal colic	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Tubulointerstitial nephritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Urinary incontinence	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	0-5 years E[R]	6-11 years N(%)	6-11 years E[R]	12-17 years N(%)	12-17 years E[R]	>=18 years N(%)	>=18 years E[R]	Total N(%)	Total E[R]
Ear and labyrinth disorders	5(14.7)	7[0.07]	2(5.9)	3[0.02]	2(8.0)	2[0.03]	2(1.1)	2[0.00]	11(4.1)	14[0.02]
Ear pain	4(11.8)	4[0.04]	1(2.9)	2[0.02]	-	-	-	-	5(1.9)	6[0.01]
Cerumen impaction	2(5.9)	2[0.02]	-	-	-	-	-	-	2(0.7)	2[0.00]
Ear deformity acquired	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Ear disorder	-	-	1(2.9)	1[0.01]	-	-	-	-	1(0.4)	1[0.00]
Excessive cerumen production	-	-	-	-	1(4.0)	1[0.01]	-	-	1(0.4)	1[0.00]
Motion sickness	-	-	-	-	1(4.0)	1[0.01]	-	-	1(0.4)	1[0.00]
Tinnitus	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Tympanic membrane perforation	1(2.9)	1[0.01]	-	-	-	-	-	-	1(0.4)	1[0.00]
Cardiac disorders	-	-	-	-	2(8.0)	3[0.04]	7(4.0)	7[0.01]	9(3.3)	10[0.01]
Ventricular extrasystoles	-	-	-	-	1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Aortic valve stenosis	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Atrial fibrillation	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Atrioventricular block first degree	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Extrasystoles	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Palpitations	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pericarditis	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sinus arrhythmia	-	-	-	-	1(4.0)	1[0.01]	-	-	1(0.4)	1[0.00]
Sinus bradycardia	-	-	-	-	1(4.0)	1[0.01]	-	-	1(0.4)	1[0.00]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-	-	7(4.0)	7[0.01]	9(3.3)	9[0.01]
Skin papilloma	1(2.9)	1[0.01]	-	-	-	-	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Eye naevus	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatocellular carcinoma	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Lipoma	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nasopharyngeal neoplasm benign	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Neuroma	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pancreatic carcinoma metastatic	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pyogenic granuloma	-	-	1(2.9)	1[0.01]	-	-	-	-	1(0.4)	1[0.00]
Congenital, familial and genetic disorders	-	-	1(2.9)	1[0.01]	2(8.0)	2[0.03]	5(2.8)	5[0.01]	8(3.0)	8[0.01]
Gilbert's syndrome	-	-	-	-	2(8.0)	2[0.03]	-	-	2(0.7)	2[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Dermoid cyst	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hydrocele	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hypertrophic cardiomyopathy	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Odontogenic cyst	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pectus carinatum	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Thalassaemia alpha	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatobiliary disorders	1(2.9)	1[0.01]	-		-		7(4.0)	7[0.01]	8(3.0)	8[0.01]
Hepatic fibrosis	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Cholecystitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatic cirrhosis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatic function abnormal	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatic steatosis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatomegaly	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Surgical and medical procedures	-		1(2.9)	1[0.01]	1(4.0)	1[0.01]	5(2.8)	7[0.01]	7(2.6)	9[0.01]
Tooth extraction	-		1(2.9)	1[0.01]	-		1(0.6)	2[0.00]	2(0.7)	3[0.00]
Wisdom teeth removal	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Dental operation	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Dental implantation	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nail operation	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Reproductive system and breast disorders	3(8.8)	3[0.03]	-		1(4.0)	2[0.03]	2(1.1)	2[0.00]	6(2.2)	7[0.01]
Acquired phimosis	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Erectile dysfunction	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Penile adhesion	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Penis disorder	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Testicular pain	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Testicular swelling	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Varicocele	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Endocrine disorders	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Adrenal insufficiency	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Goitre	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Product issues	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Device dislocation	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Device malfunction	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]

Summary of adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Social circumstances	-	-	-	1(0.6) 3[0.01]	1(0.4) 3[0.00]
Tattoo	-	-	-	1(0.6) 3[0.01]	1(0.4) 3[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

39. 5%超の被験者（基本語別）で報告された有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Number of patients	34		34		25		177		270	
Patient years of exposure	106.03		128.04		76.37		571.70		882.13	
Exposure days	11140		13481		6586		48239		79446	
All adverse events	32(94.1)	350[3.30]	33(97.1)	333[2.60]	25(100)	278[3.64]	149(84.2)	1346[2.35]	239(88.5)	2307[2.62]
Infections and infestations										
Viral upper respiratory tract infection	11(32.4)	22[0.21]	10(29.4)	18[0.14]	7(28.0)	15[0.20]	50(28.2)	75[0.13]	78(28.9)	130[0.15]
Upper respiratory tract infection	10(29.4)	16[0.15]	12(35.3)	26[0.20]	5(20.0)	11[0.14]	30(16.9)	52[0.09]	57(21.1)	105[0.12]
Influenza	3(8.8)	5[0.05]	6(17.6)	10[0.08]	2(8.0)	3[0.04]	18(10.2)	24[0.04]	29(10.7)	42[0.05]
Gastroenteritis	5(14.7)	8[0.08]	8(23.5)	11[0.09]	-		7(4.0)	9[0.02]	20(7.4)	28[0.03]
Tonsillitis	1(2.9)	1[0.01]	3(8.8)	6[0.05]	1(4.0)	1[0.01]	13(7.3)	16[0.03]	18(6.7)	24[0.03]
Rhinitis	7(20.6)	7[0.07]	4(11.8)	7[0.05]	-		4(2.3)	5[0.01]	15(5.6)	19[0.02]
Bronchitis	3(8.8)	5[0.05]	3(8.8)	3[0.02]	1(4.0)	1[0.01]	8(4.5)	8[0.01]	15(5.6)	17[0.02]
Musculoskeletal and connective tissue disorders										
Arthralgia	2(5.9)	3[0.03]	4(11.8)	4[0.03]	5(20.0)	17[0.22]	32(18.1)	42[0.07]	43(15.9)	66[0.07]
Pain in extremity	3(8.8)	9[0.08]	6(17.6)	7[0.05]	3(12.0)	3[0.04]	10(5.6)	11[0.02]	22(8.1)	30[0.03]
Musculoskeletal pain	-		1(2.9)	1[0.01]	1(4.0)	1[0.01]	15(8.5)	16[0.03]	17(6.3)	18[0.02]
Back pain	-		1(2.9)	1[0.01]	2(8.0)	3[0.04]	12(6.8)	14[0.02]	15(5.6)	18[0.02]
Injury, poisoning and procedural complications										
Contusion	2(5.9)	2[0.02]	4(11.8)	4[0.03]	1(4.0)	1[0.01]	13(7.3)	25[0.04]	20(7.4)	32[0.04]
Laceration	1(2.9)	1[0.01]	3(8.8)	3[0.02]	2(8.0)	2[0.03]	13(7.3)	15[0.03]	19(7.0)	21[0.02]
Fall	5(14.7)	7[0.07]	2(5.9)	2[0.02]	3(12.0)	3[0.04]	7(4.0)	7[0.01]	17(6.3)	19[0.02]
Limb injury	4(11.8)	4[0.04]	4(11.8)	12[0.09]	4(16.0)	5[0.07]	4(2.3)	5[0.01]	16(5.9)	26[0.03]
Gastrointestinal disorders										
Diarrhoea	5(14.7)	7[0.07]	3(8.8)	4[0.03]	3(12.0)	3[0.04]	20(11.3)	25[0.04]	31(11.5)	39[0.04]
Vomiting	8(23.5)	9[0.08]	1(2.9)	3[0.02]	1(4.0)	1[0.01]	10(5.6)	11[0.02]	20(7.4)	24[0.03]
Nausea	-		-		5(20.0)	5[0.07]	12(6.8)	17[0.03]	17(6.3)	22[0.02]
Toothache	-		1(2.9)	1[0.01]	-		14(7.9)	15[0.03]	15(5.6)	16[0.02]
Respiratory, thoracic and mediastinal disorders										

Summary of adverse events (preferred term > 5%) by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	0-5 years E[R]	6-11 years N(%)	6-11 years E[R]	12-17 years N(%)	12-17 years E[R]	>=18 years N(%)	>=18 years E[R]	Total N(%)	Total E[R]
Cough	14(41.2)	23[0.22]	5(14.7)	5[0.04]	7(28.0)	11[0.14]	11(6.2)	14[0.02]	37(13.7)	53[0.06]
Oropharyngeal pain	2(5.9)	2[0.02]	7(20.6)	9[0.07]	2(8.0)	4[0.05]	18(10.2)	20[0.03]	29(10.7)	35[0.04]
Rhinorrhoea	4(11.8)	4[0.04]	3(8.8)	4[0.03]	2(8.0)	5[0.07]	6(3.4)	7[0.01]	15(5.6)	20[0.02]
Nervous system disorders										
Headache	5(14.7)	6[0.06]	8(23.5)	12[0.09]	9(36.0)	29[0.38]	34(19.2)	71[0.12]	56(20.7)	118[0.13]
Skin and subcutaneous tissue disorders										
Eczema	2(5.9)	2[0.02]	5(14.7)	5[0.04]		-	8(4.5)	12[0.02]	15(5.6)	19[0.02]
Rash	5(14.7)	7[0.07]		-	1(4.0)	1[0.01]	8(4.5)	10[0.02]	14(5.2)	18[0.02]
General disorders and administration site conditions										
Pyrexia	7(20.6)	16[0.15]	5(14.7)	8[0.06]	1(4.0)	3[0.04]	12(6.8)	14[0.02]	25(9.3)	41[0.05]
Investigations										
Alanine aminotransferase increased		-		-	1(4.0)	1[0.01]	13(7.3)	20[0.03]	14(5.2)	21[0.02]
Vascular disorders										
Hypertension		-		-		-	19(10.7)	20[0.03]	19(7.0)	20[0.02]
Immune system disorders										
Seasonal allergy	2(5.9)	2[0.02]	1(2.9)	1[0.01]	1(4.0)	2[0.03]	10(5.6)	14[0.02]	14(5.2)	19[0.02]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

40. 治験薬との因果関係が「あり」又は「可能性あり」と判定された有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Number of patients	34	34	25	177	270
Patient years of exposure	106.03	128.04	76.37	571.70	882.13
Exposure days	11140	13481	6586	48239	79446
All adverse events	7(20.6) 12[0.11]	3(8.8) 3[0.02]	4(16.0) 8[0.10]	26(14.7) 61[0.11]	40(14.8) 84[0.10]
Investigations	-	1(2.9) 1[0.01]	2(8.0) 3[0.04]	11(6.2) 28[0.05]	14(5.2) 32[0.04]
Aspartate aminotransferase increased	-	-	1(4.0) 1[0.01]	5(2.8) 6[0.01]	6(2.2) 7[0.01]
Alanine aminotransferase increased	-	-	1(4.0) 1[0.01]	3(1.7) 4[0.01]	4(1.5) 5[0.01]
Gamma-glutamyltransferase increased	-	-	-	2(1.1) 2[0.00]	2(0.7) 2[0.00]
Coagulation factor VIII level increased	-	-	-	1(0.6) 7[0.01]	1(0.4) 7[0.01]
Anti factor VIII antibody test	-	1(2.9) 1[0.01]	-	-	1(0.4) 1[0.00]
Aspartate aminotransferase abnormal	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Blood bilirubin increased	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
C-reactive protein increased	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Electrocardiogram ST segment elevation	-	-	1(4.0) 1[0.01]	-	1(0.4) 1[0.00]
Liver function test abnormal	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Mean cell haemoglobin decreased	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Mean cell volume decreased	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Serum ferritin decreased	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Transaminases abnormal	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Transaminases increased	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Nervous system disorders	-	1(2.9) 1[0.01]	-	6(3.4) 6[0.01]	7(2.6) 7[0.01]
Headache	-	-	-	4(2.3) 4[0.01]	4(1.5) 4[0.00]
Dizziness	-	1(2.9) 1[0.01]	-	1(0.6) 1[0.00]	2(0.7) 2[0.00]
Presyncope	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]

Summary of adverse events possible or probably related to trial product by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Skin and subcutaneous tissue disorders	1(2.9)	3[0.03]	-		-		5(2.8)	8[0.01]	6(2.2)	11[0.01]
Rash	1(2.9)	3[0.03]	-		-		2(1.1)	3[0.01]	3(1.1)	6[0.01]
Erythema	-		-		-		1(0.6)	3[0.01]	1(0.4)	3[0.00]
Pruritus	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Purpura	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Injury, poisoning and procedural complications	3(8.8)	3[0.03]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	1(0.6)	1[0.00]	6(2.2)	6[0.01]
Accidental overdose	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Contusion	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Drug administration error	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Overdose	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Post procedural complication	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Product preparation error	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Musculoskeletal and connective tissue disorders	-		-		-		5(2.8)	5[0.01]	5(1.9)	5[0.01]
Arthralgia	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Joint range of motion decreased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Muscle haemorrhage	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gastrointestinal disorders	-		-		-		3(1.7)	6[0.01]	3(1.1)	6[0.01]
Nausea	-		-		-		1(0.6)	3[0.01]	1(0.4)	3[0.00]
Flatulence	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Gastritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Blood and lymphatic system disorders	-		-		2(8.0)	2[0.03]	1(0.6)	1[0.00]	3(1.1)	3[0.00]
Factor VIII inhibition	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Neutropenia	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Thrombocytopenia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
General disorders and administration site conditions	1(2.9)	1[0.01]	-		-		2(1.1)	2[0.00]	3(1.1)	3[0.00]
Injection site reaction	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Injection site swelling	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]

Summary of adverse events possible or probably related to trial product by age group - trials 3776, 3859, 4033 and 3885
- safety analysis set

Continued...

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Pyrexia	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Infections and infestations	-	-	-	2(1.1) 2[0.00]	2(0.7) 2[0.00]
Intervertebral discitis	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Tinea infection	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Vascular disorders	2(5.9) 2[0.02]	-	-	-	2(0.7) 2[0.00]
Haematoma	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Haemorrhage	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Cardiac disorders	-	-	1(4.0) 2[0.03]	-	1(0.4) 2[0.00]
Sinus arrhythmia	-	-	1(4.0) 1[0.01]	-	1(0.4) 1[0.00]
Sinus bradycardia	-	-	1(4.0) 1[0.01]	-	1(0.4) 1[0.00]
Immune system disorders	1(2.9) 2[0.02]	-	-	-	1(0.4) 2[0.00]
Hypersensitivity	1(2.9) 2[0.02]	-	-	-	1(0.4) 2[0.00]
Hepatobiliary disorders	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Hepatic function abnormal	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Metabolism and nutrition disorders	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Iron deficiency	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Respiratory, thoracic and mediastinal disorders	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Cough	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

41. 重篤な有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%)	0-5 years E[R]	6-11 years N(%)	6-11 years E[R]	12-17 years N(%)	12-17 years E[R]	>=18 years N(%)	>=18 years E[R]	Total N(%)	Total E[R]
Number of patients	34		34		25		177		270	
Patient years of exposure	106.03		128.04		76.37		571.70		882.13	
Exposure days	11140		13481		6586		48239		79446	
All adverse events	10(29.4)	12[0.11]	5(14.7)	5[0.04]	5(20.0)	7[0.09]	27(15.3)	43[0.08]	47(17.4)	67[0.08]
Infections and infestations	4(11.8)	5[0.05]	1(2.9)	1[0.01]	1(4.0)	2[0.03]	8(4.5)	12[0.02]	14(5.2)	20[0.02]
Cellulitis	1(2.9)	1[0.01]	-		-		1(0.6)	2[0.00]	2(0.7)	3[0.00]
Device related infection	1(2.9)	2[0.02]	-		-		1(0.6)	1[0.00]	2(0.7)	3[0.00]
Bacterial sepsis	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Anal abscess	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Catheter site infection	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Encephalitis	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Enteritis infectious	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Infective spondylitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Intervertebral discitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Osteomyelitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pneumonia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sepsis syndrome	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Tonsillitis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Tuberculosis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Viral infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Injury, poisoning and procedural complications	1(2.9)	1[0.01]	1(2.9)	1[0.01]	3(12.0)	3[0.04]	6(3.4)	6[0.01]	11(4.1)	11[0.01]
Fall	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Ankle fracture	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Extradural haematoma	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Face injury	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Femoral neck fracture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Forearm fracture	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Head injury	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Injury	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Road traffic accident	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Toxicity to various agents	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gastrointestinal disorders	-		2(5.9)	2[0.02]	-		5(2.8)	5[0.01]	7(2.6)	7[0.01]
Duodenal ulcer	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Abdominal hernia	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]

Summary of serious adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Gastric varices	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Gastric varices haemorrhage	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Gastritis	-	1(2.9) 1[0.01]	-	-	1(0.4) 1[0.00]
Pancreatitis acute	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Nervous system disorders	-	-	-	3(1.7) 4[0.01]	3(1.1) 4[0.00]
Cerebral infarction	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Cerebral microhaemorrhage	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Seizure	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Syncope	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Musculoskeletal and connective tissue disorders	1(2.9) 1[0.01]	-	-	2(1.1) 2[0.00]	3(1.1) 3[0.00]
Muscle haemorrhage	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Pathological fracture	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Synovitis	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	-	-	3(1.7) 3[0.01]	3(1.1) 3[0.00]
Hepatocellular carcinoma	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Neuroma	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Pancreatic carcinoma metastatic	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Renal and urinary disorders	-	-	-	3(1.7) 3[0.01]	3(1.1) 3[0.00]
Calculus urinary	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
IgA nephropathy	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Tubulointerstitial nephritis	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Congenital, familial and genetic disorders	-	-	-	2(1.1) 2[0.00]	2(0.7) 2[0.00]
Hydrocele	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
Hypertrophic cardiomyopathy	-	-	-	1(0.6) 1[0.00]	1(0.4) 1[0.00]
General disorders and administration site conditions	1(2.9) 1[0.01]	-	1(4.0) 1[0.01]	-	2(0.7) 2[0.00]

Summary of serious adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set
Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Complication associated with device	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Pyrexia	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		-		2(0.7)	2[0.00]
Adenoidal hypertrophy	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Hypoxia	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Vascular disorders	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Circulatory collapse	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Haemorrhage	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Blood and lymphatic system disorders	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Factor VIII inhibition	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Cardiac disorders	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Aortic valve stenosis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Eye disorders	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Cataract	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatobiliary disorders	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Cholecystitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Immune system disorders	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Hypersensitivity	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Product issues	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Device dislocation	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Psychiatric disorders	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Depression	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Reproductive system and breast disorders	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Acquired phimosis	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

42. 軽度の有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%)	0-5 years E[R]	6-11 years N(%)	6-11 years E[R]	12-17 years N(%)	12-17 years E[R]	>=18 years N(%)	>=18 years E[R]	Total N(%)	Total E[R]
Number of patients	34		34		25		177		270	
Patient years of exposure	106.03		128.04		76.37		571.70		882.13	
Exposure days	11140		13481		6586		48239		79446	
All adverse events	27(79.4)	278[2.62]	31(91.2)	298[2.33]	22(88.0)	241[3.16]	141(79.7)	997[1.74]	221(81.9)	1814[2.06]
Infections and infestations	21(61.8)	80[0.75]	26(76.5)	114[0.89]	12(48.0)	45[0.59]	96(54.2)	239[0.42]	155(57.4)	478[0.54]
Viral upper respiratory tract infection	8(23.5)	13[0.12]	10(29.4)	18[0.14]	7(28.0)	15[0.20]	47(26.6)	66[0.12]	72(26.7)	112[0.13]
Upper respiratory tract infection	7(20.6)	11[0.10]	11(32.4)	22[0.17]	5(20.0)	10[0.13]	29(16.4)	46[0.08]	52(19.3)	89[0.10]
Influenza	2(5.9)	4[0.04]	6(17.6)	10[0.08]	2(8.0)	3[0.04]	14(7.9)	17[0.03]	24(8.9)	34[0.04]
Gastroenteritis	5(14.7)	8[0.08]	7(20.6)	10[0.08]	-	-	3(1.7)	3[0.01]	15(5.6)	21[0.02]
Rhinitis	6(17.6)	6[0.06]	4(11.8)	7[0.05]	-	-	4(2.3)	5[0.01]	14(5.2)	18[0.02]
Tonsillitis	-	-	2(5.9)	5[0.04]	-	-	11(6.2)	13[0.02]	13(4.8)	18[0.02]
Viral infection	2(5.9)	2[0.02]	2(5.9)	2[0.02]	5(20.0)	6[0.08]	2(1.1)	3[0.01]	11(4.1)	13[0.01]
Bronchitis	2(5.9)	4[0.04]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	5(2.8)	5[0.01]	9(3.3)	11[0.01]
Ear infection	3(8.8)	3[0.03]	3(8.8)	5[0.04]	2(8.0)	3[0.04]	-	-	8(3.0)	11[0.01]
Conjunctivitis	2(5.9)	2[0.02]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	4(2.3)	4[0.01]	8(3.0)	8[0.01]
Sinusitis	1(2.9)	1[0.01]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	5(2.8)	5[0.01]	8(3.0)	8[0.01]
Otitis media	2(5.9)	2[0.02]	3(8.8)	3[0.02]	-	-	2(1.1)	3[0.01]	7(2.6)	8[0.01]
Pharyngitis	1(2.9)	1[0.01]	1(2.9)	2[0.02]	1(4.0)	1[0.01]	4(2.3)	4[0.01]	7(2.6)	8[0.01]
Nasopharyngitis	1(2.9)	1[0.01]	-	-	-	-	3(1.7)	4[0.01]	4(1.5)	5[0.01]
Pharyngitis streptococcal	2(5.9)	2[0.02]	1(2.9)	2[0.02]	-	-	1(0.6)	1[0.00]	4(1.5)	5[0.01]
Fungal skin infection	-	-	-	-	1(4.0)	1[0.01]	3(1.7)	3[0.01]	4(1.5)	4[0.00]
Tooth abscess	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-	-	1(0.6)	4[0.01]	3(1.1)	6[0.01]
Folliculitis	-	-	-	-	-	-	3(1.7)	4[0.01]	3(1.1)	4[0.00]
Periodontitis	-	-	1(2.9)	1[0.01]	-	-	2(1.1)	3[0.01]	3(1.1)	4[0.00]
Eye infection	-	-	1(2.9)	1[0.01]	1(4.0)	1[0.01]	1(0.6)	1[0.00]	3(1.1)	3[0.00]
Molluscum contagiosum	2(5.9)	2[0.02]	1(2.9)	1[0.01]	-	-	-	-	3(1.1)	3[0.00]
Otitis externa	1(2.9)	1[0.01]	-	-	-	-	2(1.1)	2[0.00]	3(1.1)	3[0.00]
Pneumonia	-	-	2(5.9)	2[0.02]	-	-	1(0.6)	1[0.00]	3(1.1)	3[0.00]
Pulpitis dental	-	-	-	-	-	-	3(1.7)	3[0.01]	3(1.1)	3[0.00]
Tinea pedis	-	-	-	-	-	-	3(1.7)	3[0.01]	3(1.1)	3[0.00]
Enterobiasis	1(2.9)	5[0.05]	1(2.9)	1[0.01]	-	-	-	-	2(0.7)	6[0.01]
Hordeolum	-	-	-	-	1(4.0)	1[0.01]	1(0.6)	2[0.00]	2(0.7)	3[0.00]
Tinea infection	-	-	-	-	-	-	2(1.1)	3[0.01]	2(0.7)	3[0.00]
Acute sinusitis	-	-	2(5.9)	2[0.02]	-	-	-	-	2(0.7)	2[0.00]
Cystitis	-	-	1(2.9)	1[0.01]	-	-	1(0.6)	1[0.00]	2(0.7)	2[0.00]

Summary of mild adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Gastrointestinal infection	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Impetigo	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		-		2(0.7)	2[0.00]
Localised infection	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Onychomycosis	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Pharyngotonsillitis	-		2(5.9)	2[0.02]	-		-		2(0.7)	2[0.00]
Respiratory tract infection	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Streptococcal infection	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		-		2(0.7)	2[0.00]
Urinary tract infection	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Viral pharyngitis	2(5.9)	2[0.02]	-		-		-		2(0.7)	2[0.00]
Otitis media acute	-		1(2.9)	3[0.02]	-		-		1(0.4)	3[0.00]
Paronychia	-		1(2.9)	3[0.02]	-		-		1(0.4)	3[0.00]
Cellulitis	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Genital herpes	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Helminthic infection	1(2.9)	2[0.02]	-		-		-		1(0.4)	2[0.00]
Lower respiratory tract infection	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Tooth infection	-		1(2.9)	2[0.02]	-		-		1(0.4)	2[0.00]
Abscess neck	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Body tinea	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Chlamydial infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Epididymitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Fungal infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
H1N1 influenza	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Helicobacter gastritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatitis C	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Infectious mononucleosis	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Labyrinthitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Laryngitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Mumps	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Oral herpes	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Postoperative wound infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Scarlet fever	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Sinusitis bacterial	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Skin infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Tracheitis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Urethritis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Varicella	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Viral diarrhoea	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Viral parotitis	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]

Summary of mild adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Wound infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gastrointestinal disorders	12(35.3)	30[0.28]	14(41.2)	25[0.20]	9(36.0)	15[0.20]	59(33.3)	119[0.21]	94(34.8)	189[0.21]
Diarrhoea	5(14.7)	7[0.07]	3(8.8)	4[0.03]	3(12.0)	3[0.04]	17(9.6)	20[0.03]	28(10.4)	34[0.04]
Vomiting	6(17.6)	7[0.07]	1(2.9)	3[0.02]	1(4.0)	1[0.01]	9(5.1)	10[0.02]	17(6.3)	21[0.02]
Nausea	-		-		5(20.0)	5[0.07]	11(6.2)	16[0.03]	16(5.9)	21[0.02]
Abdominal pain	5(14.7)	6[0.06]	1(2.9)	1[0.01]	-		6(3.4)	6[0.01]	12(4.4)	13[0.01]
Abdominal pain upper	1(2.9)	1[0.01]	1(2.9)	1[0.01]	1(4.0)	2[0.03]	7(4.0)	7[0.01]	10(3.7)	11[0.01]
Toothache	-		1(2.9)	1[0.01]	-		9(5.1)	10[0.02]	10(3.7)	11[0.01]
Dental caries	1(2.9)	3[0.03]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	5(2.8)	6[0.01]	8(3.0)	11[0.01]
Constipation	-		3(8.8)	4[0.03]	-		2(1.1)	3[0.01]	5(1.9)	7[0.01]
Gastrooesophageal reflux disease	1(2.9)	1[0.01]	-		-		4(2.3)	4[0.01]	5(1.9)	5[0.01]
Dyspepsia	-		-		-		4(2.3)	4[0.01]	4(1.5)	4[0.00]
Gastritis	-		1(2.9)	1[0.01]	-		3(1.7)	3[0.01]	4(1.5)	4[0.00]
Stomatitis	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Abdominal discomfort	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Aphthous ulcer	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Chapped lips	-		2(5.9)	2[0.02]	-		-		2(0.7)	2[0.00]
Gastrointestinal disorder	1(2.9)	1[0.01]	-		1(4.0)	1[0.01]	-		2(0.7)	2[0.00]
Irritable bowel syndrome	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Perianal erythema	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Dysphagia	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Flatulence	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Abdominal hernia	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Anal fissure	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Barrett's oesophagus	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Chronic gastritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Dental discomfort	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Dental necrosis	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Diaphragmatic hernia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Duodenitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Enterocolitis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Faeces soft	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Gastritis erosive	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gingival bleeding	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gingival swelling	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Haematochezia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Haemorrhoids	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hiatus hernia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Inguinal hernia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of mild adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	0-5 years E[R]	6-11 years N(%)	6-11 years E[R]	12-17 years N(%)	12-17 years E[R]	>=18 years N(%)	>=18 years E[R]	Total N(%)	Total E[R]
Lip ulceration	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Loose tooth	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Mouth haemorrhage	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Mouth ulceration	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Noninfective gingivitis	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Oral pain	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Pancreatitis	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Rectal haemorrhage	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Retching	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Swollen tongue	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Uvulitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Musculoskeletal and connective tissue disorders	6(17.6)	13[0.12]	13(38.2)	19[0.15]	10(40.0)	34[0.45]	61(34.5)	109[0.19]	90(33.3)	175[0.20]
Arthralgia	1(2.9)	1[0.01]	4(11.8)	4[0.03]	4(16.0)	15[0.20]	23(13.0)	29[0.05]	32(11.9)	49[0.06]
Pain in extremity	2(5.9)	8[0.08]	5(14.7)	5[0.04]	3(12.0)	3[0.04]	7(4.0)	8[0.01]	17(6.3)	24[0.03]
Musculoskeletal pain	-		1(2.9)	1[0.01]	1(4.0)	1[0.01]	10(5.6)	10[0.02]	12(4.4)	12[0.01]
Back pain	-		1(2.9)	1[0.01]	2(8.0)	2[0.03]	7(4.0)	8[0.01]	10(3.7)	11[0.01]
Myalgia	1(2.9)	1[0.01]	-		3(12.0)	5[0.07]	3(1.7)	3[0.01]	7(2.6)	9[0.01]
Arthropathy	-		1(2.9)	1[0.01]	-		4(2.3)	4[0.01]	5(1.9)	5[0.01]
Musculoskeletal stiffness	-		1(2.9)	1[0.01]	-		4(2.3)	4[0.01]	5(1.9)	5[0.01]
Tendonitis	-		-		-		5(2.8)	5[0.01]	5(1.9)	5[0.01]
Joint range of motion decreased	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		2(1.1)	2[0.00]	4(1.5)	4[0.00]
Joint swelling	1(2.9)	1[0.01]	-		-		3(1.7)	3[0.01]	4(1.5)	4[0.00]
Synovitis	-		-		-		4(2.3)	4[0.01]	4(1.5)	4[0.00]
Pain in jaw	-		-		2(8.0)	3[0.04]	1(0.6)	1[0.00]	3(1.1)	4[0.00]
Haemophilic arthropathy	-		1(2.9)	1[0.01]	-		2(1.1)	2[0.00]	3(1.1)	3[0.00]
Joint lock	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Neck pain	-		-		1(4.0)	3[0.04]	1(0.6)	1[0.00]	2(0.7)	4[0.00]
Flank pain	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Muscle spasms	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Musculoskeletal chest pain	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Plantar fasciitis	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Rotator cuff syndrome	-		-		-		1(0.6)	3[0.01]	1(0.4)	3[0.00]
Rheumatic disorder	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Bone pain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Bursitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Chondropathy	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Costochondritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Growing pains	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]

Summary of mild adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	0-5 years E[R]	6-11 years N(%)	6-11 years E[R]	12-17 years N(%)	12-17 years E[R]	>=18 years N(%)	>=18 years E[R]	Total N(%)	Total E[R]
Joint effusion	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Limb discomfort	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Muscle tightness	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Musculoskeletal discomfort	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Myositis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Osteoarthritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Periostitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Scoliosis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Synovial disorder	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Tendon pain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Torticollis	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Injury, poisoning and procedural complications	11(32.4)	24[0.23]	18(52.9)	45[0.35]	9(36.0)	23[0.30]	44(24.9)	77[0.13]	82(30.4)	169[0.19]
Contusion	1(2.9)	1[0.01]	3(8.8)	3[0.02]	1(4.0)	1[0.01]	9(5.1)	19[0.03]	14(5.2)	24[0.03]
Limb injury	3(8.8)	3[0.03]	3(8.8)	11[0.09]	4(16.0)	5[0.07]	3(1.7)	4[0.01]	13(4.8)	23[0.03]
Laceration	1(2.9)	1[0.01]	3(8.8)	3[0.02]	-		9(5.1)	11[0.02]	13(4.8)	15[0.02]
Ligament sprain	-		5(14.7)	5[0.04]	1(4.0)	1[0.01]	6(3.4)	7[0.01]	12(4.4)	13[0.01]
Fall	3(8.8)	3[0.03]	2(5.9)	2[0.02]	2(8.0)	2[0.03]	4(2.3)	4[0.01]	11(4.1)	11[0.01]
Joint injury	2(5.9)	2[0.02]	3(8.8)	4[0.03]	-		4(2.3)	4[0.01]	9(3.3)	10[0.01]
Skin abrasion	-		1(2.9)	2[0.02]	1(4.0)	1[0.01]	5(2.8)	5[0.01]	7(2.6)	8[0.01]
Head injury	2(5.9)	3[0.03]	1(2.9)	1[0.01]	3(12.0)	4[0.05]	-		6(2.2)	8[0.01]
Muscle strain	-		1(2.9)	1[0.01]	2(8.0)	3[0.04]	3(1.7)	4[0.01]	6(2.2)	8[0.01]
Arthropod bite	1(2.9)	1[0.01]	1(2.9)	1[0.01]	2(8.0)	2[0.03]	2(1.1)	2[0.00]	6(2.2)	6[0.01]
Arthropod sting	1(2.9)	3[0.03]	3(8.8)	3[0.02]	-		-		4(1.5)	6[0.01]
Excoriation	1(2.9)	1[0.01]	2(5.9)	2[0.02]	-		-		3(1.1)	3[0.00]
Scratch	-		-		1(4.0)	1[0.01]	2(1.1)	2[0.00]	3(1.1)	3[0.00]
Accidental overdose	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Post-traumatic pain	-		1(2.9)	1[0.01]	1(4.0)	1[0.01]	-		2(0.7)	2[0.00]
Road traffic accident	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Thermal burn	1(2.9)	1[0.01]	-		1(4.0)	1[0.01]	-		2(0.7)	2[0.00]
Traumatic haemorrhage	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Wound	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Abdominal injury	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Chest injury	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Drug administration error	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Electric shock	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Epicondylitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Face injury	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Foreign body in eye	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hand fracture	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]

Summary of mild adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Medication error	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Mouth injury	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Muscle rupture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Overdose	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Procedural pain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Product preparation error	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Splinter	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sunburn	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Tendon injury	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Tooth injury	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Traumatic haematoma	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	13(38.2)	51[0.48]	14(41.2)	26[0.20]	11(44.0)	33[0.43]	41(23.2)	66[0.12]	79(29.3)	176[0.20]
Cough	11(32.4)	19[0.18]	5(14.7)	5[0.04]	7(28.0)	11[0.14]	10(5.6)	13[0.02]	33(12.2)	48[0.05]
Oropharyngeal pain	2(5.9)	2[0.02]	7(20.6)	9[0.07]	2(8.0)	4[0.05]	16(9.0)	17[0.03]	27(10.0)	32[0.04]
Rhinorrhoea	4(11.8)	4[0.04]	2(5.9)	3[0.02]	2(8.0)	5[0.07]	6(3.4)	7[0.01]	14(5.2)	19[0.02]
Epistaxis	4(11.8)	17[0.16]	1(2.9)	3[0.02]	4(16.0)	6[0.08]	4(2.3)	4[0.01]	13(4.8)	30[0.03]
Nasal congestion	2(5.9)	3[0.03]	2(5.9)	2[0.02]	2(8.0)	4[0.05]	1(0.6)	1[0.00]	7(2.6)	10[0.01]
Respiratory disorder	-		-		-		4(2.3)	10[0.02]	4(1.5)	10[0.01]
Asthma	1(2.9)	2[0.02]	1(2.9)	1[0.01]	-		2(1.1)	2[0.00]	4(1.5)	5[0.01]
Rhinitis allergic	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	3(1.1)	3[0.00]
Sneezing	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Haemoptysis	-		-		-		1(0.6)	3[0.01]	1(0.4)	3[0.00]
Dysphonia	-		-		1(4.0)	2[0.03]	-		1(0.4)	2[0.00]
Asthma exercise induced	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Asthmatic crisis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Bronchial hyperreactivity	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Dyspnoea	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Middle lobe syndrome	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nasal obstruction	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Productive cough	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sinus congestion	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sleep apnoea syndrome	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Upper respiratory tract congestion	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Upper respiratory tract inflammation	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Wheezing	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]

Summary of mild adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	0-5 years E[R]	6-11 years N(%)	6-11 years E[R]	12-17 years N(%)	12-17 years E[R]	>=18 years N(%)	>=18 years E[R]	Total N(%)	Total E[R]
Skin and subcutaneous tissue disorders	11(32.4)	25[0.24]	12(35.3)	16[0.12]	7(28.0)	11[0.14]	40(22.6)	70[0.12]	70(25.9)	122[0.14]
Eczema	2(5.9)	2[0.02]	5(14.7)	5[0.04]	-	-	8(4.5)	12[0.02]	15(5.6)	19[0.02]
Rash	5(14.7)	7[0.07]	-	-	1(4.0)	1[0.01]	8(4.5)	8[0.01]	14(5.2)	16[0.02]
Urticaria	1(2.9)	1[0.01]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	4(2.3)	4[0.01]	7(2.6)	7[0.01]
Acne	-	-	1(2.9)	1[0.01]	4(16.0)	5[0.07]	1(0.6)	1[0.00]	6(2.2)	7[0.01]
Erythema	3(8.8)	5[0.05]	-	-	-	-	1(0.6)	3[0.01]	4(1.5)	8[0.01]
Dry skin	-	-	1(2.9)	1[0.01]	-	-	3(1.7)	3[0.01]	4(1.5)	4[0.00]
Pruritus	-	-	-	-	-	-	4(2.3)	4[0.01]	4(1.5)	4[0.00]
Blister	-	-	-	-	-	-	3(1.7)	5[0.01]	3(1.1)	5[0.01]
Dermatitis contact	1(2.9)	1[0.01]	2(5.9)	2[0.02]	-	-	-	-	3(1.1)	3[0.00]
Hyperhidrosis	-	-	-	-	-	-	3(1.7)	3[0.01]	3(1.1)	3[0.00]
Skin lesion	1(2.9)	1[0.01]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	-	-	3(1.1)	3[0.00]
Skin erosion	-	-	-	-	-	-	2(1.1)	4[0.01]	2(0.7)	4[0.00]
Alopecia	-	-	-	-	-	-	2(1.1)	2[0.00]	2(0.7)	2[0.00]
Dermal cyst	-	-	-	-	-	-	2(1.1)	2[0.00]	2(0.7)	2[0.00]
Dermatitis	-	-	1(2.9)	1[0.01]	-	-	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Purpura	-	-	1(2.9)	1[0.01]	-	-	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Rash pruritic	-	-	-	-	-	-	2(1.1)	2[0.00]	2(0.7)	2[0.00]
Miliaria	1(2.9)	3[0.03]	-	-	-	-	-	-	1(0.4)	3[0.00]
Papule	-	-	-	-	-	-	1(0.6)	2[0.00]	1(0.4)	2[0.00]
Petechiae	-	-	-	-	1(4.0)	2[0.03]	-	-	1(0.4)	2[0.00]
Alopecia areata	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Blood blister	-	-	1(2.9)	1[0.01]	-	-	-	-	1(0.4)	1[0.00]
Dermatitis diaper	1(2.9)	1[0.01]	-	-	-	-	-	-	1(0.4)	1[0.00]
Drug eruption	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Eczema asteatotic	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hangnail	-	-	1(2.9)	1[0.01]	-	-	-	-	1(0.4)	1[0.00]
Mechanical urticaria	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nail disorder	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Onychalgia	-	-	1(2.9)	1[0.01]	-	-	-	-	1(0.4)	1[0.00]
Photosensitivity reaction	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pigmentation disorder	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pruritus allergic	-	-	-	-	1(4.0)	1[0.01]	-	-	1(0.4)	1[0.00]
Pruritus generalised	1(2.9)	1[0.01]	-	-	-	-	-	-	1(0.4)	1[0.00]
Psoriasis	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Rash papular	1(2.9)	1[0.01]	-	-	-	-	-	-	1(0.4)	1[0.00]
Scab	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sebaceous gland disorder	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Skin disorder	-	-	-	-	-	-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Skin irritation	1(2.9)	1[0.01]	-	-	-	-	-	-	1(0.4)	1[0.00]

Summary of mild adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Skin ulcer	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Telangiectasia	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Vitiligo	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nervous system disorders	2(5.9)	3[0.03]	12(35.3)	16[0.12]	11(44.0)	32[0.42]	42(23.7)	70[0.12]	67(24.8)	121[0.14]
Headache	2(5.9)	3[0.03]	8(23.5)	12[0.09]	9(36.0)	29[0.38]	31(17.5)	53[0.09]	50(18.5)	97[0.11]
Dizziness	-		1(2.9)	1[0.01]	1(4.0)	1[0.01]	6(3.4)	6[0.01]	8(3.0)	8[0.01]
Paraesthesia	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Carpal tunnel syndrome	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Altered state of consciousness	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Cognitive disorder	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Dizziness exertional	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Dizziness postural	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Migraine	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Post-traumatic headache	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Presyncope	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Restless legs syndrome	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sensory loss	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sinus headache	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Tongue biting	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
General disorders and administration site conditions	7(20.6)	17[0.16]	11(32.4)	16[0.12]	8(32.0)	16[0.21]	29(16.4)	35[0.06]	55(20.4)	84[0.10]
Pyrexia	6(17.6)	15[0.14]	5(14.7)	8[0.06]	1(4.0)	3[0.04]	10(5.6)	12[0.02]	22(8.1)	38[0.04]
Influenza like illness	-		1(2.9)	2[0.02]	4(16.0)	4[0.05]	1(0.6)	1[0.00]	6(2.2)	7[0.01]
Fatigue	-		-		1(4.0)	2[0.03]	3(1.7)	3[0.01]	4(1.5)	5[0.01]
Chest pain	-		-		-		4(2.3)	4[0.01]	4(1.5)	4[0.00]
Oedema peripheral	-		1(2.9)	1[0.01]	-		3(1.7)	3[0.01]	4(1.5)	4[0.00]
Hyperthermia	2(5.9)	2[0.02]	1(2.9)	1[0.01]	-		-		3(1.1)	3[0.00]
Local swelling	-		1(2.9)	1[0.01]	1(4.0)	1[0.01]	1(0.6)	1[0.00]	3(1.1)	3[0.00]
Peripheral swelling	-		2(5.9)	2[0.02]	1(4.0)	1[0.01]	-		3(1.1)	3[0.00]
Chills	-		-		1(4.0)	2[0.03]	1(0.6)	1[0.00]	2(0.7)	3[0.00]
Adverse drug reaction	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
General physical health deterioration	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Infusion site reaction	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Injection site erythema	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Injection site rash	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Injection site reaction	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of mild adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Localised oedema		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Oedema		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pain		-		-	1(4.0)	1[0.01]		-	1(0.4)	1[0.00]
Tenderness		-	1(2.9)	1[0.01]		-		-	1(0.4)	1[0.00]
Ulcer		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vessel puncture site haematoma		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vessel puncture site pain		-		-	1(4.0)	1[0.01]		-	1(0.4)	1[0.00]
Investigations	2(5.9)	3[0.03]	1(2.9)	1[0.01]	5(20.0)	8[0.10]	37(20.9)	88[0.15]	45(16.7)	100[0.11]
Alanine aminotransferase increased		-		-	1(4.0)	1[0.01]	9(5.1)	14[0.02]	10(3.7)	15[0.02]
Aspartate aminotransferase increased		-		-	1(4.0)	1[0.01]	9(5.1)	13[0.02]	10(3.7)	14[0.02]
Gamma-glutamyltransferase increased		-		-		-	7(4.0)	12[0.02]	7(2.6)	12[0.01]
C-reactive protein increased		-		-	1(4.0)	1[0.01]	5(2.8)	7[0.01]	6(2.2)	8[0.01]
Blood cholesterol increased		-		-		-	5(2.8)	5[0.01]	5(1.9)	5[0.01]
Blood bilirubin increased		-		-		-	3(1.7)	3[0.01]	3(1.1)	3[0.00]
Blood creatinine increased	1(2.9)	1[0.01]		-		-	2(1.1)	2[0.00]	3(1.1)	3[0.00]
Red blood cell count increased		-		-	3(12.0)	3[0.04]		-	3(1.1)	3[0.00]
Blood pressure increased		-		-		-	2(1.1)	2[0.00]	2(0.7)	2[0.00]
Haemoglobin increased		-		-	2(8.0)	2[0.03]		-	2(0.7)	2[0.00]
Weight decreased		-		-		-	2(1.1)	2[0.00]	2(0.7)	2[0.00]
Coagulation factor VIII level increased		-		-		-	1(0.6)	6[0.01]	1(0.4)	6[0.01]
Anti factor VIII antibody test		-	1(2.9)	1[0.01]		-		-	1(0.4)	1[0.00]
Aspartate aminotransferase abnormal		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Blood HIV RNA increased		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Blood alkaline phosphatase increased	1(2.9)	1[0.01]		-		-		-	1(0.4)	1[0.00]
Blood creatine phosphokinase increased		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Blood sodium increased	1(2.9)	1[0.01]		-		-		-	1(0.4)	1[0.00]
Blood triglycerides increased		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of mild adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	0-5 years E[R]	6-11 years N(%)	6-11 years E[R]	12-17 years N(%)	12-17 years E[R]	>=18 years N(%)	>=18 years E[R]	Total N(%)	Total E[R]
C-reactive protein abnormal		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Electrocardiogram T wave inversion		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatic enzyme increased		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Intraocular pressure test		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Laboratory test abnormal		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Liver function test abnormal		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Mean cell haemoglobin decreased		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Mean cell volume decreased		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Monocyte count increased		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Neutrophil count increased		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Platelet count decreased		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Prostatic specific antigen abnormal		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Serum ferritin decreased		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sputum abnormal		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Transaminases abnormal		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Transaminases increased		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vitamin D decreased		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
White blood cell count increased		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vascular disorders	3(8.8)	3[0.03]		-		-	22(12.4)	23[0.04]	25(9.3)	26[0.03]
Hypertension		-		-		-	18(10.2)	19[0.03]	18(6.7)	19[0.02]
Haematoma	1(2.9)	1[0.01]		-		-	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Essential hypertension		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Flushing	1(2.9)	1[0.01]		-		-		-	1(0.4)	1[0.00]
Peripheral venous disease		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vein disorder	1(2.9)	1[0.01]		-		-		-	1(0.4)	1[0.00]
Vein rupture		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Immune system disorders	5(14.7)	10[0.09]	4(11.8)	5[0.04]	1(4.0)	3[0.04]	14(7.9)	19[0.03]	24(8.9)	37[0.04]
Seasonal allergy	2(5.9)	2[0.02]	1(2.9)	1[0.01]	1(4.0)	2[0.03]	8(4.5)	12[0.02]	12(4.4)	17[0.02]
Food allergy	1(2.9)	2[0.02]	2(5.9)	3[0.02]		-	1(0.6)	1[0.00]	4(1.5)	6[0.01]
Allergy to arthropod sting	1(2.9)	1[0.01]		-	1(4.0)	1[0.01]		-	2(0.7)	2[0.00]
Hypersensitivity	1(2.9)	1[0.01]		-		-	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Allergy to animal	1(2.9)	2[0.02]		-		-		-	1(0.4)	2[0.00]
Allergy to arthropod bite		-	1(2.9)	1[0.01]		-		-	1(0.4)	1[0.00]

Summary of mild adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Allergy to chemicals		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Allergy to metals		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Allergy to plants		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Drug hypersensitivity		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Mite allergy	1(2.9)	1[0.01]		-		-		-	1(0.4)	1[0.00]
Mycotic allergy	1(2.9)	1[0.01]		-		-		-	1(0.4)	1[0.00]
Rubber sensitivity		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Eye disorders	3(8.8)	3[0.03]	5(14.7)	6[0.05]	1(4.0)	1[0.01]	8(4.5)	17[0.03]	17(6.3)	27[0.03]
Cataract		-		-		-	3(1.7)	4[0.01]	3(1.1)	4[0.00]
Conjunctivitis allergic		-	3(8.8)	4[0.03]		-		-	3(1.1)	4[0.00]
Dry eye		-		-	1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Eye pruritus	1(2.9)	1[0.01]		-		-	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Myopia	1(2.9)	1[0.01]	1(2.9)	1[0.01]		-		-	2(0.7)	2[0.00]
Blepharospasm		-		-		-	1(0.6)	4[0.01]	1(0.4)	4[0.00]
Ocular myasthenia		-		-		-	1(0.6)	2[0.00]	1(0.4)	2[0.00]
Blepharitis		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Corneal disorder		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Diplopia		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Eye allergy		-	1(2.9)	1[0.01]		-		-	1(0.4)	1[0.00]
Eye irritation		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Eye swelling	1(2.9)	1[0.01]		-		-		-	1(0.4)	1[0.00]
Glaucoma		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Metabolism and nutrition disorders		-		-	2(8.0)	2[0.03]	15(8.5)	15[0.03]	17(6.3)	17[0.02]
Vitamin D deficiency		-		-	2(8.0)	2[0.03]	4(2.3)	4[0.01]	6(2.2)	6[0.01]
Hyperlipidaemia		-		-		-	3(1.7)	3[0.01]	3(1.1)	3[0.00]
Hypercholesterolaemia		-		-		-	2(1.1)	2[0.00]	2(0.7)	2[0.00]
Iron deficiency		-		-		-	2(1.1)	2[0.00]	2(0.7)	2[0.00]
Decreased appetite		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Diabetes mellitus		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gout		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hyperuricaemia		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Blood and lymphatic system disorders	3(8.8)	3[0.03]	3(8.8)	3[0.02]	3(12.0)	3[0.04]	7(4.0)	9[0.02]	16(5.9)	18[0.02]
Anaemia	2(5.9)	2[0.02]	1(2.9)	1[0.01]		-	3(1.7)	3[0.01]	6(2.2)	6[0.01]
Leukocytosis	1(2.9)	1[0.01]		-		-	1(0.6)	3[0.01]	2(0.7)	4[0.00]
Neutropenia		-		-	1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Eosinophilia		-	1(2.9)	1[0.01]		-		-	1(0.4)	1[0.00]

Summary of mild adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Iron deficiency anaemia	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Lymphadenitis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Lymphadenopathy	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Monocytosis	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Thrombocytopenia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Psychiatric disorders	-		1(2.9)	1[0.01]	4(16.0)	4[0.05]	8(4.5)	8[0.01]	13(4.8)	13[0.01]
Insomnia	-		-		1(4.0)	1[0.01]	4(2.3)	4[0.01]	5(1.9)	5[0.01]
Depression	-		-		2(8.0)	2[0.03]	2(1.1)	2[0.00]	4(1.5)	4[0.00]
Anxiety	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Attention deficit/hyperactivity disorder	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Illusion	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Ear and labyrinth disorders	5(14.7)	7[0.07]	2(5.9)	3[0.02]	2(8.0)	2[0.03]	2(1.1)	2[0.00]	11(4.1)	14[0.02]
Ear pain	4(11.8)	4[0.04]	1(2.9)	2[0.02]	-		-		5(1.9)	6[0.01]
Cerumen impaction	2(5.9)	2[0.02]	-		-		-		2(0.7)	2[0.00]
Ear deformity acquired	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Ear disorder	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Excessive cerumen production	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Motion sickness	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Tinnitus	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Tympanic membrane perforation	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Cardiac disorders	-		-		2(8.0)	3[0.04]	5(2.8)	5[0.01]	7(2.6)	8[0.01]
Ventricular extrasystoles	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Aortic valve stenosis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Atrial fibrillation	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Extrasystoles	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Palpitations	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sinus arrhythmia	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Sinus bradycardia	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Renal and urinary disorders	1(2.9)	1[0.01]	-		1(4.0)	1[0.01]	5(2.8)	5[0.01]	7(2.6)	7[0.01]
Dysuria	-		-		1(4.0)	1[0.01]	3(1.7)	3[0.01]	4(1.5)	4[0.00]
Pollakiuria	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Renal colic	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Urinary incontinence	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of mild adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		4(2.3)	4[0.01]	6(2.2)	6[0.01]
Skin papilloma	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Eye naevus	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Lipoma	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nasopharyngeal neoplasm benign	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pyogenic granuloma	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Reproductive system and breast disorders	2(5.9)	2[0.02]	-		1(4.0)	2[0.03]	2(1.1)	2[0.00]	5(1.9)	6[0.01]
Erectile dysfunction	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Penile adhesion	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Penis disorder	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Testicular pain	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Testicular swelling	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Varicocele	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Surgical and medical procedures	-		1(2.9)	1[0.01]	1(4.0)	1[0.01]	3(1.7)	4[0.01]	5(1.9)	6[0.01]
Dental operation	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Dental implantation	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nail operation	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Tooth extraction	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Wisdom teeth removal	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Hepatobiliary disorders	1(2.9)	1[0.01]	-		-		4(2.3)	4[0.01]	5(1.9)	5[0.01]
Hepatic fibrosis	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Hepatic function abnormal	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatomegaly	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Congenital, familial and genetic disorders	-		-		2(8.0)	2[0.03]	2(1.1)	2[0.00]	4(1.5)	4[0.00]
Gilbert's syndrome	-		-		2(8.0)	2[0.03]	-		2(0.7)	2[0.00]
Dermoid cyst	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Thalassaemia alpha	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Endocrine disorders	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Adrenal insufficiency	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Goitre	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of mild adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%) E[R]	6-11 years N(%) E[R]	12-17 years N(%) E[R]	>=18 years N(%) E[R]	Total N(%) E[R]
Social circumstances	-	-	-	1(0.6) 3[0.01]	1(0.4) 3[0.00]
Tattoo	-	-	-	1(0.6) 3[0.01]	1(0.4) 3[0.00]
Product issues	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Device malfunction	1(2.9) 1[0.01]	-	-	-	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

43. 中等度の有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%)	0-5 years E[R]	6-11 years N(%)	6-11 years E[R]	12-17 years N(%)	12-17 years E[R]	>=18 years N(%)	>=18 years E[R]	Total N(%)	Total E[R]
Number of patients	34		34		25		177		270	
Patient years of exposure	106.03		128.04		76.37		571.70		882.13	
Exposure days	11140		13481		6586		48239		79446	
All adverse events	25(73.5)	63[0.59]	17(50.0)	33[0.26]	13(52.0)	32[0.42]	99(55.9)	298[0.52]	154(57.0)	426[0.48]
Infections and infestations	15(44.1)	29[0.27]	7(20.6)	14[0.11]	7(28.0)	14[0.18]	39(22.0)	68[0.12]	68(25.2)	125[0.14]
Upper respiratory tract infection	4(11.8)	5[0.05]	3(8.8)	4[0.03]	1(4.0)	1[0.01]	5(2.8)	6[0.01]	13(4.8)	16[0.02]
Viral upper respiratory tract infection	4(11.8)	9[0.08]	-		-		6(3.4)	9[0.02]	10(3.7)	18[0.02]
Influenza	1(2.9)	1[0.01]	-		-		6(3.4)	7[0.01]	7(2.6)	8[0.01]
Gastroenteritis	-		1(2.9)	1[0.01]	-		5(2.8)	6[0.01]	6(2.2)	7[0.01]
Bronchitis	1(2.9)	1[0.01]	2(5.9)	2[0.02]	-		3(1.7)	3[0.01]	6(2.2)	6[0.01]
Ear infection	2(5.9)	2[0.02]	-		1(4.0)	1[0.01]	2(1.1)	2[0.00]	5(1.9)	5[0.01]
Tonsillitis	1(2.9)	1[0.01]	-		1(4.0)	1[0.01]	3(1.7)	3[0.01]	5(1.9)	5[0.01]
Cellulitis	1(2.9)	1[0.01]	-		-		2(1.1)	2[0.00]	3(1.1)	3[0.00]
Device related infection	1(2.9)	1[0.01]	-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	3(1.1)	3[0.00]
Eye infection	-		1(2.9)	1[0.01]	1(4.0)	1[0.01]	1(0.6)	1[0.00]	3(1.1)	3[0.00]
Gastroenteritis viral	-		2(5.9)	2[0.02]	-		1(0.6)	1[0.00]	3(1.1)	3[0.00]
Varicella	2(5.9)	2[0.02]	1(2.9)	1[0.01]	-		-		3(1.1)	3[0.00]
Tooth infection	-		-		2(8.0)	3[0.04]	-		2(0.7)	3[0.00]
Herpes zoster	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Otitis media	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		-		2(0.7)	2[0.00]
Pharyngitis	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Pharyngitis streptococcal	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Pneumonia	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Tooth abscess	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Upper respiratory tract infection bacterial	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		-		2(0.7)	2[0.00]
Viral infection	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Urinary tract infection	-		-		-		1(0.6)	4[0.01]	1(0.4)	4[0.00]
Lower respiratory tract infection	-		-		1(4.0)	2[0.03]	-		1(0.4)	2[0.00]
Acute sinusitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Catheter site infection	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Citrobacter infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Conjunctivitis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Conjunctivitis bacterial	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]

Summary of moderate adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Genital infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
bacterial										
Helicobacter infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Localised infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nasopharyngitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Orchitis	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Periodontitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pulpitis dental	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Respiratory tract	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
infection										
Rhinitis	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Scarlet fever	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sinusitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Subcutaneous abscess	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Tonsillitis streptococcal	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Tuberculosis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vestibular neuronitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Injury, poisoning and	6(17.6)	9[0.08]	9(26.5)	10[0.08]	7(28.0)	7[0.09]	27(15.3)	33[0.06]	49(18.1)	59[0.07]
procedural complications										
Contusion	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		6(3.4)	6[0.01]	8(3.0)	8[0.01]
Laceration	-		-		2(8.0)	2[0.03]	4(2.3)	4[0.01]	6(2.2)	6[0.01]
Head injury	-		3(8.8)	3[0.02]	1(4.0)	1[0.01]	-		4(1.5)	4[0.00]
Fall	2(5.9)	3[0.03]	-		1(4.0)	1[0.01]	-		3(1.1)	4[0.00]
Face injury	-		2(5.9)	2[0.02]	-		1(0.6)	1[0.00]	3(1.1)	3[0.00]
Limb injury	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	3(1.1)	3[0.00]
Hand fracture	-		-		-		2(1.1)	3[0.01]	2(0.7)	3[0.00]
Arthropod bite	1(2.9)	1[0.01]	1(2.9)	1[0.01]	-		-		2(0.7)	2[0.00]
Joint injury	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Alcohol poisoning	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Animal bite	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Back injury	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Chest injury	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Compression fracture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Concussion	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Corneal abrasion	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Epiphyseal injury	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Femoral neck fracture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Foot fracture	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Forearm fracture	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Injury	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]

Summary of moderate adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Ligament sprain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Lower limb fracture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Muscle strain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Post procedural complication	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Post-traumatic pain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Procedural pain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Rib fracture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Road traffic accident	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Tendon injury	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Toxicity to various agents	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vaccination complication	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Wound	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Musculoskeletal and connective tissue disorders	3(8.8)	4[0.04]	2(5.9)	3[0.02]	3(12.0)	3[0.04]	34(19.2)	55[0.10]	42(15.6)	65[0.07]
Arthralgia	2(5.9)	2[0.02]	-		2(8.0)	2[0.03]	12(6.8)	13[0.02]	16(5.9)	17[0.02]
Arthropathy	-		-		-		6(3.4)	6[0.01]	6(2.2)	6[0.01]
Back pain	-		-		1(4.0)	1[0.01]	5(2.8)	5[0.01]	6(2.2)	6[0.01]
Haemophilic arthropathy	-		-		-		6(3.4)	6[0.01]	6(2.2)	6[0.01]
Pain in extremity	1(2.9)	1[0.01]	1(2.9)	2[0.02]	-		3(1.7)	3[0.01]	5(1.9)	6[0.01]
Synovitis	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Musculoskeletal pain	-		-		-		2(1.1)	3[0.01]	2(0.7)	3[0.00]
Bursitis	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Joint swelling	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Osteoarthritis	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Tendonitis	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Tenosynovitis	-		-		-		1(0.6)	3[0.01]	1(0.4)	3[0.00]
Neck pain	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Arthritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Groin pain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Musculoskeletal chest pain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Rhabdomyolysis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Spinal osteoarthritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nervous system disorders	4(11.8)	4[0.04]	-		-		20(11.3)	34[0.06]	24(8.9)	38[0.04]
Headache	3(8.8)	3[0.03]	-		-		10(5.6)	18[0.03]	13(4.8)	21[0.02]
Paraesthesia	-		-		-		4(2.3)	4[0.01]	4(1.5)	4[0.00]
Seizure	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Cerebral infarction	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Dizziness	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of moderate adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Epilepsy	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Facial paralysis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hypoaesthesia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Lethargy	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nerve compression	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Neuropathy peripheral	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Post-traumatic headache	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Presyncope	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sciatica	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gastrointestinal disorders	5(14.7)	5[0.05]	-		3(12.0)	4[0.05]	16(9.0)	25[0.04]	24(8.9)	34[0.04]
Diarrhoea	-		-		-		5(2.8)	5[0.01]	5(1.9)	5[0.01]
Constipation	2(5.9)	2[0.02]	-		2(8.0)	2[0.03]	-		4(1.5)	4[0.00]
Toothache	-		-		-		4(2.3)	4[0.01]	4(1.5)	4[0.00]
Vomiting	2(5.9)	2[0.02]	-		-		1(0.6)	1[0.00]	3(1.1)	3[0.00]
Abdominal pain upper	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Dental caries	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Gastrooesophageal reflux disease	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Food poisoning	-		-		1(4.0)	2[0.03]	-		1(0.4)	2[0.00]
Gastric varices	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Abdominal discomfort	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Abdominal pain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Dyspepsia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gastritis	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Glossodynia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Haemorrhoids	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Irritable bowel syndrome	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nausea	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	3(8.8)	4[0.04]	2(5.9)	2[0.02]	-		10(5.6)	11[0.02]	15(5.6)	17[0.02]
Cough	3(8.8)	4[0.04]	-		-		1(0.6)	1[0.00]	4(1.5)	5[0.01]
Respiratory disorder	-		-		-		3(1.7)	4[0.01]	3(1.1)	4[0.00]
Oropharyngeal pain	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Adenoidal hypertrophy	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Allergic respiratory disease	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Dyspnoea exertional	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Productive cough	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Rhinorrhoea	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]

Summary of moderate adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
General disorders and administration site conditions	2(5.9)	2[0.02]	1(2.9)	1[0.01]	-		9(5.1)	12[0.02]	12(4.4)	15[0.02]
Fatigue	-		1(2.9)	1[0.01]	-		3(1.7)	3[0.01]	4(1.5)	4[0.00]
Pyrexia	1(2.9)	1[0.01]	-		-		2(1.1)	2[0.00]	3(1.1)	3[0.00]
Influenza like illness	-		-		-		1(0.6)	4[0.01]	1(0.4)	4[0.00]
Chest pain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Injection site swelling	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Oedema peripheral	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Peripheral swelling	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Investigations	-		-		1(4.0)	1[0.01]	9(5.1)	18[0.03]	10(3.7)	19[0.02]
Alanine aminotransferase increased	-		-		-		4(2.3)	5[0.01]	4(1.5)	5[0.01]
Aspartate aminotransferase increased	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
C-reactive protein increased	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Gamma-glutamyltransferase increased	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Blood creatinine increased	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Haemoglobin decreased	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Coagulation factor VIII level increased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Electrocardiogram ST segment elevation	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
White blood cells urine positive	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Psychiatric disorders	-		-		1(4.0)	1[0.01]	9(5.1)	9[0.02]	10(3.7)	10[0.01]
Depression	-		-		-		4(2.3)	4[0.01]	4(1.5)	4[0.00]
Adjustment disorder with depressed mood	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Anxiety	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Attention deficit/hyperactivity disorder	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Depressed mood	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Mental status changes	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sleep disorder	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]

Summary of moderate adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Skin and subcutaneous tissue disorders	-		2(5.9)	2[0.02]	1(4.0)	1[0.01]	6(3.4)	6[0.01]	9(3.3)	9[0.01]
Acne	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Ingrowing nail	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Rash	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Dermatitis contact	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Erythema	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Photosensitivity reaction	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Blood and lymphatic system disorders	-		-		1(4.0)	1[0.01]	5(2.8)	5[0.01]	6(2.2)	6[0.01]
Lymphadenopathy	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Anaemia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Factor VIII inhibition	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Pancytopenia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Thrombocytopenia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Renal and urinary disorders	-		-		-		4(2.3)	4[0.01]	4(1.5)	4[0.00]
Dysuria	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Haematuria	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nephrolithiasis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Eye disorders	-		-		-		3(1.7)	4[0.01]	3(1.1)	4[0.00]
Diplopia	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Conjunctival haemorrhage	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Glaucoma	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Immune system disorders	1(2.9)	2[0.02]	-		-		2(1.1)	2[0.00]	3(1.1)	4[0.00]
Seasonal allergy	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Allergic oedema	1(2.9)	2[0.02]	-		-		-		1(0.4)	2[0.00]
Congenital, familial and genetic disorders	-		1(2.9)	1[0.01]	-		2(1.1)	2[0.00]	3(1.1)	3[0.00]
Hydrocele	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Odontogenic cyst	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pectus carinatum	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Hepatobiliary disorders	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Cholecystitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatic cirrhosis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hepatic steatosis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of moderate adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Metabolism and nutrition disorders	1(2.9)	1[0.01]	-		-		2(1.1)	2[0.00]	3(1.1)	3[0.00]
Diabetes mellitus	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gout	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Iron deficiency	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Vascular disorders	2(5.9)	2[0.02]	-		-		1(0.6)	1[0.00]	3(1.1)	3[0.00]
Haematoma	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Haemorrhage	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Hypertension	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Hepatocellular carcinoma	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pancreatic carcinoma metastatic	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Cardiac disorders	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pericarditis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Reproductive system and breast disorders	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Acquired phimosis	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Surgical and medical procedures	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Wisdom teeth removal	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

44. 重度の有害事象の要約 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N(%) E[R]		6-11 years N(%) E[R]		12-17 years N(%) E[R]		>=18 years N(%) E[R]		Total N(%) E[R]	
Number of patients	34		34		25		177		270	
Patient years of exposure	106.03		128.04		76.37		571.70		882.13	
Exposure days	11140		13481		6586		48239		79446	
All adverse events	7(20.6)	9[0.08]	2(5.9)	2[0.02]	5(20.0)	5[0.07]	28(15.8)	50[0.09]	42(15.6)	66[0.07]
Infections and infestations	3(8.8)	4[0.04]	1(2.9)	1[0.01]	1(4.0)	1[0.01]	8(4.5)	9[0.02]	13(4.8)	15[0.02]
Bacterial sepsis	-		-		1(4.0)	1[0.01]	1(0.6)	1[0.00]	2(0.7)	2[0.00]
Device related infection	1(2.9)	2[0.02]	-		-		-		1(0.4)	2[0.00]
Anal abscess	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Cellulitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Encephalitis	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Enteritis infectious	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gastroenteritis viral	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Infective spondylitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Intervertebral discitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Lower respiratory tract infection	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Osteomyelitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sepsis syndrome	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Tonsillitis	-		1(2.9)	1[0.01]	-		-		1(0.4)	1[0.00]
Injury, poisoning and procedural complications	1(2.9)	1[0.01]	-		3(12.0)	3[0.04]	4(2.3)	5[0.01]	8(3.0)	9[0.01]
Fall	1(2.9)	1[0.01]	-		-		3(1.7)	3[0.01]	4(1.5)	4[0.00]
Ankle fracture	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Extradural haematoma	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Foot fracture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Injury	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Radius fracture	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Musculoskeletal and connective tissue disorders	1(2.9)	1[0.01]	-		-		7(4.0)	8[0.01]	8(3.0)	9[0.01]
Musculoskeletal pain	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Muscle haemorrhage	1(2.9)	1[0.01]	-		-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Back pain	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Joint swelling	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pathological fracture	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Synovitis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

Summary of severe adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Gastrointestinal disorders	-		1(2.9)	1[0.01]	-		6(3.4)	6[0.01]	7(2.6)	7[0.01]
Duodenal ulcer	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Gastritis	-		1(2.9)	1[0.01]	-		1(0.6)	1[0.00]	2(0.7)	2[0.00]
Gastric varices haemorrhage	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Pancreatitis acute	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Toothache	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nervous system disorders	-		-		-		4(2.3)	4[0.01]	4(1.5)	4[0.00]
Cerebral microhaemorrhage	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Nervous system disorder	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Sciatica	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Syncope	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Renal and urinary disorders	-		-		-		3(1.7)	3[0.01]	3(1.1)	3[0.00]
Calculus urinary	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
IgA nephropathy	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Tubulointerstitial nephritis	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Metabolism and nutrition disorders	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Gout	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vitamin D deficiency	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Psychiatric disorders	-		-		-		2(1.1)	2[0.00]	2(0.7)	2[0.00]
Alcohol abuse	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Stress	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Investigations	-		-		-		1(0.6)	3[0.01]	1(0.4)	3[0.00]
Alanine aminotransferase increased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Aspartate aminotransferase increased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Gamma-glutamyltransferase increased	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	1(2.9)	2[0.02]	-		-		-		1(0.4)	2[0.00]
Asthma	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Hypoxia	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]

Summary of severe adverse events by age group - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	0-5 years N(%)	E[R]	6-11 years N(%)	E[R]	12-17 years N(%)	E[R]	>=18 years N(%)	E[R]	Total N(%)	E[R]
Surgical and medical procedures	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Tooth extraction	-		-		-		1(0.6)	2[0.00]	1(0.4)	2[0.00]
Blood and lymphatic system disorders	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Anaemia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Congenital, familial and genetic disorders	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Hypertrophic cardiomyopathy	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Eye disorders	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Diplopia	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
General disorders and administration site conditions	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Complication associated with device	-		-		1(4.0)	1[0.01]	-		1(0.4)	1[0.00]
Immune system disorders	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Hypersensitivity	1(2.9)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Neuroma	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Product issues	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Device dislocation	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Vascular disorders	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]
Circulatory collapse	-		-		-		1(0.6)	1[0.00]	1(0.4)	1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

45. 有害事象の概要 – 人種別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	Asian N(%) E[R]		Black or African American N(%) E[R]		White N(%) E[R]		Other N(%) E[R]		Total N(%) E[R]	
Number of patients	43		15		203		5		270	
Patient years of exposure	123.05		31.71		702.74		9.24		882.13	
Exposure days	11311		2439		63362		884		79446	
All adverse events	36(83.7)	357[2.90]	13(86.7)	87[2.74]	182(89.7)	1769[2.52]	4(80.0)	35[3.79]	239(88.5)	2307[2.62]
Serious adverse events	8(18.6)	16[0.13]	3(20.0)	6[0.19]	35(17.2)	44[0.06]	1(20.0)	1[0.11]	47(17.4)	67[0.08]
Non serious adverse events	36(83.7)	341[2.77]	13(86.7)	81[2.55]	180(88.7)	1725[2.45]	4(80.0)	34[3.68]	237(87.8)	2240[2.54]
Severity										
Mild	35(81.4)	307[2.49]	9(60.0)	70[2.21]	169(83.3)	1349[1.92]	4(80.0)	34[3.68]	221(81.9)	1814[2.06]
Moderate	20(46.5)	40[0.33]	8(53.3)	12[0.38]	124(61.1)	369[0.53]	-		154(57.0)	426[0.48]
Severe	7(16.3)	10[0.08]	3(20.0)	4[0.13]	31(15.3)	51[0.07]	1(20.0)	1[0.11]	42(15.6)	66[0.07]
Missing	-		1(6.7)	1[0.03]	-		-		1(0.4)	1[0.00]
Relationship										
Probably or possibly	8(18.6)	11[0.09]	2(13.3)	5[0.16]	29(14.3)	66[0.09]	1(20.0)	2[0.22]	40(14.8)	84[0.10]
Unlikely	36(83.7)	345[2.80]	13(86.7)	82[2.59]	181(89.2)	1701[2.42]	3(60.0)	28[3.03]	237(87.8)	2215[2.51]
Missing	1(2.3)	1[0.01]	-		2(1.0)	2[0.00]	1(20.0)	5[0.54]	4(1.5)	8[0.01]
Adverse events										
Leading to withdrawal	1(2.3)	1[0.01]	-		6(3.0)	6[0.01]	-		7(2.6)	7[0.01]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Other: algerian, caucasian/ black carribean, parent stated other (latin decent), puerto rican (multi-racial), unknown
Four patients with Race=NA and their events are accounted in the Total column.

46. 有害事象の要約 – 人種別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	Asian N(%) E[R]		Black or African American N(%) E[R]		White N(%) E[R]		Other N(%) E[R]		Total N(%) E[R]	
Number of patients	43		15		203		5		270	
Patient years of exposure	123.05		31.71		702.74		9.24		882.13	
Exposure days	11311		2439		63362		884		79446	
All adverse events	36(83.7)	357[2.90]	13(86.7)	87[2.74]	182(89.7)	1769[2.52]	4(80.0)	35[3.79]	239(88.5)	2307[2.62]
Infections and infestations	31(72.1)	112[0.91]	6(40.0)	22[0.69]	130(64.0)	462[0.66]	2(40.0)	9[0.97]	173(64.1)	618[0.70]
Viral upper respiratory tract infection	16(37.2)	27[0.22]	2(13.3)	5[0.16]	55(27.1)	88[0.13]	1(20.0)	5[0.54]	78(28.9)	130[0.15]
Upper respiratory tract infection	6(14.0)	17[0.14]	3(20.0)	3[0.09]	45(22.2)	81[0.12]	1(20.0)	1[0.11]	57(21.1)	105[0.12]
Influenza	3(7.0)	5[0.04]	1(6.7)	1[0.03]	25(12.3)	36[0.05]	-		29(10.7)	42[0.05]
Gastroenteritis	2(4.7)	5[0.04]	-		18(8.9)	23[0.03]	-		20(7.4)	28[0.03]
Tonsillitis	5(11.6)	5[0.04]	-		13(6.4)	19[0.03]	-		18(6.7)	24[0.03]
Rhinitis	2(4.7)	3[0.02]	-		12(5.9)	15[0.02]	1(20.0)	1[0.11]	15(5.6)	19[0.02]
Bronchitis	3(7.0)	3[0.02]	1(6.7)	1[0.03]	11(5.4)	13[0.02]	-		15(5.6)	17[0.02]
Ear infection	-		-		13(6.4)	16[0.02]	-		13(4.8)	16[0.02]
Viral infection	1(2.3)	1[0.01]	1(6.7)	1[0.03]	10(4.9)	11[0.02]	1(20.0)	2[0.22]	13(4.8)	15[0.02]
Otitis media	2(4.7)	2[0.02]	-		6(3.0)	7[0.01]	-		9(3.3)	10[0.01]
Conjunctivitis	1(2.3)	1[0.01]	-		8(3.9)	8[0.01]	-		9(3.3)	9[0.01]
Sinusitis	-		1(6.7)	1[0.03]	7(3.4)	7[0.01]	-		9(3.3)	9[0.01]
Pharyngitis	-		-		8(3.9)	10[0.01]	-		8(3.0)	10[0.01]
Pharyngitis streptococcal	-		1(6.7)	1[0.03]	5(2.5)	6[0.01]	-		6(2.2)	7[0.01]
Tooth abscess	-		-		5(2.5)	8[0.01]	-		5(1.9)	8[0.01]
Eye infection	1(2.3)	1[0.01]	-		4(2.0)	5[0.01]	-		5(1.9)	6[0.01]
Pneumonia	-		-		5(2.5)	5[0.01]	-		5(1.9)	5[0.01]
Nasopharyngitis	1(2.3)	2[0.02]	-		2(1.0)	2[0.00]	-		4(1.5)	6[0.01]
Device related infection	-		2(13.3)	3[0.09]	2(1.0)	2[0.00]	-		4(1.5)	5[0.01]
Periodontitis	4(9.3)	5[0.04]	-		-		-		4(1.5)	5[0.01]
Fungal skin infection	1(2.3)	1[0.01]	-		3(1.5)	3[0.00]	-		4(1.5)	4[0.00]
Gastroenteritis viral	-		-		4(2.0)	4[0.01]	-		4(1.5)	4[0.00]
Pulpitis dental	1(2.3)	1[0.01]	-		3(1.5)	3[0.00]	-		4(1.5)	4[0.00]
Varicella	-		-		4(2.0)	4[0.01]	-		4(1.5)	4[0.00]
Cellulitis	1(2.3)	4[0.03]	-		2(1.0)	2[0.00]	-		3(1.1)	6[0.01]
Urinary tract infection	-		-		3(1.5)	6[0.01]	-		3(1.1)	6[0.01]
Lower respiratory tract infection	-		-		3(1.5)	5[0.01]	-		3(1.1)	5[0.01]
Tooth infection	-		-		3(1.5)	5[0.01]	-		3(1.1)	5[0.01]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
Folliculitis	3(7.0) 4[0.03]	-	-	-	3(1.1) 4[0.00]
Acute sinusitis	-	-	2(1.0) 2[0.00]	-	3(1.1) 3[0.00]
Localised infection	1(2.3) 1[0.01]	-	2(1.0) 2[0.00]	-	3(1.1) 3[0.00]
Molluscum contagiosum	-	-	3(1.5) 3[0.00]	-	3(1.1) 3[0.00]
Otitis externa	1(2.3) 1[0.01]	-	2(1.0) 2[0.00]	-	3(1.1) 3[0.00]
Respiratory tract infection	-	-	3(1.5) 3[0.00]	-	3(1.1) 3[0.00]
Tinea pedis	2(4.7) 2[0.02]	-	1(0.5) 1[0.00]	-	3(1.1) 3[0.00]
Enterobiasis	-	-	2(1.0) 6[0.01]	-	2(0.7) 6[0.01]
Hordeolum	1(2.3) 2[0.02]	-	1(0.5) 1[0.00]	-	2(0.7) 3[0.00]
Tinea infection	-	-	2(1.0) 3[0.00]	-	2(0.7) 3[0.00]
Bacterial sepsis	1(2.3) 1[0.01]	1(6.7) 1[0.03]	-	-	2(0.7) 2[0.00]
Cystitis	1(2.3) 1[0.01]	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Gastrointestinal infection	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Herpes zoster	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Impetigo	1(2.3) 1[0.01]	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Onychomycosis	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Pharyngotonsillitis	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Scarlet fever	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Streptococcal infection	1(2.3) 1[0.01]	1(6.7) 1[0.03]	-	-	2(0.7) 2[0.00]
Upper respiratory tract infection bacterial	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Viral pharyngitis	-	1(6.7) 1[0.03]	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Otitis media acute	1(2.3) 3[0.02]	-	-	-	1(0.4) 3[0.00]
Paronychia	-	-	1(0.5) 3[0.00]	-	1(0.4) 3[0.00]
Genital herpes	-	-	1(0.5) 2[0.00]	-	1(0.4) 2[0.00]
Helminthic infection	-	-	1(0.5) 2[0.00]	-	1(0.4) 2[0.00]
Abscess neck	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Anal abscess	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Body tinea	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Catheter site infection	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Chlamydial infection	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Citrobacter infection	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Conjunctivitis bacterial	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Encephalitis	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Enteritis infectious	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Epididymitis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Fungal infection	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Genital infection bacterial	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
H1N1 influenza	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Helicobacter gastritis	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Helicobacter infection	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Hepatitis C	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Infectious mononucleosis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Infective spondylitis	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Intervertebral discitis	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Labyrinthitis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Laryngitis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Mumps	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Oral herpes	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Orchitis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Osteomyelitis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Postoperative wound infection	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Sepsis syndrome	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Sinusitis bacterial	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Skin infection	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Subcutaneous abscess	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Tonsillitis streptococcal	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Tracheitis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Tuberculosis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Urethritis	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Vestibular neuronitis	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Viral diarrhoea	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Viral parotitis	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Wound infection	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Musculoskeletal and connective tissue disorders	13(30.2) 20[0.16]	5(33.3) 6[0.19]	88(43.3) 211[0.30]	3(60.0) 4[0.43]	113(41.9) 249[0.28]
Arthralgia	7(16.3) 7[0.06]	1(6.7) 1[0.03]	33(16.3) 56[0.08]	-	43(15.9) 66[0.07]
Pain in extremity	2(4.7) 2[0.02]	-	17(8.4) 25[0.04]	2(40.0) 2[0.22]	22(8.1) 30[0.03]
Musculoskeletal pain	2(4.7) 2[0.02]	-	15(7.4) 16[0.02]	-	17(6.3) 18[0.02]
Back pain	1(2.3) 1[0.01]	2(13.3) 2[0.06]	11(5.4) 14[0.02]	-	15(5.6) 18[0.02]
Arthropathy	-	-	8(3.9) 10[0.01]	-	9(3.3) 11[0.01]
Haemophilic arthropathy	-	-	8(3.9) 8[0.01]	1(20.0) 1[0.11]	9(3.3) 9[0.01]
Myalgia	1(2.3) 1[0.01]	1(6.7) 1[0.03]	5(2.5) 7[0.01]	-	7(2.6) 9[0.01]
Tendonitis	-	-	6(3.0) 6[0.01]	-	7(2.6) 7[0.01]
Synovitis	-	-	6(3.0) 8[0.01]	-	6(2.2) 8[0.01]
Joint swelling	1(2.3) 1[0.01]	-	5(2.5) 6[0.01]	-	6(2.2) 7[0.01]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]		Black or African American N(%) E[R]		White N(%) E[R]		Other N(%) E[R]		Total N(%) E[R]	
Musculoskeletal stiffness	-		-		5(2.5)	5[0.01]	-		5(1.9)	5[0.01]
Joint range of motion decreased	-		1(6.7)	1[0.03]	2(1.0)	2[0.00]	-		4(1.5)	4[0.00]
Neck pain	1(2.3)	1[0.01]	-		2(1.0)	5[0.01]	-		3(1.1)	6[0.01]
Pain in jaw	-		-		3(1.5)	4[0.01]	-		3(1.1)	4[0.00]
Bursitis	-		-		3(1.5)	3[0.00]	-		3(1.1)	3[0.00]
Joint lock	1(2.3)	1[0.01]	-		2(1.0)	2[0.00]	-		3(1.1)	3[0.00]
Musculoskeletal chest pain	-		-		2(1.0)	2[0.00]	1(20.0)	1[0.11]	3(1.1)	3[0.00]
Osteoarthritis	1(2.3)	1[0.01]	-		2(1.0)	2[0.00]	-		3(1.1)	3[0.00]
Flank pain	-		-		2(1.0)	2[0.00]	-		2(0.7)	2[0.00]
Muscle haemorrhage	-		-		2(1.0)	2[0.00]	-		2(0.7)	2[0.00]
Muscle spasms	-		-		2(1.0)	2[0.00]	-		2(0.7)	2[0.00]
Plantar fasciitis	-		-		2(1.0)	2[0.00]	-		2(0.7)	2[0.00]
Rotator cuff syndrome	-		-		1(0.5)	3[0.00]	-		1(0.4)	3[0.00]
Tenosynovitis	-		-		1(0.5)	3[0.00]	-		1(0.4)	3[0.00]
Rheumatic disorder	1(2.3)	2[0.02]	-		-		-		1(0.4)	2[0.00]
Arthritis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Bone pain	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Chondropathy	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Costochondritis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Groin pain	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Growing pains	-		-		-		-		1(0.4)	1[0.00]
Joint effusion	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Limb discomfort	-		1(6.7)	1[0.03]	-		-		1(0.4)	1[0.00]
Muscle tightness	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Musculoskeletal discomfort	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Myositis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Pathological fracture	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Periostitis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Rhabdomyolysis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Scoliosis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Spinal osteoarthritis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Synovial disorder	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Tendon pain	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Torticollis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Injury, poisoning and procedural complications	15(34.9)	43[0.35]	4(26.7)	7[0.22]	83(40.9)	174[0.25]	2(40.0)	4[0.43]	106(39.3)	237[0.27]
Contusion	7(16.3)	19[0.15]	-		13(6.4)	13[0.02]	-		20(7.4)	32[0.04]
Laceration	5(11.6)	5[0.04]	1(6.7)	1[0.03]	13(6.4)	15[0.02]	-		19(7.0)	21[0.02]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
Fall	1(2.3) 1[0.01]	1(6.7) 1[0.03]	15(7.4) 17[0.02]	-	17(6.3) 19[0.02]
Limb injury	-	-	14(6.9) 22[0.03]	1(20.0) 1[0.11]	16(5.9) 26[0.03]
Ligament sprain	3(7.0) 3[0.02]	-	9(4.4) 10[0.01]	1(20.0) 1[0.11]	13(4.8) 14[0.02]
Joint injury	1(2.3) 1[0.01]	-	9(4.4) 10[0.01]	-	11(4.1) 12[0.01]
Head injury	-	1(6.7) 2[0.06]	8(3.9) 10[0.01]	-	9(3.3) 12[0.01]
Muscle strain	-	-	6(3.0) 8[0.01]	1(20.0) 1[0.11]	7(2.6) 9[0.01]
Arthropod bite	1(2.3) 1[0.01]	-	6(3.0) 7[0.01]	-	7(2.6) 8[0.01]
Skin abrasion	3(7.0) 3[0.02]	-	3(1.5) 3[0.00]	-	7(2.6) 8[0.01]
Arthropod sting	-	-	4(2.0) 6[0.01]	-	4(1.5) 6[0.01]
Face injury	1(2.3) 1[0.01]	-	3(1.5) 3[0.00]	-	4(1.5) 4[0.00]
Hand fracture	-	-	3(1.5) 4[0.01]	-	3(1.1) 4[0.00]
Excoriation	-	-	3(1.5) 3[0.00]	-	3(1.1) 3[0.00]
Post-traumatic pain	-	-	3(1.5) 3[0.00]	-	3(1.1) 3[0.00]
Road traffic accident	-	-	3(1.5) 3[0.00]	-	3(1.1) 3[0.00]
Scratch	2(4.7) 2[0.02]	-	1(0.5) 1[0.00]	-	3(1.1) 3[0.00]
Wound	-	-	3(1.5) 3[0.00]	-	3(1.1) 3[0.00]
Accidental overdose	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Chest injury	1(2.3) 1[0.01]	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Foot fracture	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Procedural pain	-	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Tendon injury	1(2.3) 1[0.01]	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Thermal burn	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Traumatic haemorrhage	1(2.3) 1[0.01]	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Injury	-	1(6.7) 2[0.06]	-	-	1(0.4) 2[0.00]
Abdominal injury	-	-	-	1(20.0) 1[0.11]	1(0.4) 1[0.00]
Alcohol poisoning	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Animal bite	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Ankle fracture	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Back injury	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Compression fracture	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Concussion	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Corneal abrasion	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Drug administration error	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Electric shock	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Epicondylitis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Epiphyseal injury	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Extradural haematoma	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Femoral neck fracture	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Forearm fracture	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Foreign body in eye	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
Lower limb fracture	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Medication error	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Mouth injury	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Muscle rupture	-	-	-	-	1(0.4) 1[0.00]
Overdose	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Post procedural complication	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Product preparation error	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Radius fracture	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Rib fracture	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Splinter	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Sunburn	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Tooth injury	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Toxicity to various agents	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Traumatic haematoma	-	-	-	-	1(0.4) 1[0.00]
Vaccination complication	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Gastrointestinal disorders	14(32.6) 35[0.28]	6(40.0) 11[0.35]	80(39.4) 170[0.24]	2(40.0) 6[0.65]	105(38.9) 230[0.26]
Diarrhoea	3(7.0) 3[0.02]	3(20.0) 4[0.13]	22(10.8) 27[0.04]	1(20.0) 1[0.11]	31(11.5) 39[0.04]
Vomiting	1(2.3) 1[0.01]	1(6.7) 1[0.03]	17(8.4) 21[0.03]	1(20.0) 1[0.11]	20(7.4) 24[0.03]
Nausea	1(2.3) 1[0.01]	-	16(7.9) 21[0.03]	-	17(6.3) 22[0.02]
Toothache	2(4.7) 2[0.02]	-	13(6.4) 14[0.02]	-	15(5.6) 16[0.02]
Abdominal pain	-	1(6.7) 2[0.06]	11(5.4) 11[0.02]	-	13(4.8) 14[0.02]
Abdominal pain upper	2(4.7) 2[0.02]	-	7(3.4) 8[0.01]	2(40.0) 3[0.32]	11(4.1) 13[0.01]
Dental caries	5(11.6) 5[0.04]	-	5(2.5) 8[0.01]	-	10(3.7) 13[0.01]
Constipation	1(2.3) 1[0.01]	1(6.7) 1[0.03]	7(3.4) 9[0.01]	-	9(3.3) 11[0.01]
Gastritis	2(4.7) 2[0.02]	-	5(2.5) 5[0.01]	-	7(2.6) 7[0.01]
Gastrooesophageal reflux disease	1(2.3) 1[0.01]	-	4(2.0) 5[0.01]	-	6(2.2) 7[0.01]
Dyspepsia	-	2(13.3) 2[0.06]	3(1.5) 3[0.00]	-	5(1.9) 5[0.01]
Abdominal discomfort	-	-	2(1.0) 2[0.00]	1(20.0) 1[0.11]	3(1.1) 3[0.00]
Stomatitis	3(7.0) 3[0.02]	-	-	-	3(1.1) 3[0.00]
Irritable bowel syndrome	1(2.3) 2[0.02]	-	1(0.5) 1[0.00]	-	2(0.7) 3[0.00]
Aphthous ulcer	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Chapped lips	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Duodenal ulcer	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Gastrointestinal disorder	-	1(6.7) 1[0.03]	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Haemorrhoids	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Perianal erythema	1(2.3) 1[0.01]	-	-	-	2(0.7) 2[0.00]
Dysphagia	-	-	1(0.5) 2[0.00]	-	1(0.4) 2[0.00]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]		Black or African American N(%) E[R]		White N(%) E[R]		Other N(%) E[R]		Total N(%) E[R]	
Flatulence	-		-		1(0.5)	2[0.00]	-		1(0.4)	2[0.00]
Food poisoning	-		-		1(0.5)	2[0.00]	-		1(0.4)	2[0.00]
Gastric varices	1(2.3)	2[0.02]	-		-		-		1(0.4)	2[0.00]
Abdominal hernia	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Anal fissure	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Barrett's oesophagus	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Chronic gastritis	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Dental discomfort	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Dental necrosis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Diaphragmatic hernia	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Duodenitis	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Enterocolitis	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Faeces soft	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Gastric varices haemorrhage	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Gastritis erosive	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Gingival bleeding	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Gingival swelling	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Glossodynia	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Haematochezia	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Hiatus hernia	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Inguinal hernia	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Lip ulceration	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Loose tooth	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Mouth haemorrhage	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Mouth ulceration	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Noninfective gingivitis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Oral pain	-		-		-		-		1(0.4)	1[0.00]
Pancreatitis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Pancreatitis acute	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Rectal haemorrhage	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Retching	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Swollen tongue	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Uvulitis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	13(30.2)	24[0.20]	3(20.0)	8[0.25]	69(34.0)	152[0.22]	3(60.0)	4[0.43]	89(33.0)	195[0.22]
Cough	5(11.6)	7[0.06]	1(6.7)	2[0.06]	28(13.8)	40[0.06]	2(40.0)	3[0.32]	37(13.7)	53[0.06]
Oropharyngeal pain	3(7.0)	4[0.03]	1(6.7)	1[0.03]	24(11.8)	29[0.04]	-		29(10.7)	35[0.04]
Rhinorrhoea	3(7.0)	3[0.02]	1(6.7)	1[0.03]	10(4.9)	14[0.02]	-		15(5.6)	20[0.02]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%)	Asian E[R]	Black or African American N(%)	Black or African American E[R]	White N(%)	White E[R]	Other N(%)	Other E[R]	Total N(%)	Total E[R]
Epistaxis	1(2.3)	1[0.01]	-		11(5.4)	26[0.04]	-		13(4.8)	30[0.03]
Nasal congestion	-		1(6.7)	1[0.03]	6(3.0)	9[0.01]	-		7(2.6)	10[0.01]
Respiratory disorder	-		-		5(2.5)	14[0.02]	-		5(1.9)	14[0.02]
Asthma	2(4.7)	2[0.02]	-		2(1.0)	4[0.01]	-		4(1.5)	6[0.01]
Rhinitis allergic	-		-		2(1.0)	2[0.00]	1(20.0)	1[0.11]	3(1.1)	3[0.00]
Productive cough	-		-		2(1.0)	2[0.00]	-		2(0.7)	2[0.00]
Sneezing	-		-		2(1.0)	2[0.00]	-		2(0.7)	2[0.00]
Haemoptysis	1(2.3)	3[0.02]	-		-		-		1(0.4)	3[0.00]
Dysphonia	-		-		1(0.5)	2[0.00]	-		1(0.4)	2[0.00]
Adenoidal hypertrophy	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Allergic respiratory disease	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Asthma exercise induced	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Asthmatic crisis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Bronchial hyperreactivity	-		1(6.7)	1[0.03]	-		-		1(0.4)	1[0.00]
Dyspnoea	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Dyspnoea exertional	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Hypoxia	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Middle lobe syndrome	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Nasal obstruction	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Sinus congestion	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Sleep apnoea syndrome	-		1(6.7)	1[0.03]	-		-		1(0.4)	1[0.00]
Upper respiratory tract congestion	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Upper respiratory tract inflammation	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Wheezing	-		1(6.7)	1[0.03]	-		-		1(0.4)	1[0.00]
Nervous system disorders	9(20.9)	11[0.09]	4(26.7)	6[0.19]	63(31.0)	142[0.20]	1(20.0)	1[0.11]	79(29.3)	163[0.18]
Headache	7(16.3)	7[0.06]	2(13.3)	3[0.09]	44(21.7)	104[0.15]	1(20.0)	1[0.11]	56(20.7)	118[0.13]
Dizziness	1(2.3)	1[0.01]	-		7(3.4)	8[0.01]	-		8(3.0)	9[0.01]
Paraesthesia	-		-		7(3.4)	7[0.01]	-		7(2.6)	7[0.01]
Carpal tunnel syndrome	-		-		2(1.0)	2[0.00]	-		2(0.7)	2[0.00]
Post-traumatic headache	-		2(13.3)	2[0.06]	-		-		2(0.7)	2[0.00]
Presyncope	-		-		2(1.0)	2[0.00]	-		2(0.7)	2[0.00]
Sciatica	-		-		2(1.0)	2[0.00]	-		2(0.7)	2[0.00]
Seizure	-		-		2(1.0)	2[0.00]	-		2(0.7)	2[0.00]
Altered state of consciousness	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Cerebral infarction	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
Cerebral microhaemorrhage	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Cognitive disorder	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Dizziness exertional	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Dizziness postural	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Epilepsy	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Facial paralysis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Hypoaesthesia	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Lethargy	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Migraine	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Nerve compression	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Nervous system disorder	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Neuropathy peripheral	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Restless legs syndrome	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Sensory loss	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Sinus headache	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Syncope	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Tongue biting	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Skin and subcutaneous tissue disorders	17(39.5) 33[0.27]	3(20.0) 3[0.09]	52(25.6) 90[0.13]	1(20.0) 2[0.22]	75(27.8) 131[0.15]
Eczema	5(11.6) 6[0.05]	1(6.7) 1[0.03]	8(3.9) 11[0.02]	1(20.0) 1[0.11]	15(5.6) 19[0.02]
Rash	2(4.7) 2[0.02]	-	12(5.9) 16[0.02]	-	14(5.2) 18[0.02]
Acne	2(4.7) 2[0.02]	-	6(3.0) 7[0.01]	-	8(3.0) 9[0.01]
Urticaria	3(7.0) 3[0.02]	-	4(2.0) 4[0.01]	-	7(2.6) 7[0.01]
Erythema	-	-	4(2.0) 8[0.01]	1(20.0) 1[0.11]	5(1.9) 9[0.01]
Dermatitis contact	-	-	4(2.0) 4[0.01]	-	4(1.5) 4[0.00]
Dry skin	2(4.7) 2[0.02]	-	2(1.0) 2[0.00]	-	4(1.5) 4[0.00]
Pruritus	2(4.7) 2[0.02]	-	2(1.0) 2[0.00]	-	4(1.5) 4[0.00]
Blister	2(4.7) 4[0.03]	-	1(0.5) 1[0.00]	-	3(1.1) 5[0.01]
Hyperhidrosis	1(2.3) 1[0.01]	-	2(1.0) 2[0.00]	-	3(1.1) 3[0.00]
Skin lesion	-	-	2(1.0) 2[0.00]	-	3(1.1) 3[0.00]
Skin erosion	1(2.3) 3[0.02]	-	1(0.5) 1[0.00]	-	2(0.7) 4[0.00]
Alopecia	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Dermal cyst	1(2.3) 1[0.01]	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Dermatitis	-	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Ingrowing nail	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Photosensitivity reaction	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Purpura	1(2.3) 1[0.01]	-	-	-	2(0.7) 2[0.00]
Rash pruritic	1(2.3) 1[0.01]	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Miliaria	-	-	1(0.5) 3[0.00]	-	1(0.4) 3[0.00]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
Papule	-	-	1(0.5) 2[0.00]	-	1(0.4) 2[0.00]
Petechiae	-	-	1(0.5) 2[0.00]	-	1(0.4) 2[0.00]
Alopecia areata	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Blood blister	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Dermatitis diaper	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Drug eruption	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Eczema asteatotic	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Hangnail	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Mechanical urticaria	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Nail disorder	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Onychalgia	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Pigmentation disorder	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Pruritus allergic	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Pruritus generalised	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Psoriasis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Rash papular	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Scab	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Sebaceous gland disorder	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Skin disorder	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Skin irritation	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Skin ulcer	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Telangiectasia	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Vitiligo	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
General disorders and administration site conditions	10(23.3) 14[0.11]	1(6.7) 3[0.09]	48(23.6) 79[0.11]	1(20.0) 1[0.11]	63(23.3) 100[0.11]
Pyrexia	7(16.3) 8[0.07]	1(6.7) 3[0.09]	16(7.9) 29[0.04]	-	25(9.3) 41[0.05]
Fatigue	1(2.3) 1[0.01]	-	7(3.4) 8[0.01]	-	8(3.0) 9[0.01]
Influenza like illness	-	-	6(3.0) 10[0.01]	-	7(2.6) 11[0.01]
Chest pain	-	-	5(2.5) 5[0.01]	-	5(1.9) 5[0.01]
Oedema peripheral	-	-	5(2.5) 5[0.01]	-	5(1.9) 5[0.01]
Peripheral swelling	-	-	3(1.5) 3[0.00]	-	4(1.5) 4[0.00]
Hyperthermia	-	-	3(1.5) 3[0.00]	-	3(1.1) 3[0.00]
Local swelling	1(2.3) 1[0.01]	-	2(1.0) 2[0.00]	-	3(1.1) 3[0.00]
Chills	-	-	2(1.0) 3[0.00]	-	2(0.7) 3[0.00]
Adverse drug reaction	1(2.3) 1[0.01]	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Complication associated with device	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
General physical health deterioration	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Infusion site reaction	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Injection site erythema	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Injection site rash	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Injection site reaction	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Injection site swelling	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Localised oedema	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Oedema	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Pain	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Tenderness	-	-	-	1(20.0) 1[0.11]	1(0.4) 1[0.00]
Ulcer	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Vessel puncture site haematoma	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Vessel puncture site pain	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Investigations	10(23.3) 26[0.21]	3(20.0) 5[0.16]	35(17.2) 88[0.13]	1(20.0) 2[0.22]	50(18.5) 122[0.14]
Alanine aminotransferase increased	3(7.0) 6[0.05]	-	11(5.4) 15[0.02]	-	14(5.2) 21[0.02]
Aspartate aminotransferase increased	2(4.7) 3[0.02]	-	10(4.9) 15[0.02]	-	12(4.4) 18[0.02]
Gamma-glutamyltransferase increased	3(7.0) 5[0.04]	-	6(3.0) 10[0.01]	-	9(3.3) 15[0.02]
C-reactive protein increased	2(4.7) 3[0.02]	-	6(3.0) 7[0.01]	-	8(3.0) 10[0.01]
Blood cholesterol increased	2(4.7) 2[0.02]	1(6.7) 1[0.03]	2(1.0) 2[0.00]	-	5(1.9) 5[0.01]
Blood creatinine increased	1(2.3) 1[0.01]	-	2(1.0) 4[0.01]	-	3(1.1) 5[0.01]
Blood bilirubin increased	2(4.7) 2[0.02]	1(6.7) 1[0.03]	-	-	3(1.1) 3[0.00]
Red blood cell count increased	-	-	2(1.0) 2[0.00]	1(20.0) 1[0.11]	3(1.1) 3[0.00]
Blood pressure increased	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Haemoglobin increased	-	-	1(0.5) 1[0.00]	1(20.0) 1[0.11]	2(0.7) 2[0.00]
Weight decreased	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Coagulation factor VIII level increased	-	-	1(0.5) 7[0.01]	-	1(0.4) 7[0.01]
Haemoglobin decreased	-	-	1(0.5) 2[0.00]	-	1(0.4) 2[0.00]
Anti factor VIII antibody test	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]		Black or African American N(%) E[R]		White N(%) E[R]		Other N(%) E[R]	Total N(%) E[R]	
Aspartate aminotransferase abnormal	1(2.3)	1[0.01]	-		-		-	1(0.4)	1[0.00]
Blood HIV RNA increased	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Blood alkaline phosphatase increased	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Blood creatine phosphokinase increased	-		1(6.7)	1[0.03]	-		-	1(0.4)	1[0.00]
Blood sodium increased	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Blood triglycerides increased	-		1(6.7)	1[0.03]	-		-	1(0.4)	1[0.00]
C-reactive protein abnormal	1(2.3)	1[0.01]	-		-		-	1(0.4)	1[0.00]
Electrocardiogram ST segment elevation	-		1(6.7)	1[0.03]	-		-	1(0.4)	1[0.00]
Electrocardiogram T wave inversion	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Hepatic enzyme increased	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Intraocular pressure test	-		-		-		-	1(0.4)	1[0.00]
Laboratory test abnormal	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Liver function test abnormal	1(2.3)	1[0.01]	-		-		-	1(0.4)	1[0.00]
Mean cell haemoglobin decreased	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Mean cell volume decreased	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Monocyte count increased	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Neutrophil count increased	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Platelet count decreased	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Prostatic specific antigen abnormal	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Serum ferritin decreased	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Sputum abnormal	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Transaminases abnormal	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Transaminases increased	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Vitamin D decreased	1(2.3)	1[0.01]	-		-		-	1(0.4)	1[0.00]
White blood cell count increased	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
White blood cells urine positive	-		-		1(0.5)	1[0.00]	-	1(0.4)	1[0.00]
Vascular disorders	7(16.3)	7[0.06]	1(6.7)	1[0.03]	21(10.3)	22[0.03]	-	29(10.7)	30[0.03]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
Hypertension	5(11.6) 5[0.04]	-	14(6.9) 15[0.02]	-	19(7.0) 20[0.02]
Haematoma	-	-	3(1.5) 3[0.00]	-	3(1.1) 3[0.00]
Circulatory collapse	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Essential hypertension	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Flushing	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Haemorrhage	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Peripheral venous disease	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Vein disorder	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Vein rupture	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Immune system disorders	4(9.3) 4[0.03]	2(13.3) 7[0.22]	19(9.4) 28[0.04]	1(20.0) 2[0.22]	27(10.0) 42[0.05]
Seasonal allergy	3(7.0) 3[0.02]	1(6.7) 1[0.03]	10(4.9) 15[0.02]	-	14(5.2) 19[0.02]
Food allergy	1(2.3) 1[0.01]	1(6.7) 2[0.06]	2(1.0) 3[0.00]	-	4(1.5) 6[0.01]
Hypersensitivity	-	-	1(0.5) 1[0.00]	1(20.0) 2[0.22]	2(0.7) 3[0.00]
Allergy to arthropod sting	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Allergic oedema	-	-	1(0.5) 2[0.00]	-	1(0.4) 2[0.00]
Allergy to animal	-	1(6.7) 2[0.06]	-	-	1(0.4) 2[0.00]
Allergy to arthropod bite	-	-	-	-	1(0.4) 1[0.00]
Allergy to chemicals	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Allergy to metals	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Allergy to plants	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Drug hypersensitivity	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Mite allergy	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Mycotic allergy	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Rubber sensitivity	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Psychiatric disorders	2(4.7) 2[0.02]	1(6.7) 1[0.03]	21(10.3) 22[0.03]	-	24(8.9) 25[0.03]
Depression	-	-	8(3.9) 8[0.01]	-	8(3.0) 8[0.01]
Insomnia	1(2.3) 1[0.01]	1(6.7) 1[0.03]	3(1.5) 3[0.00]	-	5(1.9) 5[0.01]
Anxiety	-	-	3(1.5) 3[0.00]	-	3(1.1) 3[0.00]
Attention deficit/hyperactivity disorder	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Adjustment disorder with depressed mood	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Alcohol abuse	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Depressed mood	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Illusion	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Mental status changes	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Sleep disorder	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
Stress	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Blood and lymphatic system disorders	2(4.7) 2[0.02]	2(13.3) 2[0.06]	17(8.4) 21[0.03]	-	21(7.8) 25[0.03]
Anaemia	1(2.3) 1[0.01]	-	6(3.0) 7[0.01]	-	7(2.6) 8[0.01]
Lymphadenopathy	-	-	3(1.5) 3[0.00]	-	3(1.1) 3[0.00]
Leukocytosis	1(2.3) 1[0.01]	-	1(0.5) 3[0.00]	-	2(0.7) 4[0.00]
Neutropenia	-	1(6.7) 1[0.03]	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Thrombocytopenia	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Eosinophilia	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Factor VIII inhibition	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Iron deficiency anaemia	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Lymphadenitis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Monocytosis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Pancytopenia	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Metabolism and nutrition disorders	5(11.6) 5[0.04]	-	16(7.9) 17[0.02]	-	21(7.8) 22[0.02]
Vitamin D deficiency	-	-	7(3.4) 7[0.01]	-	7(2.6) 7[0.01]
Hyperlipidaemia	2(4.7) 2[0.02]	-	1(0.5) 1[0.00]	-	3(1.1) 3[0.00]
Iron deficiency	-	-	3(1.5) 3[0.00]	-	3(1.1) 3[0.00]
Gout	-	-	2(1.0) 3[0.00]	-	2(0.7) 3[0.00]
Diabetes mellitus	2(4.7) 2[0.02]	-	-	-	2(0.7) 2[0.00]
Hypercholesterolaemia	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Decreased appetite	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Hyperuricaemia	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Eye disorders	4(9.3) 7[0.06]	1(6.7) 1[0.03]	14(6.9) 23[0.03]	-	20(7.4) 32[0.04]
Cataract	1(2.3) 1[0.01]	-	2(1.0) 3[0.00]	-	3(1.1) 4[0.00]
Conjunctivitis allergic	1(2.3) 1[0.01]	-	2(1.0) 3[0.00]	-	3(1.1) 4[0.00]
Diplopia	1(2.3) 1[0.01]	-	1(0.5) 3[0.00]	-	2(0.7) 4[0.00]
Dry eye	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Eye pruritus	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Glaucoma	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Myopia	1(2.3) 1[0.01]	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Blepharospasm	-	-	1(0.5) 4[0.01]	-	1(0.4) 4[0.00]
Ocular myasthenia	1(2.3) 2[0.02]	-	-	-	1(0.4) 2[0.00]
Blepharitis	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Conjunctival haemorrhage	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Corneal disorder	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
Eye allergy	-	-	-	-	1(0.4) 1[0.00]
Eye irritation	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Eye swelling	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Renal and urinary disorders	1(2.3) 1[0.01]	-	13(6.4) 13[0.02]	-	14(5.2) 14[0.02]
Dysuria	-	-	6(3.0) 6[0.01]	-	6(2.2) 6[0.01]
Calculus urinary	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Haematuria	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
IgA nephropathy	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Nephrolithiasis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Pollakiuria	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Renal colic	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Tubulointerstitial nephritis	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Urinary incontinence	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Ear and labyrinth disorders	-	-	10(4.9) 12[0.02]	-	11(4.1) 14[0.02]
Ear pain	-	-	4(2.0) 4[0.01]	-	5(1.9) 6[0.01]
Cerumen impaction	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Ear deformity acquired	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Ear disorder	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Excessive cerumen production	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Motion sickness	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Tinnitus	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Tympanic membrane perforation	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Cardiac disorders	1(2.3) 1[0.01]	2(13.3) 3[0.09]	6(3.0) 6[0.01]	-	9(3.3) 10[0.01]
Ventricular extrasystoles	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Aortic valve stenosis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Atrial fibrillation	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Atrioventricular block first degree	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Extrasystoles	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Palpitations	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Pericarditis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Sinus arrhythmia	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Sinus bradycardia	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3(7.0) 3[0.02]	-	6(3.0) 6[0.01]	-	9(3.3) 9[0.01]
Skin papilloma	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Eye naevus	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Hepatocellular carcinoma	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Lipoma	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Nasopharyngeal neoplasm benign	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Neuroma	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Pancreatic carcinoma metastatic	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Pyogenic granuloma	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Congenital, familial and genetic disorders	2(4.7) 2[0.02]	-	6(3.0) 6[0.01]	-	8(3.0) 8[0.01]
Gilbert's syndrome	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Dermoid cyst	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Hydrocele	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Hypertrophic cardiomyopathy	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Odontogenic cyst	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Pectus carinatum	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Thalassaemia alpha	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Hepatobiliary disorders	2(4.7) 2[0.02]	-	6(3.0) 6[0.01]	-	8(3.0) 8[0.01]
Hepatic fibrosis	1(2.3) 1[0.01]	-	2(1.0) 2[0.00]	-	3(1.1) 3[0.00]
Cholecystitis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Hepatic cirrhosis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Hepatic function abnormal	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Hepatic steatosis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Hepatomegaly	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Surgical and medical procedures	1(2.3) 1[0.01]	1(6.7) 1[0.03]	5(2.5) 7[0.01]	-	7(2.6) 9[0.01]
Tooth extraction	-	-	2(1.0) 3[0.00]	-	2(0.7) 3[0.00]
Wisdom teeth removal	1(2.3) 1[0.01]	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Dental operation	-	-	1(0.5) 2[0.00]	-	1(0.4) 2[0.00]
Dental implantation	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Nail operation	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]

Summary of adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
Reproductive system and breast disorders	1(2.3) 1[0.01]	-	5(2.5) 6[0.01]	-	6(2.2) 7[0.01]
Acquired phimosis	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Erectile dysfunction	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Penile adhesion	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Penis disorder	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Testicular pain	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Testicular swelling	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Varicocele	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Endocrine disorders	1(2.3) 1[0.01]	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Adrenal insufficiency	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Goitre	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Product issues	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Device dislocation	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Device malfunction	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Social circumstances	-	-	1(0.5) 3[0.00]	-	1(0.4) 3[0.00]
Tattoo	-	-	1(0.5) 3[0.00]	-	1(0.4) 3[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Other: algerian, caucasian/ black carribean, parent stated other (latin decent), puerto rican (multi-racial), unknown
Four patients with Race=NA and their events are accounted in the Total column.
MedDRA version: 20.0

47. 重篤な有害事象の要約 – 人種別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	Asian N(%) E[R]		Black or African American N(%) E[R]		White N(%) E[R]		Other N(%) E[R]		Total N(%) E[R]	
Number of patients	43		15		203		5		270	
Patient years of exposure	123.05		31.71		702.74		9.24		882.13	
Exposure days	11311		2439		63362		884		79446	
All adverse events	8(18.6)	16[0.13]	3(20.0)	6[0.19]	35(17.2)	44[0.06]	1(20.0)	1[0.11]	47(17.4)	67[0.08]
Infections and infestations	6(14.0)	8[0.07]	2(13.3)	4[0.13]	6(3.0)	8[0.01]	-		14(5.2)	20[0.02]
Cellulitis	1(2.3)	2[0.02]	-		1(0.5)	1[0.00]	-		2(0.7)	3[0.00]
Device related infection	-		1(6.7)	2[0.06]	1(0.5)	1[0.00]	-		2(0.7)	3[0.00]
Bacterial sepsis	1(2.3)	1[0.01]	1(6.7)	1[0.03]	-		-		2(0.7)	2[0.00]
Anal abscess	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Catheter site infection	-		1(6.7)	1[0.03]	-		-		1(0.4)	1[0.00]
Encephalitis	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Enteritis infectious	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Infective spondylitis	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Intervertebral discitis	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Osteomyelitis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Pneumonia	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Sepsis syndrome	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Tonsillitis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Tuberculosis	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Viral infection	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Injury, poisoning and procedural complications	1(2.3)	1[0.01]	1(6.7)	1[0.03]	9(4.4)	9[0.01]	-		11(4.1)	11[0.01]
Fall	-		-		2(1.0)	2[0.00]	-		2(0.7)	2[0.00]
Ankle fracture	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Extradural haematoma	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Face injury	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Femoral neck fracture	1(2.3)	1[0.01]	-		-		-		1(0.4)	1[0.00]
Forearm fracture	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Head injury	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Injury	-		1(6.7)	1[0.03]	-		-		1(0.4)	1[0.00]
Road traffic accident	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Toxicity to various agents	-		-		1(0.5)	1[0.00]	-		1(0.4)	1[0.00]
Gastrointestinal disorders	2(4.7)	2[0.02]	-		5(2.5)	5[0.01]	-		7(2.6)	7[0.01]
Duodenal ulcer	-		-		2(1.0)	2[0.00]	-		2(0.7)	2[0.00]

Summary of serious adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
Abdominal hernia	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Gastric varices	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Gastric varices haemorrhage	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Gastritis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Pancreatitis acute	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Nervous system disorders	-	-	3(1.5) 4[0.01]	-	3(1.1) 4[0.00]
Cerebral infarction	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Cerebral microhaemorrhage	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Seizure	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Syncope	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Musculoskeletal and connective tissue disorders	-	-	3(1.5) 3[0.00]	-	3(1.1) 3[0.00]
Muscle haemorrhage	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Pathological fracture	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Synovitis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(2.3) 1[0.01]	-	2(1.0) 2[0.00]	-	3(1.1) 3[0.00]
Hepatocellular carcinoma	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Neuroma	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Pancreatic carcinoma metastatic	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Renal and urinary disorders	1(2.3) 1[0.01]	-	2(1.0) 2[0.00]	-	3(1.1) 3[0.00]
Calculus urinary	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
IgA nephropathy	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Tubulointerstitial nephritis	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Congenital, familial and genetic disorders	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Hydrocele	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Hypertrophic cardiomyopathy	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]

Summary of serious adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
General disorders and administration site conditions	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Complication associated with device	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Pyrexia	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Respiratory, thoracic and mediastinal disorders	-	-	2(1.0) 2[0.00]	-	2(0.7) 2[0.00]
Adenoidal hypertrophy	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Hypoxia	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Vascular disorders	1(2.3) 1[0.01]	-	1(0.5) 1[0.00]	-	2(0.7) 2[0.00]
Circulatory collapse	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Haemorrhage	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Blood and lymphatic system disorders	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Factor VIII inhibition	-	1(6.7) 1[0.03]	-	-	1(0.4) 1[0.00]
Cardiac disorders	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Aortic valve stenosis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Eye disorders	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Cataract	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]
Hepatobiliary disorders	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Cholecystitis	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Immune system disorders	-	-	-	1(20.0) 1[0.11]	1(0.4) 1[0.00]
Hypersensitivity	-	-	-	1(20.0) 1[0.11]	1(0.4) 1[0.00]
Product issues	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Device dislocation	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Psychiatric disorders	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Depression	-	-	1(0.5) 1[0.00]	-	1(0.4) 1[0.00]
Reproductive system and breast disorders	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]

Summary of serious adverse events by race - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Asian N(%) E[R]	Black or African American N(%) E[R]	White N(%) E[R]	Other N(%) E[R]	Total N(%) E[R]
Acquired phimosis	1(2.3) 1[0.01]	-	-	-	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Other: algerian, caucasian/ black carribean, parent stated other (latin decent), puerto rican (multi-racial), unknown
MedDRA version: 20.0

48. 有害事象の概要 – 民族別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	Hispanic or Latino N(%)	E[R]	Not Hispanic or Latino N(%)	E[R]	Total N(%)	E[R]
Number of patients	16		252		270	
Patient years of exposure	53.68		820.54		882.13	
Exposure days	4984		73812		79446	
All adverse events	16(100)	104[1.94]	221(87.7)	2166[2.64]	239(88.5)	2307[2.62]
Serious adverse events	-		47(18.7)	67[0.08]	47(17.4)	67[0.08]
Non serious adverse events	16(100)	104[1.94]	219(86.9)	2099[2.56]	237(87.8)	2240[2.54]
Severity						
Mild	15(93.8)	84[1.56]	204(81.0)	1697[2.07]	221(81.9)	1814[2.06]
Moderate	7(43.8)	17[0.32]	146(57.9)	405[0.49]	154(57.0)	426[0.48]
Severe	3(18.8)	3[0.06]	39(15.5)	63[0.08]	42(15.6)	66[0.07]
Missing	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Relationship						
Probably or possibly	3(18.8)	10[0.19]	37(14.7)	74[0.09]	40(14.8)	84[0.10]
Unlikely	16(100)	94[1.75]	219(86.9)	2084[2.54]	237(87.8)	2215[2.51]
Missing	-		4(1.6)	8[0.01]	4(1.5)	8[0.01]
Adverse events						
Leading to withdrawal	-		7(2.8)	7[0.01]	7(2.6)	7[0.01]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Two patients with Ethnicity=NA and his evetns are accounted in the Total column.

49. 有害事象の要約 – 民族別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Number of patients	16		252		270	
Patient years of exposure	53.68		820.54		882.13	
Exposure days	4984		73812		79446	
All adverse events	16(100)	104[1.94]	221(87.7)	2166[2.64]	239(88.5)	2307[2.62]
Infections and infestations	8(50.0)	19[0.35]	163(64.7)	594[0.72]	173(64.1)	618[0.70]
Viral upper respiratory tract infection	2(12.5)	2[0.04]	74(29.4)	126[0.15]	78(28.9)	130[0.15]
Upper respiratory tract infection	4(25.0)	5[0.09]	52(20.6)	99[0.12]	57(21.1)	105[0.12]
Influenza	1(6.3)	1[0.02]	28(11.1)	41[0.05]	29(10.7)	42[0.05]
Gastroenteritis	-		20(7.9)	28[0.03]	20(7.4)	28[0.03]
Tonsillitis	1(6.3)	1[0.02]	17(6.7)	23[0.03]	18(6.7)	24[0.03]
Rhinitis	1(6.3)	1[0.02]	14(5.6)	18[0.02]	15(5.6)	19[0.02]
Bronchitis	2(12.5)	2[0.04]	13(5.2)	15[0.02]	15(5.6)	17[0.02]
Ear infection	1(6.3)	1[0.02]	12(4.8)	15[0.02]	13(4.8)	16[0.02]
Viral infection	-		13(5.2)	15[0.02]	13(4.8)	15[0.02]
Otitis media	1(6.3)	2[0.04]	8(3.2)	8[0.01]	9(3.3)	10[0.01]
Conjunctivitis	-		9(3.6)	9[0.01]	9(3.3)	9[0.01]
Sinusitis	-		9(3.6)	9[0.01]	9(3.3)	9[0.01]
Pharyngitis	-		8(3.2)	10[0.01]	8(3.0)	10[0.01]
Pharyngitis streptococcal	-		6(2.4)	7[0.01]	6(2.2)	7[0.01]
Tooth abscess	-		5(2.0)	8[0.01]	5(1.9)	8[0.01]
Eye infection	-		5(2.0)	6[0.01]	5(1.9)	6[0.01]
Pneumonia	-		5(2.0)	5[0.01]	5(1.9)	5[0.01]
Nasopharyngitis	-		3(1.2)	4[0.00]	4(1.5)	6[0.01]
Device related infection	-		4(1.6)	5[0.01]	4(1.5)	5[0.01]
Periodontitis	-		4(1.6)	5[0.01]	4(1.5)	5[0.01]
Fungal skin infection	-		4(1.6)	4[0.00]	4(1.5)	4[0.00]
Gastroenteritis viral	1(6.3)	1[0.02]	3(1.2)	3[0.00]	4(1.5)	4[0.00]
Pulpitis dental	-		4(1.6)	4[0.00]	4(1.5)	4[0.00]
Varicella	-		4(1.6)	4[0.00]	4(1.5)	4[0.00]
Cellulitis	-		3(1.2)	6[0.01]	3(1.1)	6[0.01]
Urinary tract infection	-		3(1.2)	6[0.01]	3(1.1)	6[0.01]
Lower respiratory tract infection	-		3(1.2)	5[0.01]	3(1.1)	5[0.01]
Tooth infection	-		3(1.2)	5[0.01]	3(1.1)	5[0.01]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Folliculitis	-		3(1.2)	4[0.00]	3(1.1)	4[0.00]
Acute sinusitis	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Localised infection	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Molluscum contagiosum	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Otitis externa	1(6.3)	1[0.02]	2(0.8)	2[0.00]	3(1.1)	3[0.00]
Respiratory tract infection	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Tinea pedis	1(6.3)	1[0.02]	2(0.8)	2[0.00]	3(1.1)	3[0.00]
Enterobiasis	-		2(0.8)	6[0.01]	2(0.7)	6[0.01]
Hordeolum	-		2(0.8)	3[0.00]	2(0.7)	3[0.00]
Tinea infection	-		2(0.8)	3[0.00]	2(0.7)	3[0.00]
Bacterial sepsis	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Cystitis	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Gastrointestinal infection	1(6.3)	1[0.02]	1(0.4)	1[0.00]	2(0.7)	2[0.00]
Herpes zoster	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Impetigo	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Onychomycosis	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Pharyngotonsillitis	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Scarlet fever	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Streptococcal infection	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Upper respiratory tract infection bacterial	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Viral pharyngitis	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Otitis media acute	-		1(0.4)	3[0.00]	1(0.4)	3[0.00]
Paronychia	-		1(0.4)	3[0.00]	1(0.4)	3[0.00]
Genital herpes	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Helminthic infection	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Abscess neck	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Anal abscess	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Body tinea	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Catheter site infection	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Chlamydial infection	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Citrobacter infection	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Conjunctivitis bacterial	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Encephalitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Enteritis infectious	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Epididymitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Fungal infection	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Genital infection bacterial	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
H1N1 influenza	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Helicobacter gastritis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Helicobacter infection	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hepatitis C	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Infectious mononucleosis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Infective spondylitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Intervertebral discitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Labyrinthitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Laryngitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Mumps	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Oral herpes	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Orchitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Osteomyelitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Postoperative wound infection	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Sepsis syndrome	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Sinusitis bacterial	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Skin infection	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Subcutaneous abscess	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Tonsillitis streptococcal	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Tracheitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Tuberculosis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Urethritis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Vestibular neuronitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Viral diarrhoea	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Viral parotitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Wound infection	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Musculoskeletal and connective tissue disorders	8(50.0)	16[0.30]	103(40.9)	230[0.28]	113(41.9)	249[0.28]
Arthralgia	1(6.3)	2[0.04]	42(16.7)	64[0.08]	43(15.9)	66[0.07]
Pain in extremity	3(18.8)	4[0.07]	19(7.5)	26[0.03]	22(8.1)	30[0.03]
Musculoskeletal pain	1(6.3)	1[0.02]	16(6.3)	17[0.02]	17(6.3)	18[0.02]
Back pain	-		15(6.0)	18[0.02]	15(5.6)	18[0.02]
Arthropathy	1(6.3)	1[0.02]	7(2.8)	9[0.01]	9(3.3)	11[0.01]
Haemophilic arthropathy	1(6.3)	1[0.02]	8(3.2)	8[0.01]	9(3.3)	9[0.01]
Myalgia	1(6.3)	1[0.02]	6(2.4)	8[0.01]	7(2.6)	9[0.01]
Tendonitis	-		7(2.8)	7[0.01]	7(2.6)	7[0.01]
Synovitis	1(6.3)	1[0.02]	5(2.0)	7[0.01]	6(2.2)	8[0.01]
Joint swelling	-		6(2.4)	7[0.01]	6(2.2)	7[0.01]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%)	E[R]	Not Hispanic or Latino N(%)	E[R]	Total N(%)	E[R]
Musculoskeletal stiffness	-		5(2.0)	5[0.01]	5(1.9)	5[0.01]
Joint range of motion decreased	1(6.3)	1[0.02]	2(0.8)	2[0.00]	4(1.5)	4[0.00]
Neck pain	-		3(1.2)	6[0.01]	3(1.1)	6[0.01]
Pain in jaw	1(6.3)	1[0.02]	2(0.8)	3[0.00]	3(1.1)	4[0.00]
Bursitis	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Joint lock	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Musculoskeletal chest pain	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Osteoarthritis	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Flank pain	1(6.3)	1[0.02]	1(0.4)	1[0.00]	2(0.7)	2[0.00]
Muscle haemorrhage	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Muscle spasms	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Plantar fasciitis	1(6.3)	1[0.02]	1(0.4)	1[0.00]	2(0.7)	2[0.00]
Rotator cuff syndrome	-		1(0.4)	3[0.00]	1(0.4)	3[0.00]
Tenosynovitis	-		1(0.4)	3[0.00]	1(0.4)	3[0.00]
Rheumatic disorder	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Arthritis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Bone pain	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Chondropathy	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Costochondritis	1(6.3)	1[0.02]	-		1(0.4)	1[0.00]
Groin pain	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Growing pains	-		-		1(0.4)	1[0.00]
Joint effusion	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Limb discomfort	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Muscle tightness	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Musculoskeletal discomfort	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Myositis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pathological fracture	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Periostitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Rhabdomyolysis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Scoliosis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Spinal osteoarthritis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Synovial disorder	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Tendon pain	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Torticollis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Injury, poisoning and procedural complications	6(37.5)	8[0.15]	98(38.9)	220[0.27]	106(39.3)	237[0.27]
Contusion	1(6.3)	1[0.02]	19(7.5)	31[0.04]	20(7.4)	32[0.04]
Laceration	1(6.3)	1[0.02]	18(7.1)	20[0.02]	19(7.0)	21[0.02]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Fall	1(6.3)	1[0.02]	16(6.3)	18[0.02]	17(6.3)	19[0.02]
Limb injury	1(6.3)	1[0.02]	14(5.6)	22[0.03]	16(5.9)	26[0.03]
Ligament sprain	-		13(5.2)	14[0.02]	13(4.8)	14[0.02]
Joint injury	-		10(4.0)	11[0.01]	11(4.1)	12[0.01]
Head injury	-		9(3.6)	12[0.01]	9(3.3)	12[0.01]
Muscle strain	-		7(2.8)	9[0.01]	7(2.6)	9[0.01]
Arthropod bite	2(12.5)	2[0.04]	5(2.0)	6[0.01]	7(2.6)	8[0.01]
Skin abrasion	-		6(2.4)	6[0.01]	7(2.6)	8[0.01]
Arthropod sting	-		4(1.6)	6[0.01]	4(1.5)	6[0.01]
Face injury	-		4(1.6)	4[0.00]	4(1.5)	4[0.00]
Hand fracture	-		3(1.2)	4[0.00]	3(1.1)	4[0.00]
Excoriation	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Post-traumatic pain	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Road traffic accident	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Scratch	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Wound	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Accidental overdose	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Chest injury	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Foot fracture	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Procedural pain	1(6.3)	1[0.02]	-		2(0.7)	2[0.00]
Tendon injury	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Thermal burn	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Traumatic haemorrhage	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Injury	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Abdominal injury	1(6.3)	1[0.02]	-		1(0.4)	1[0.00]
Alcohol poisoning	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Animal bite	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Ankle fracture	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Back injury	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Compression fracture	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Concussion	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Corneal abrasion	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Drug administration error	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Electric shock	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Epicondylitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Epiphyseal injury	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Extradural haematoma	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Femoral neck fracture	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Forearm fracture	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Foreign body in eye	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Lower limb fracture	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Medication error	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Mouth injury	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Muscle rupture	-		-		1(0.4)	1[0.00]
Overdose	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Post procedural complication	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Product preparation error	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Radius fracture	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Rib fracture	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Splinter	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Sunburn	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Tooth injury	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Toxicity to various agents	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Traumatic haematoma	-		-		1(0.4)	1[0.00]
Vaccination complication	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Gastrointestinal disorders	6(37.5)	9[0.17]	97(38.5)	216[0.26]	105(38.9)	230[0.26]
Diarrhoea	1(6.3)	1[0.02]	29(11.5)	36[0.04]	31(11.5)	39[0.04]
Vomiting	1(6.3)	1[0.02]	19(7.5)	23[0.03]	20(7.4)	24[0.03]
Nausea	1(6.3)	1[0.02]	16(6.3)	21[0.03]	17(6.3)	22[0.02]
Toothache	3(18.8)	3[0.06]	12(4.8)	13[0.02]	15(5.6)	16[0.02]
Abdominal pain	-		12(4.8)	13[0.02]	13(4.8)	14[0.02]
Abdominal pain upper	-		11(4.4)	13[0.02]	11(4.1)	13[0.01]
Dental caries	-		10(4.0)	13[0.02]	10(3.7)	13[0.01]
Constipation	1(6.3)	2[0.04]	8(3.2)	9[0.01]	9(3.3)	11[0.01]
Gastritis	-		7(2.8)	7[0.01]	7(2.6)	7[0.01]
Gastrooesophageal reflux disease	-		5(2.0)	6[0.01]	6(2.2)	7[0.01]
Dyspepsia	1(6.3)	1[0.02]	4(1.6)	4[0.00]	5(1.9)	5[0.01]
Abdominal discomfort	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Stomatitis	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Irritable bowel syndrome	-		2(0.8)	3[0.00]	2(0.7)	3[0.00]
Aphthous ulcer	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Chapped lips	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Duodenal ulcer	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Gastrointestinal disorder	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Haemorrhoids	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Perianal erythema	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Dysphagia	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Flatulence	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Food poisoning	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Gastric varices	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Abdominal hernia	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Anal fissure	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Barrett's oesophagus	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Chronic gastritis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Dental discomfort	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Dental necrosis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Diaphragmatic hernia	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Duodenitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Enterocolitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Faeces soft	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Gastric varices haemorrhage	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Gastritis erosive	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Gingival bleeding	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Gingival swelling	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Glossodynia	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Haematochezia	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hiatus hernia	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Inguinal hernia	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Lip ulceration	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Loose tooth	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Mouth haemorrhage	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Mouth ulceration	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Noninfective gingivitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Oral pain	-		-		1(0.4)	1[0.00]
Pancreatitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pancreatitis acute	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Rectal haemorrhage	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Retching	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Swollen tongue	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Uvulitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	10(62.5)	13[0.24]	78(31.0)	175[0.21]	89(33.0)	195[0.22]
Cough	5(31.3)	6[0.11]	31(12.3)	46[0.06]	37(13.7)	53[0.06]
Oropharyngeal pain	1(6.3)	1[0.02]	27(10.7)	33[0.04]	29(10.7)	35[0.04]
Rhinorrhoea	1(6.3)	1[0.02]	13(5.2)	17[0.02]	15(5.6)	20[0.02]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Epistaxis	2(12.5)	2[0.04]	10(4.0)	25[0.03]	13(4.8)	30[0.03]
Nasal congestion	1(6.3)	1[0.02]	6(2.4)	9[0.01]	7(2.6)	10[0.01]
Respiratory disorder	-		5(2.0)	14[0.02]	5(1.9)	14[0.02]
Asthma	-		4(1.6)	6[0.01]	4(1.5)	6[0.01]
Rhinitis allergic	1(6.3)	1[0.02]	2(0.8)	2[0.00]	3(1.1)	3[0.00]
Productive cough	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Sneezing	1(6.3)	1[0.02]	1(0.4)	1[0.00]	2(0.7)	2[0.00]
Haemoptysis	-		1(0.4)	3[0.00]	1(0.4)	3[0.00]
Dysphonia	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Adenoidal hypertrophy	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Allergic respiratory disease	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Asthma exercise induced	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Asthmatic crisis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Bronchial hyperreactivity	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Dyspnoea	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Dyspnoea exertional	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hypoxia	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Middle lobe syndrome	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Nasal obstruction	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Sinus congestion	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Sleep apnoea syndrome	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Upper respiratory tract congestion	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Upper respiratory tract inflammation	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Wheezing	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Nervous system disorders	6(37.5)	6[0.11]	71(28.2)	154[0.19]	79(29.3)	163[0.18]
Headache	5(31.3)	5[0.09]	49(19.4)	110[0.13]	56(20.7)	118[0.13]
Dizziness	-		8(3.2)	9[0.01]	8(3.0)	9[0.01]
Paraesthesia	1(6.3)	1[0.02]	6(2.4)	6[0.01]	7(2.6)	7[0.01]
Carpal tunnel syndrome	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Post-traumatic headache	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Presyncope	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Sciatica	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Seizure	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Altered state of consciousness	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Cerebral infarction	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Cerebral microhaemorrhage		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Cognitive disorder		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Dizziness exertional		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Dizziness postural		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Epilepsy		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Facial paralysis		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hypoaesthesia		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Lethargy		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Migraine		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Nerve compression		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Nervous system disorder		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Neuropathy peripheral		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Restless legs syndrome		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Sensory loss		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Sinus headache		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Syncope		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Tongue biting		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Skin and subcutaneous tissue disorders	5(31.3)	7[0.13]	69(27.4)	122[0.15]	75(27.8)	131[0.15]
Eczema		-	15(6.0)	19[0.02]	15(5.6)	19[0.02]
Rash		-	14(5.6)	18[0.02]	14(5.2)	18[0.02]
Acne		-	8(3.2)	9[0.01]	8(3.0)	9[0.01]
Urticaria		-	7(2.8)	7[0.01]	7(2.6)	7[0.01]
Erythema	2(12.5)	4[0.07]	3(1.2)	5[0.01]	5(1.9)	9[0.01]
Dermatitis contact		-	4(1.6)	4[0.00]	4(1.5)	4[0.00]
Dry skin		-	4(1.6)	4[0.00]	4(1.5)	4[0.00]
Pruritus	1(6.3)	1[0.02]	3(1.2)	3[0.00]	4(1.5)	4[0.00]
Blister		-	3(1.2)	5[0.01]	3(1.1)	5[0.01]
Hyperhidrosis	2(12.5)	2[0.04]	1(0.4)	1[0.00]	3(1.1)	3[0.00]
Skin lesion		-	2(0.8)	2[0.00]	3(1.1)	3[0.00]
Skin erosion		-	2(0.8)	4[0.00]	2(0.7)	4[0.00]
Alopecia		-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Dermal cyst		-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Dermatitis		-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Ingrowing nail		-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Photosensitivity reaction		-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Purpura		-	1(0.4)	1[0.00]	2(0.7)	2[0.00]
Rash pruritic		-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Miliaria		-	1(0.4)	3[0.00]	1(0.4)	3[0.00]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%)	E[R]	Not Hispanic or Latino N(%)	E[R]	Total N(%)	E[R]
Papule	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Petechiae	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Alopecia areata	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Blood blister	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Dermatitis diaper	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Drug eruption	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Eczema asteatotic	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hangnail	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Mechanical urticaria	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Nail disorder	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Onychalgia	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pigmentation disorder	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pruritus allergic	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pruritus generalised	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Psoriasis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Rash papular	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Scab	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Sebaceous gland disorder	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Skin disorder	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Skin irritation	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Skin ulcer	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Telangiectasia	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Vitiligo	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
General disorders and administration site conditions	10(62.5)	10[0.19]	51(20.2)	88[0.11]	63(23.3)	100[0.11]
Pyrexia	1(6.3)	1[0.02]	23(9.1)	39[0.05]	25(9.3)	41[0.05]
Fatigue	2(12.5)	2[0.04]	6(2.4)	7[0.01]	8(3.0)	9[0.01]
Influenza like illness	1(6.3)	1[0.02]	5(2.0)	9[0.01]	7(2.6)	11[0.01]
Chest pain	-		5(2.0)	5[0.01]	5(1.9)	5[0.01]
Oedema peripheral	1(6.3)	1[0.02]	4(1.6)	4[0.00]	5(1.9)	5[0.01]
Peripheral swelling	1(6.3)	1[0.02]	3(1.2)	3[0.00]	4(1.5)	4[0.00]
Hyperthermia	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Local swelling	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Chills	1(6.3)	1[0.02]	1(0.4)	2[0.00]	2(0.7)	3[0.00]
Adverse drug reaction	1(6.3)	1[0.02]	1(0.4)	1[0.00]	2(0.7)	2[0.00]
Complication associated with device	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
General physical health deterioration	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Infusion site reaction	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Injection site erythema	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Injection site rash	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Injection site reaction	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Injection site swelling	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Localised oedema	1(6.3)	1[0.02]	-		1(0.4)	1[0.00]
Oedema	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pain	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Tenderness	1(6.3)	1[0.02]	-		1(0.4)	1[0.00]
Ulcer	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Vessel puncture site haematoma	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Vessel puncture site pain	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Investigations	4(25.0)	8[0.15]	45(17.9)	113[0.14]	50(18.5)	122[0.14]
Alanine aminotransferase increased	2(12.5)	3[0.06]	12(4.8)	18[0.02]	14(5.2)	21[0.02]
Aspartate aminotransferase increased	2(12.5)	2[0.04]	10(4.0)	16[0.02]	12(4.4)	18[0.02]
Gamma-glutamyltransferase increased	-		9(3.6)	15[0.02]	9(3.3)	15[0.02]
C-reactive protein increased	-		8(3.2)	10[0.01]	8(3.0)	10[0.01]
Blood cholesterol increased	-		5(2.0)	5[0.01]	5(1.9)	5[0.01]
Blood creatinine increased	-		3(1.2)	5[0.01]	3(1.1)	5[0.01]
Blood bilirubin increased	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Red blood cell count increased	1(6.3)	1[0.02]	2(0.8)	2[0.00]	3(1.1)	3[0.00]
Blood pressure increased	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Haemoglobin increased	1(6.3)	1[0.02]	1(0.4)	1[0.00]	2(0.7)	2[0.00]
Weight decreased	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Coagulation factor VIII level increased	-		1(0.4)	7[0.01]	1(0.4)	7[0.01]
Haemoglobin decreased	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Anti factor VIII antibody test	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Aspartate aminotransferase abnormal	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Blood HIV RNA increased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Blood alkaline phosphatase increased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Blood creatine phosphokinase increased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Blood sodium increased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Blood triglycerides increased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
C-reactive protein abnormal	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Electrocardiogram ST segment elevation	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Electrocardiogram T wave inversion	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hepatic enzyme increased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Intraocular pressure test	-		-		1(0.4)	1[0.00]
Laboratory test abnormal	1(6.3)	1[0.02]	-		1(0.4)	1[0.00]
Liver function test abnormal	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Mean cell haemoglobin decreased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Mean cell volume decreased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Monocyte count increased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Neutrophil count increased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Platelet count decreased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Prostatic specific antigen abnormal	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Serum ferritin decreased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Sputum abnormal	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Transaminases abnormal	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Transaminases increased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Vitamin D decreased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
White blood cell count increased	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
White blood cells urine positive	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Vascular disorders	1(6.3)	1[0.02]	28(11.1)	29[0.04]	29(10.7)	30[0.03]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Hypertension	-		19(7.5)	20[0.02]	19(7.0)	20[0.02]
Haematoma	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Circulatory collapse	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Essential hypertension	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Flushing	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Haemorrhage	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Peripheral venous disease	1(6.3)	1[0.02]	-		1(0.4)	1[0.00]
Vein disorder	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Vein rupture	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Immune system disorders	-		27(10.7)	42[0.05]	27(10.0)	42[0.05]
Seasonal allergy	-		14(5.6)	19[0.02]	14(5.2)	19[0.02]
Food allergy	-		4(1.6)	6[0.01]	4(1.5)	6[0.01]
Hypersensitivity	-		2(0.8)	3[0.00]	2(0.7)	3[0.00]
Allergy to arthropod sting	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Allergic oedema	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Allergy to animal	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Allergy to arthropod bite	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Allergy to chemicals	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Allergy to metals	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Allergy to plants	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Drug hypersensitivity	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Mite allergy	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Mycotic allergy	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Rubber sensitivity	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Psychiatric disorders	1(6.3)	1[0.02]	23(9.1)	24[0.03]	24(8.9)	25[0.03]
Depression	-		8(3.2)	8[0.01]	8(3.0)	8[0.01]
Insomnia	1(6.3)	1[0.02]	4(1.6)	4[0.00]	5(1.9)	5[0.01]
Anxiety	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Attention deficit/hyperactivity disorder	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Adjustment disorder with depressed mood	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Alcohol abuse	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Depressed mood	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Illusion	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Mental status changes	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Sleep disorder	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Stress		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Blood and lymphatic system disorders	1(6.3)	1[0.02]	20(7.9)	24[0.03]	21(7.8)	25[0.03]
Anaemia		-	7(2.8)	8[0.01]	7(2.6)	8[0.01]
Lymphadenopathy		-	3(1.2)	3[0.00]	3(1.1)	3[0.00]
Leukocytosis		-	2(0.8)	4[0.00]	2(0.7)	4[0.00]
Neutropenia	1(6.3)	1[0.02]	1(0.4)	1[0.00]	2(0.7)	2[0.00]
Thrombocytopenia		-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Eosinophilia		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Factor VIII inhibition		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Iron deficiency anaemia		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Lymphadenitis		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Monocytosis		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pancytopenia		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Metabolism and nutrition disorders		-	21(8.3)	22[0.03]	21(7.8)	22[0.02]
Vitamin D deficiency		-	7(2.8)	7[0.01]	7(2.6)	7[0.01]
Hyperlipidaemia		-	3(1.2)	3[0.00]	3(1.1)	3[0.00]
Iron deficiency		-	3(1.2)	3[0.00]	3(1.1)	3[0.00]
Gout		-	2(0.8)	3[0.00]	2(0.7)	3[0.00]
Diabetes mellitus		-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Hypercholesterolaemia		-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Decreased appetite		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hyperuricaemia		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Eye disorders	2(12.5)	3[0.06]	18(7.1)	29[0.04]	20(7.4)	32[0.04]
Cataract	1(6.3)	2[0.04]	2(0.8)	2[0.00]	3(1.1)	4[0.00]
Conjunctivitis allergic		-	3(1.2)	4[0.00]	3(1.1)	4[0.00]
Diplopia		-	2(0.8)	4[0.00]	2(0.7)	4[0.00]
Dry eye		-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Eye pruritus	1(6.3)	1[0.02]	1(0.4)	1[0.00]	2(0.7)	2[0.00]
Glaucoma		-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Myopia		-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Blepharospasm		-	1(0.4)	4[0.00]	1(0.4)	4[0.00]
Ocular myasthenia		-	1(0.4)	2[0.00]	1(0.4)	2[0.00]
Blepharitis		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Conjunctival haemorrhage		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Corneal disorder		-	1(0.4)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]	Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Eye allergy	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Eye irritation	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Eye swelling	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Renal and urinary disorders	-	14(5.6)	14[0.02]	14(5.2)	14[0.02]
Dysuria	-	6(2.4)	6[0.01]	6(2.2)	6[0.01]
Calculus urinary	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Haematuria	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
IgA nephropathy	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Nephrolithiasis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pollakiuria	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Renal colic	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Tubulointerstitial nephritis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Urinary incontinence	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Ear and labyrinth disorders	-	11(4.4)	14[0.02]	11(4.1)	14[0.02]
Ear pain	-	5(2.0)	6[0.01]	5(1.9)	6[0.01]
Cerumen impaction	-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Ear deformity acquired	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Ear disorder	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Excessive cerumen production	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Motion sickness	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Tinnitus	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Tympanic membrane perforation	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Cardiac disorders	-	9(3.6)	10[0.01]	9(3.3)	10[0.01]
Ventricular extrasystoles	-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Aortic valve stenosis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Atrial fibrillation	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Atrioventricular block first degree	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Extrasystoles	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Palpitations	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pericarditis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Sinus arrhythmia	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Sinus bradycardia	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-		9(3.6)	9[0.01]	9(3.3)	9[0.01]
Skin papilloma	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Eye naevus	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hepatocellular carcinoma	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Lipoma	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Nasopharyngeal neoplasm benign	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Neuroma	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pancreatic carcinoma metastatic	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pyogenic granuloma	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Congenital, familial and genetic disorders	-		8(3.2)	8[0.01]	8(3.0)	8[0.01]
Gilbert's syndrome	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Dermoid cyst	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hydrocele	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hypertrophic cardiomyopathy	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Odontogenic cyst	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pectus carinatum	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Thalassaemia alpha	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hepatobiliary disorders	-		8(3.2)	8[0.01]	8(3.0)	8[0.01]
Hepatic fibrosis	-		3(1.2)	3[0.00]	3(1.1)	3[0.00]
Cholecystitis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hepatic cirrhosis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hepatic function abnormal	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hepatic steatosis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hepatomegaly	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Surgical and medical procedures	1(6.3)	1[0.02]	6(2.4)	8[0.01]	7(2.6)	9[0.01]
Tooth extraction	-		2(0.8)	3[0.00]	2(0.7)	3[0.00]
Wisdom teeth removal	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Dental operation	-		1(0.4)	2[0.00]	1(0.4)	2[0.00]
Dental implantation	1(6.3)	1[0.02]	-		1(0.4)	1[0.00]
Nail operation	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]

Summary of adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]		Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Reproductive system and breast disorders	1(6.3)	1[0.02]	5(2.0)	6[0.01]	6(2.2)	7[0.01]
Acquired phimosis	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Erectile dysfunction	1(6.3)	1[0.02]	-		1(0.4)	1[0.00]
Penile adhesion	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Penis disorder	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Testicular pain	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Testicular swelling	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Varicocele	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Endocrine disorders	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Adrenal insufficiency	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Goitre	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Product issues	-		2(0.8)	2[0.00]	2(0.7)	2[0.00]
Device dislocation	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Device malfunction	-		1(0.4)	1[0.00]	1(0.4)	1[0.00]
Social circumstances	-		1(0.4)	3[0.00]	1(0.4)	3[0.00]
Tattoo	-		1(0.4)	3[0.00]	1(0.4)	3[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Two patients with Ethnicity=NA and his evetns are accounted in the Total column.
MedDRA version: 20.0

50. 重篤な有害事象の要約 – 民族別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	Hispanic or Latino N(%) E[R]	Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Number of patients	16	252		270	
Patient years of exposure	53.68	820.54		882.13	
Exposure days	4984	73812		79446	
All adverse events	-	47(18.7)	67[0.08]	47(17.4)	67[0.08]
Infections and infestations	-	14(5.6)	20[0.02]	14(5.2)	20[0.02]
Cellulitis	-	2(0.8)	3[0.00]	2(0.7)	3[0.00]
Device related infection	-	2(0.8)	3[0.00]	2(0.7)	3[0.00]
Bacterial sepsis	-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Anal abscess	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Catheter site infection	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Encephalitis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Enteritis infectious	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Infective spondylitis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Intervertebral discitis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Osteomyelitis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pneumonia	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Sepsis syndrome	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Tonsillitis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Tuberculosis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Viral infection	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Injury, poisoning and procedural complications	-	11(4.4)	11[0.01]	11(4.1)	11[0.01]
Fall	-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Ankle fracture	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Extradural haematoma	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Face injury	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Femoral neck fracture	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Forearm fracture	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Head injury	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Injury	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Road traffic accident	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Toxicity to various agents	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Gastrointestinal disorders	-	7(2.8)	7[0.01]	7(2.6)	7[0.01]
Duodenal ulcer	-	2(0.8)	2[0.00]	2(0.7)	2[0.00]

Summary of serious adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]	Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
Abdominal hernia	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Gastric varices	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Gastric varices haemorrhage	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Gastritis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pancreatitis acute	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Nervous system disorders	-	3(1.2)	4[0.00]	3(1.1)	4[0.00]
Cerebral infarction	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Cerebral microhaemorrhage	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Seizure	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Syncope	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Musculoskeletal and connective tissue disorders	-	3(1.2)	3[0.00]	3(1.1)	3[0.00]
Muscle haemorrhage	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pathological fracture	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Synovitis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	3(1.2)	3[0.00]	3(1.1)	3[0.00]
Hepatocellular carcinoma	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Neuroma	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pancreatic carcinoma metastatic	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Renal and urinary disorders	-	3(1.2)	3[0.00]	3(1.1)	3[0.00]
Calculus urinary	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
IgA nephropathy	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Tubulointerstitial nephritis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Congenital, familial and genetic disorders	-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Hydrocele	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hypertrophic cardiomyopathy	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]

Summary of serious adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]	Not Hispanic or Latino N(%) E[R]		Total N(%) E[R]	
General disorders and administration site conditions	-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Complication associated with device	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Pyrexia	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Adenoidal hypertrophy	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hypoxia	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Vascular disorders	-	2(0.8)	2[0.00]	2(0.7)	2[0.00]
Circulatory collapse	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Haemorrhage	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Blood and lymphatic system disorders	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Factor VIII inhibition	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Cardiac disorders	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Aortic valve stenosis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Eye disorders	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Cataract	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hepatobiliary disorders	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Cholecystitis	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Immune system disorders	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Hypersensitivity	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Product issues	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Device dislocation	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Psychiatric disorders	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Depression	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]
Reproductive system and breast disorders	-	1(0.4)	1[0.00]	1(0.4)	1[0.00]

Summary of serious adverse events by ethnicity - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

	Hispanic or Latino N(%) E[R]	Not Hispanic or Latino N(%) E[R]	Total N(%) E[R]
Acquired phimosis	-	1(0.4) 1[0.00]	1(0.4) 1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

51. 有害事象の概要 – 原薬製造工程別 – 安全性解析対象集団（3859 及び 3885 試験）

	Pivotal process N(%) E[R]	Commercial process N(%) E[R]	Total N(%) E[R]
Number of patients	254	92	254
Patient years of exposure	824.02	54.40	878.43
Exposure days	74076	5217	79293
All adverse events	233(91.7) 2186[2.65]	48(52.2) 98[1.80]	234(92.1) 2284[2.60]
Serious adverse events	45(17.7) 65[0.08]	1(1.1) 1[0.02]	46(18.1) 66[0.08]
Non serious adverse events	231(90.9) 2121[2.57]	48(52.2) 97[1.78]	232(91.3) 2218[2.52]
Severity			
Mild	217(85.4) 1714[2.08]	42(45.7) 82[1.51]	218(85.8) 1796[2.04]
Moderate	147(57.9) 405[0.49]	14(15.2) 16[0.29]	150(59.1) 421[0.48]
Severe	42(16.5) 66[0.08]	-	42(16.5) 66[0.08]
Missing	1(0.4) 1[0.00]	-	1(0.4) 1[0.00]
Relationship			
Probably or possibly	39(15.4) 82[0.10]	-	39(15.4) 82[0.09]
Unlikely	230(90.6) 2096[2.54]	48(52.2) 98[1.80]	232(91.3) 2194[2.50]
Missing	4(1.6) 8[0.01]	-	4(1.6) 8[0.01]
Adverse events			
Leading to withdrawal	7(2.8) 7[0.01]	-	7(2.8) 7[0.01]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Exposure to N8-GP from the different production methods is accounted from the scheduled visit where product was first dispensed.

52. 有害事象の要約 – 原薬製造工程別 – 安全性解析対象集団（3859 及び 3885 試験）

	Pivotal process N(%) E[R]		Commercial process N(%) E[R]		Total N(%) E[R]	
Number of patients	254		92		254	
Patient years of exposure	824.02		54.40		878.43	
Exposure days	74076		5217		79293	
All adverse events	233(91.7)	2186[2.65]	48(52.2)	98[1.80]	234(92.1)	2284[2.60]
Infections and infestations	170(66.9)	578[0.70]	24(26.1)	35[0.64]	171(67.3)	613[0.70]
Viral upper respiratory tract infection	76(29.9)	124[0.15]	4(4.3)	4[0.07]	76(29.9)	128[0.15]
Upper respiratory tract infection	55(21.7)	97[0.12]	6(6.5)	7[0.13]	57(22.4)	104[0.12]
Influenza	27(10.6)	37[0.04]	5(5.4)	5[0.09]	29(11.4)	42[0.05]
Gastroenteritis	19(7.5)	25[0.03]	3(3.3)	3[0.06]	20(7.9)	28[0.03]
Tonsillitis	18(7.1)	24[0.03]		-	18(7.1)	24[0.03]
Rhinitis	14(5.5)	18[0.02]	1(1.1)	1[0.02]	15(5.9)	19[0.02]
Bronchitis	14(5.5)	16[0.02]	1(1.1)	1[0.02]	15(5.9)	17[0.02]
Ear infection	12(4.7)	15[0.02]	1(1.1)	1[0.02]	13(5.1)	16[0.02]
Viral infection	12(4.7)	14[0.02]	1(1.1)	1[0.02]	13(5.1)	15[0.02]
Otitis media	8(3.1)	9[0.01]	1(1.1)	1[0.02]	9(3.5)	10[0.01]
Conjunctivitis	9(3.5)	9[0.01]		-	9(3.5)	9[0.01]
Sinusitis	9(3.5)	9[0.01]		-	9(3.5)	9[0.01]
Pharyngitis	8(3.1)	10[0.01]		-	8(3.1)	10[0.01]
Pharyngitis streptococcal	6(2.4)	7[0.01]		-	6(2.4)	7[0.01]
Tooth abscess	4(1.6)	5[0.01]	2(2.2)	3[0.06]	5(2.0)	8[0.01]
Eye infection	4(1.6)	5[0.01]	1(1.1)	1[0.02]	5(2.0)	6[0.01]
Pneumonia	5(2.0)	5[0.01]		-	5(2.0)	5[0.01]
Nasopharyngitis	3(1.2)	5[0.01]	1(1.1)	1[0.02]	4(1.6)	6[0.01]
Device related infection	4(1.6)	5[0.01]		-	4(1.6)	5[0.01]
Periodontitis	4(1.6)	5[0.01]		-	4(1.6)	5[0.01]
Fungal skin infection	4(1.6)	4[0.00]		-	4(1.6)	4[0.00]
Gastroenteritis viral	4(1.6)	4[0.00]		-	4(1.6)	4[0.00]
Pulpitis dental	4(1.6)	4[0.00]		-	4(1.6)	4[0.00]
Varicella	4(1.6)	4[0.00]		-	4(1.6)	4[0.00]
Cellulitis	3(1.2)	6[0.01]		-	3(1.2)	6[0.01]
Urinary tract infection	3(1.2)	6[0.01]		-	3(1.2)	6[0.01]
Lower respiratory tract infection	3(1.2)	5[0.01]		-	3(1.2)	5[0.01]
Tooth infection	3(1.2)	4[0.00]	1(1.1)	1[0.02]	3(1.2)	5[0.01]
Folliculitis	3(1.2)	4[0.00]		-	3(1.2)	4[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	E[R]	Commercial process N(%)	E[R]	Total N(%)	E[R]
Acute sinusitis	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Localised infection	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Molluscum contagiosum	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Otitis externa	2(0.8)	2[0.00]	1(1.1)	1[0.02]	3(1.2)	3[0.00]
Respiratory tract infection	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Tinea pedis	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Enterobiasis	2(0.8)	5[0.01]	1(1.1)	1[0.02]	2(0.8)	6[0.01]
Hordeolum	2(0.8)	3[0.00]	-		2(0.8)	3[0.00]
Tinea infection	2(0.8)	3[0.00]	-		2(0.8)	3[0.00]
Bacterial sepsis	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Cystitis	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Gastrointestinal infection	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Herpes zoster	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Impetigo	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Onychomycosis	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Pharyngotonsillitis	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Scarlet fever	1(0.4)	1[0.00]	1(1.1)	1[0.02]	2(0.8)	2[0.00]
Streptococcal infection	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Upper respiratory tract infection bacterial	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Viral pharyngitis	1(0.4)	1[0.00]	1(1.1)	1[0.02]	2(0.8)	2[0.00]
Otitis media acute	1(0.4)	3[0.00]	-		1(0.4)	3[0.00]
Paronychia	1(0.4)	2[0.00]	1(1.1)	1[0.02]	1(0.4)	3[0.00]
Genital herpes	1(0.4)	2[0.00]	-		1(0.4)	2[0.00]
Helminthic infection	1(0.4)	2[0.00]	-		1(0.4)	2[0.00]
Abscess neck	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Anal abscess	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Body tinea	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Catheter site infection	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Chlamydial infection	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Citrobacter infection	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Conjunctivitis bacterial	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Encephalitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Enteritis infectious	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Epididymitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Fungal infection	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Genital infection bacterial	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Helicobacter gastritis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Helicobacter infection	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	Pivotal process E[R]	Commercial process N(%)	Commercial process E[R]	Total N(%)	Total E[R]
Hepatitis C	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Infectious mononucleosis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Infective spondylitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Intervertebral discitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Labyrinthitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Laryngitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Mumps	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Oral herpes	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Orchitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Osteomyelitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Postoperative wound infection	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Sepsis syndrome	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Sinusitis bacterial	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Skin infection	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Subcutaneous abscess	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Tonsillitis streptococcal	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Tracheitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Urethritis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Vestibular neuronitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Viral diarrhoea	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Viral parotitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Wound infection	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Musculoskeletal and connective tissue disorders	109(42.9)	241[0.29]	6(6.5)	6[0.11]	111(43.7)	247[0.28]
Arthralgia	42(16.5)	63[0.08]	3(3.3)	3[0.06]	43(16.9)	66[0.08]
Pain in extremity	22(8.7)	30[0.04]	-		22(8.7)	30[0.03]
Musculoskeletal pain	17(6.7)	18[0.02]	-		17(6.7)	18[0.02]
Back pain	14(5.5)	17[0.02]	-		14(5.5)	17[0.02]
Arthropathy	9(3.5)	11[0.01]	-		9(3.5)	11[0.01]
Haemophilic arthropathy	8(3.1)	8[0.01]	1(1.1)	1[0.02]	9(3.5)	9[0.01]
Myalgia	7(2.8)	9[0.01]	-		7(2.8)	9[0.01]
Tendonitis	6(2.4)	6[0.01]	1(1.1)	1[0.02]	7(2.8)	7[0.01]
Synovitis	6(2.4)	8[0.01]	-		6(2.4)	8[0.01]
Joint swelling	6(2.4)	7[0.01]	-		6(2.4)	7[0.01]
Musculoskeletal stiffness	5(2.0)	5[0.01]	-		5(2.0)	5[0.01]
Joint range of motion decreased	4(1.6)	4[0.00]	-		4(1.6)	4[0.00]
Neck pain	3(1.2)	6[0.01]	-		3(1.2)	6[0.01]
Pain in jaw	3(1.2)	4[0.00]	-		3(1.2)	4[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	Pivotal process E[R]	Commercial process N(%)	Commercial process E[R]	Total N(%)	Total E[R]
Bursitis	3(1.2)	3[0.00]		-	3(1.2)	3[0.00]
Joint lock	3(1.2)	3[0.00]		-	3(1.2)	3[0.00]
Musculoskeletal chest pain	3(1.2)	3[0.00]		-	3(1.2)	3[0.00]
Osteoarthritis	3(1.2)	3[0.00]		-	3(1.2)	3[0.00]
Flank pain	2(0.8)	2[0.00]		-	2(0.8)	2[0.00]
Muscle haemorrhage	2(0.8)	2[0.00]		-	2(0.8)	2[0.00]
Muscle spasms	2(0.8)	2[0.00]		-	2(0.8)	2[0.00]
Plantar fasciitis	2(0.8)	2[0.00]		-	2(0.8)	2[0.00]
Rotator cuff syndrome	1(0.4)	3[0.00]		-	1(0.4)	3[0.00]
Tenosynovitis	1(0.4)	3[0.00]		-	1(0.4)	3[0.00]
Rheumatic disorder	1(0.4)	2[0.00]		-	1(0.4)	2[0.00]
Arthritis	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Bone pain	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Chondropathy	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Costochondritis	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Groin pain	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Growing pains	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Joint effusion	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Limb discomfort	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Muscle tightness	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Musculoskeletal discomfort	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Myositis	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Pathological fracture	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Periostitis	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Scoliosis	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Spinal osteoarthritis		-	1(1.1)	1[0.02]	1(0.4)	1[0.00]
Synovial disorder	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Tendon pain	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Torticollis	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Injury, poisoning and procedural complications	104(40.9)	222[0.27]	12(13.0)	15[0.28]	106(41.7)	237[0.27]
Contusion	20(7.9)	31[0.04]	1(1.1)	1[0.02]	20(7.9)	32[0.04]
Laceration	17(6.7)	19[0.02]	2(2.2)	2[0.04]	19(7.5)	21[0.02]
Fall	17(6.7)	19[0.02]		-	17(6.7)	19[0.02]
Limb injury	15(5.9)	24[0.03]	2(2.2)	2[0.04]	16(6.3)	26[0.03]
Ligament sprain	13(5.1)	14[0.02]		-	13(5.1)	14[0.02]
Joint injury	10(3.9)	11[0.01]	1(1.1)	1[0.02]	11(4.3)	12[0.01]
Head injury	8(3.1)	11[0.01]	1(1.1)	1[0.02]	9(3.5)	12[0.01]
Muscle strain	7(2.8)	9[0.01]		-	7(2.8)	9[0.01]
Arthropod bite	7(2.8)	8[0.01]		-	7(2.8)	8[0.01]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	E[R]	Commercial process N(%)	E[R]	Total N(%)	E[R]
Skin abrasion	6(2.4)	6[0.01]	2(2.2)	2[0.04]	7(2.8)	8[0.01]
Arthropod sting	4(1.6)	6[0.01]	-		4(1.6)	6[0.01]
Face injury	2(0.8)	2[0.00]	2(2.2)	2[0.04]	4(1.6)	4[0.00]
Hand fracture	2(0.8)	3[0.00]	1(1.1)	1[0.02]	3(1.2)	4[0.00]
Excoriation	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Post-traumatic pain	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Road traffic accident	2(0.8)	2[0.00]	1(1.1)	1[0.02]	3(1.2)	3[0.00]
Scratch	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Wound	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Accidental overdose	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Chest injury	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Foot fracture	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Procedural pain	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Tendon injury	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Thermal burn	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Traumatic haemorrhage	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Injury	1(0.4)	2[0.00]	-		1(0.4)	2[0.00]
Abdominal injury	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Alcohol poisoning	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Animal bite	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Ankle fracture	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Back injury	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Compression fracture	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Concussion	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Corneal abrasion	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Drug administration error	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Electric shock	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Epicondylitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Epiphyseal injury	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Extradural haematoma	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Femoral neck fracture	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Forearm fracture	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Foreign body in eye	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Lower limb fracture	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Medication error	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Mouth injury	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Muscle rupture	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Overdose	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Post procedural complication	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Product preparation error	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	Pivotal process E[R]	Commercial process N(%)	Commercial process E[R]	Total N(%)	Total E[R]
Radius fracture	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Rib fracture	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Splinter	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Sunburn		-	1(1.1)	1[0.02]	1(0.4)	1[0.00]
Tooth injury	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Toxicity to various agents	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Traumatic haematoma		-	1(1.1)	1[0.02]	1(0.4)	1[0.00]
Vaccination complication	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Gastrointestinal disorders	102(40.2)	218[0.26]	6(6.5)	10[0.18]	105(41.3)	228[0.26]
Diarrhoea	29(11.4)	36[0.04]	2(2.2)	3[0.06]	31(12.2)	39[0.04]
Vomiting	19(7.5)	22[0.03]	2(2.2)	2[0.04]	20(7.9)	24[0.03]
Nausea	16(6.3)	20[0.02]	1(1.1)	1[0.02]	17(6.7)	21[0.02]
Toothache	15(5.9)	16[0.02]		-	15(5.9)	16[0.02]
Abdominal pain	12(4.7)	13[0.02]		-	12(4.7)	13[0.01]
Abdominal pain upper	11(4.3)	13[0.02]		-	11(4.3)	13[0.01]
Dental caries	10(3.9)	13[0.02]		-	10(3.9)	13[0.01]
Constipation	9(3.5)	11[0.01]		-	9(3.5)	11[0.01]
Gastritis	7(2.8)	7[0.01]		-	7(2.8)	7[0.01]
Gastrooesophageal reflux disease	6(2.4)	7[0.01]		-	6(2.4)	7[0.01]
Dyspepsia	4(1.6)	4[0.00]	1(1.1)	1[0.02]	5(2.0)	5[0.01]
Abdominal discomfort	3(1.2)	3[0.00]		-	3(1.2)	3[0.00]
Stomatitis	3(1.2)	3[0.00]		-	3(1.2)	3[0.00]
Irritable bowel syndrome	2(0.8)	3[0.00]		-	2(0.8)	3[0.00]
Aphthous ulcer	2(0.8)	2[0.00]		-	2(0.8)	2[0.00]
Chapped lips	2(0.8)	2[0.00]		-	2(0.8)	2[0.00]
Duodenal ulcer	2(0.8)	2[0.00]		-	2(0.8)	2[0.00]
Gastrointestinal disorder	2(0.8)	2[0.00]		-	2(0.8)	2[0.00]
Haemorrhoids	2(0.8)	2[0.00]		-	2(0.8)	2[0.00]
Perianal erythema	1(0.4)	1[0.00]	1(1.1)	1[0.02]	2(0.8)	2[0.00]
Dysphagia	1(0.4)	2[0.00]		-	1(0.4)	2[0.00]
Flatulence	1(0.4)	2[0.00]		-	1(0.4)	2[0.00]
Food poisoning	1(0.4)	2[0.00]		-	1(0.4)	2[0.00]
Gastric varices	1(0.4)	2[0.00]		-	1(0.4)	2[0.00]
Abdominal hernia		-	1(1.1)	1[0.02]	1(0.4)	1[0.00]
Anal fissure	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Barrett's oesophagus	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Chronic gastritis	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Dental discomfort	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Dental necrosis	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	Pivotal process E[R]	Commercial process N(%)	Commercial process E[R]	Total N(%)	Total E[R]
Diaphragmatic hernia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Duodenitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Enterocolitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Faeces soft	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Gastric varices haemorrhage	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Gastritis erosive	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Gingival bleeding	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Gingival swelling	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Glossodynia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Haematochezia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hiatus hernia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Inguinal hernia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Lip ulceration	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Loose tooth	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Mouth haemorrhage	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Mouth ulceration	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Noninfective gingivitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Oral pain	-		1(1.1)	1[0.02]	1(0.4)	1[0.00]
Pancreatitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pancreatitis acute	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Rectal haemorrhage	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Retching	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Swollen tongue	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Uvulitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	83(32.7)	180[0.22]	13(14.1)	13[0.24]	88(34.6)	193[0.22]
Cough	32(12.6)	46[0.06]	6(6.5)	6[0.11]	36(14.2)	52[0.06]
Oropharyngeal pain	26(10.2)	32[0.04]	2(2.2)	2[0.04]	28(11.0)	34[0.04]
Rhinorrhoea	15(5.9)	20[0.02]	-		15(5.9)	20[0.02]
Epistaxis	12(4.7)	28[0.03]	2(2.2)	2[0.04]	13(5.1)	30[0.03]
Nasal congestion	6(2.4)	9[0.01]	1(1.1)	1[0.02]	7(2.8)	10[0.01]
Respiratory disorder	5(2.0)	14[0.02]	-		5(2.0)	14[0.02]
Asthma	4(1.6)	6[0.01]	-		4(1.6)	6[0.01]
Rhinitis allergic	2(0.8)	2[0.00]	1(1.1)	1[0.02]	3(1.2)	3[0.00]
Productive cough	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Sneezing	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Haemoptysis	1(0.4)	3[0.00]	-		1(0.4)	3[0.00]
Dysphonia	1(0.4)	2[0.00]	-		1(0.4)	2[0.00]
Adenoidal hypertrophy	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	Pivotal process E[R]	Commercial process N(%)	Commercial process E[R]	Total N(%)	Total E[R]
Allergic respiratory disease	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Asthma exercise induced	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Asthmatic crisis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Bronchial hyperreactivity	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Dyspnoea	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Dyspnoea exertional	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hypoxia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Middle lobe syndrome	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Nasal obstruction	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Sinus congestion	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Sleep apnoea syndrome	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Upper respiratory tract congestion	-		1(1.1)	1[0.02]	1(0.4)	1[0.00]
Upper respiratory tract inflammation	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Wheezing	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Nervous system disorders	76(29.9)	158[0.19]	1(1.1)	2[0.04]	76(29.9)	160[0.18]
Headache	54(21.3)	115[0.14]	1(1.1)	1[0.02]	54(21.3)	116[0.13]
Dizziness	8(3.1)	9[0.01]	-		8(3.1)	9[0.01]
Paraesthesia	7(2.8)	7[0.01]	-		7(2.8)	7[0.01]
Carpal tunnel syndrome	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Post-traumatic headache	1(0.4)	1[0.00]	1(1.1)	1[0.02]	2(0.8)	2[0.00]
Presyncope	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Sciatica	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Seizure	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Altered state of consciousness	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Cerebral infarction	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Cerebral microhaemorrhage	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Cognitive disorder	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Dizziness exertional	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Dizziness postural	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Epilepsy	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Facial paralysis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Lethargy	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Migraine	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Nerve compression	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Nervous system disorder	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Neuropathy peripheral	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	Pivotal process E[R]	Commercial process N(%)	Commercial process E[R]	Total N(%)	Total E[R]
Restless legs syndrome	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Sensory loss	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Sinus headache	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Syncope	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Tongue biting	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Skin and subcutaneous tissue disorders	70(27.6)	124[0.15]	5(5.4)	5[0.09]	73(28.7)	129[0.15]
Eczema	15(5.9)	19[0.02]	-		15(5.9)	19[0.02]
Rash	14(5.5)	18[0.02]	-		14(5.5)	18[0.02]
Acne	8(3.1)	9[0.01]	-		8(3.1)	9[0.01]
Urticaria	5(2.0)	5[0.01]	2(2.2)	2[0.04]	7(2.8)	7[0.01]
Erythema	4(1.6)	8[0.01]	1(1.1)	1[0.02]	5(2.0)	9[0.01]
Dermatitis contact	4(1.6)	4[0.00]	-		4(1.6)	4[0.00]
Dry skin	4(1.6)	4[0.00]	-		4(1.6)	4[0.00]
Blister	3(1.2)	5[0.01]	-		3(1.2)	5[0.01]
Hyperhidrosis	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Pruritus	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Skin lesion	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Skin erosion	2(0.8)	4[0.00]	-		2(0.8)	4[0.00]
Alopecia	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Dermal cyst	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Dermatitis	1(0.4)	1[0.00]	1(1.1)	1[0.02]	2(0.8)	2[0.00]
Ingrowing nail	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Photosensitivity reaction	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Purpura	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Rash pruritic	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Miliaria	1(0.4)	3[0.00]	-		1(0.4)	3[0.00]
Papule	1(0.4)	2[0.00]	-		1(0.4)	2[0.00]
Petechiae	1(0.4)	2[0.00]	-		1(0.4)	2[0.00]
Alopecia areata	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Blood blister	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Dermatitis diaper	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Drug eruption	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Eczema asteatotic	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hangnail	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Mechanical urticaria	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Nail disorder	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Onychalgia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pigmentation disorder	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pruritus allergic	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	Pivotal process E[R]	Commercial process N(%)	Commercial process E[R]	Total N(%)	Total E[R]
Pruritus generalised	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Psoriasis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Rash papular	-		1(1.1)	1[0.02]	1(0.4)	1[0.00]
Sebaceous gland disorder	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Skin disorder	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Skin irritation	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Skin ulcer	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Telangiectasia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Vitiligo	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
General disorders and administration site conditions	61(24.0)	96[0.12]	3(3.3)	3[0.06]	62(24.4)	99[0.11]
Pyrexia	25(9.8)	40[0.05]	1(1.1)	1[0.02]	25(9.8)	41[0.05]
Influenza like illness	7(2.8)	11[0.01]	-		7(2.8)	11[0.01]
Fatigue	7(2.8)	8[0.01]	-		7(2.8)	8[0.01]
Chest pain	4(1.6)	4[0.00]	1(1.1)	1[0.02]	5(2.0)	5[0.01]
Oedema peripheral	4(1.6)	4[0.00]	1(1.1)	1[0.02]	5(2.0)	5[0.01]
Peripheral swelling	4(1.6)	4[0.00]	-		4(1.6)	4[0.00]
Hyperthermia	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Local swelling	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Chills	2(0.8)	3[0.00]	-		2(0.8)	3[0.00]
Adverse drug reaction	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Complication associated with device	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
General physical health deterioration	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Infusion site reaction	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Injection site erythema	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Injection site rash	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Injection site reaction	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Injection site swelling	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Localised oedema	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Oedema	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pain	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Tenderness	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Ulcer	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Vessel puncture site haematoma	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Vessel puncture site pain	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	Pivotal process E[R]	Commercial process N(%)	Commercial process E[R]	Total N(%)	Total E[R]
Investigations	48(18.9)	118[0.14]	2(2.2)	2[0.04]	49(19.3)	120[0.14]
Alanine aminotransferase increased	14(5.5)	21[0.03]		-	14(5.5)	21[0.02]
Aspartate aminotransferase increased	11(4.3)	17[0.02]	1(1.1)	1[0.02]	12(4.7)	18[0.02]
Gamma-glutamyltransferase increased	9(3.5)	15[0.02]		-	9(3.5)	15[0.02]
C-reactive protein increased	8(3.1)	10[0.01]		-	8(3.1)	10[0.01]
Blood cholesterol increased	5(2.0)	5[0.01]		-	5(2.0)	5[0.01]
Blood creatinine increased	3(1.2)	5[0.01]		-	3(1.2)	5[0.01]
Blood bilirubin increased	3(1.2)	3[0.00]		-	3(1.2)	3[0.00]
Red blood cell count increased	3(1.2)	3[0.00]		-	3(1.2)	3[0.00]
Haemoglobin increased	2(0.8)	2[0.00]		-	2(0.8)	2[0.00]
Weight decreased	2(0.8)	2[0.00]		-	2(0.8)	2[0.00]
Coagulation factor VIII level increased	1(0.4)	6[0.01]		-	1(0.4)	6[0.01]
Haemoglobin decreased	1(0.4)	2[0.00]		-	1(0.4)	2[0.00]
Anti factor VIII antibody test	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Aspartate aminotransferase abnormal	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Blood HIV RNA increased	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Blood alkaline phosphatase increased	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Blood creatine phosphokinase increased	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Blood pressure increased	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Blood sodium increased	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Blood triglycerides increased	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
C-reactive protein abnormal	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Electrocardiogram ST segment elevation	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Electrocardiogram T wave inversion		-	1(1.1)	1[0.02]	1(0.4)	1[0.00]
Hepatic enzyme increased	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]
Intraocular pressure test	1(0.4)	1[0.00]		-	1(0.4)	1[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	Pivotal process E[R]	Commercial process N(%)	Commercial process E[R]	Total N(%)	Total E[R]
Laboratory test abnormal	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Liver function test abnormal	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Mean cell haemoglobin decreased	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Mean cell volume decreased	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Monocyte count increased	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Neutrophil count increased	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Platelet count decreased	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Prostatic specific antigen abnormal	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Serum ferritin decreased	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Sputum abnormal	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Transaminases abnormal	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Transaminases increased	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Vitamin D decreased	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
White blood cell count increased	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
White blood cells urine positive	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Immune system disorders	26(10.2)	40[0.05]	2(2.2)	2[0.04]	27(10.6)	42[0.05]
Seasonal allergy	14(5.5)	19[0.02]	-		14(5.5)	19[0.02]
Food allergy	4(1.6)	5[0.01]	1(1.1)	1[0.02]	4(1.6)	6[0.01]
Hypersensitivity	2(0.8)	3[0.00]	-		2(0.8)	3[0.00]
Allergy to arthropod sting	1(0.4)	1[0.00]	1(1.1)	1[0.02]	2(0.8)	2[0.00]
Allergic oedema	1(0.4)	2[0.00]	-		1(0.4)	2[0.00]
Allergy to animal	1(0.4)	2[0.00]	-		1(0.4)	2[0.00]
Allergy to arthropod bite	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Allergy to chemicals	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Allergy to metals	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Allergy to plants	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Drug hypersensitivity	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Mite allergy	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Mycotic allergy	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Rubber sensitivity	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Vascular disorders	27(10.6)	28[0.03]	-		27(10.6)	28[0.03]
Hypertension	18(7.1)	19[0.02]	-		18(7.1)	19[0.02]
Haematoma	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Circulatory collapse	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	Pivotal process E[R]	Commercial process N(%)	Commercial process E[R]	Total N(%)	Total E[R]
Essential hypertension	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Flushing	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Haemorrhage	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Peripheral venous disease	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Vein disorder	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Psychiatric disorders	22(8.7)	23[0.03]	1(1.1)	1[0.02]	23(9.1)	24[0.03]
Depression	7(2.8)	7[0.01]	1(1.1)	1[0.02]	8(3.1)	8[0.01]
Insomnia	5(2.0)	5[0.01]	-		5(2.0)	5[0.01]
Anxiety	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Attention deficit/hyperactivity disorder	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Adjustment disorder with depressed mood	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Alcohol abuse	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Depressed mood	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Mental status changes	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Sleep disorder	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Stress	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Blood and lymphatic system disorders	20(7.9)	24[0.03]	1(1.1)	1[0.02]	21(8.3)	25[0.03]
Anaemia	6(2.4)	7[0.01]	1(1.1)	1[0.02]	7(2.8)	8[0.01]
Lymphadenopathy	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Leukocytosis	2(0.8)	4[0.00]	-		2(0.8)	4[0.00]
Neutropenia	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Thrombocytopenia	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Eosinophilia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Factor VIII inhibition	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Iron deficiency anaemia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Lymphadenitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Monocytosis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pancytopenia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Metabolism and nutrition disorders	20(7.9)	21[0.03]	1(1.1)	1[0.02]	21(8.3)	22[0.03]
Vitamin D deficiency	7(2.8)	7[0.01]	-		7(2.8)	7[0.01]
Hyperlipidaemia	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Iron deficiency	2(0.8)	2[0.00]	1(1.1)	1[0.02]	3(1.2)	3[0.00]
Gout	2(0.8)	3[0.00]	-		2(0.8)	3[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	Pivotal process E[R]	Commercial process N(%)	Commercial process E[R]	Total N(%)	Total E[R]
Diabetes mellitus	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Hypercholesterolaemia	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Decreased appetite	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hyperuricaemia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Eye disorders	19(7.5)	31[0.04]	1(1.1)	1[0.02]	20(7.9)	32[0.04]
Cataract	3(1.2)	4[0.00]	-		3(1.2)	4[0.00]
Conjunctivitis allergic	3(1.2)	4[0.00]	-		3(1.2)	4[0.00]
Diplopia	2(0.8)	4[0.00]	-		2(0.8)	4[0.00]
Dry eye	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Eye pruritus	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Glaucoma	1(0.4)	1[0.00]	1(1.1)	1[0.02]	2(0.8)	2[0.00]
Myopia	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Blepharospasm	1(0.4)	4[0.00]	-		1(0.4)	4[0.00]
Ocular myasthenia	1(0.4)	2[0.00]	-		1(0.4)	2[0.00]
Blepharitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Conjunctival haemorrhage	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Corneal disorder	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Eye allergy	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Eye irritation	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Eye swelling	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Renal and urinary disorders	14(5.5)	14[0.02]	-		14(5.5)	14[0.02]
Dysuria	6(2.4)	6[0.01]	-		6(2.4)	6[0.01]
Calculus urinary	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Haematuria	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
IgA nephropathy	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Nephrolithiasis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pollakiuria	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Renal colic	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Tubulointerstitial nephritis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Urinary incontinence	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Ear and labyrinth disorders	11(4.3)	14[0.02]	-		11(4.3)	14[0.02]
Ear pain	5(2.0)	6[0.01]	-		5(2.0)	6[0.01]
Cerumen impaction	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Ear deformity acquired	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Ear disorder	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Excessive cerumen production	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	E[R]	Commercial process N(%)	E[R]	Total N(%)	E[R]
Motion sickness	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Tinnitus	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Tympanic membrane perforation	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9(3.5)	9[0.01]	-		9(3.5)	9[0.01]
Skin papilloma	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Eye naevus	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hepatocellular carcinoma	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Lipoma	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Nasopharyngeal neoplasm benign	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Neuroma	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pancreatic carcinoma metastatic	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pyogenic granuloma	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Cardiac disorders	8(3.1)	9[0.01]	-		8(3.1)	9[0.01]
Ventricular extrasystoles	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Aortic valve stenosis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Atrial fibrillation	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Atrioventricular block first degree	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Extrasystoles	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pericarditis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Sinus arrhythmia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Sinus bradycardia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Congenital, familial and genetic disorders	7(2.8)	7[0.01]	1(1.1)	1[0.02]	8(3.1)	8[0.01]
Gilbert's syndrome	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Dermoid cyst	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hydrocele	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hypertrophic cardiomyopathy	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Odontogenic cyst	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pectus carinatum	-		1(1.1)	1[0.02]	1(0.4)	1[0.00]
Thalassaemia alpha	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

Summary of adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	E[R]	Commercial process N(%)	E[R]	Total N(%)	E[R]
Hepatobiliary disorders	8(3.1)	8[0.01]	-		8(3.1)	8[0.01]
Hepatic fibrosis	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Cholecystitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hepatic cirrhosis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hepatic function abnormal	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hepatic steatosis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hepatomegaly	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Surgical and medical procedures	7(2.8)	9[0.01]	-		7(2.8)	9[0.01]
Tooth extraction	2(0.8)	3[0.00]	-		2(0.8)	3[0.00]
Wisdom teeth removal	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Dental operation	1(0.4)	2[0.00]	-		1(0.4)	2[0.00]
Dental implantation	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Nail operation	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Reproductive system and breast disorders	6(2.4)	7[0.01]	-		6(2.4)	7[0.01]
Acquired phimosis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Erectile dysfunction	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Penile adhesion	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Penis disorder	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Testicular pain	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Testicular swelling	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Varicocele	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Endocrine disorders	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Adrenal insufficiency	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Goitre	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Product issues	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Device dislocation	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Device malfunction	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Social circumstances	1(0.4)	3[0.00]	-		1(0.4)	3[0.00]
Tattoo	1(0.4)	3[0.00]	-		1(0.4)	3[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Exposure to N8-GP from the different production methods is accounted from the scheduled visit where product was first dispensed.
MedDRA version: 20.0

53. 重篤な有害事象の概要 – 原薬製造工程別 – 安全性解析対象集団（3859 及び 3885 試験）

	Pivotal process N(%)	Pivotal process E[R]	Commercial process N(%)	Commercial process E[R]	Total N(%)	Total E[R]
Number of patients	254		92		254	
Patient years of exposure	824.02		54.40		878.43	
Exposure days	74076		5217		79293	
All adverse events	45(17.7)	65[0.08]	1(1.1)	1[0.02]	46(18.1)	66[0.08]
Serious adverse events	45(17.7)	65[0.08]	1(1.1)	1[0.02]	46(18.1)	66[0.08]
Severity						
Mild	2(0.8)	2[0.00]	1(1.1)	1[0.02]	3(1.2)	3[0.00]
Moderate	21(8.3)	25[0.03]	-		21(8.3)	25[0.03]
Severe	29(11.4)	38[0.05]	-		29(11.4)	38[0.04]
Relationship						
Probably or possibly	4(1.6)	4[0.00]	-		4(1.6)	4[0.00]
Unlikely	42(16.5)	61[0.07]	1(1.1)	1[0.02]	43(16.9)	62[0.07]
Adverse events						
Leading to withdrawal	6(2.4)	6[0.01]	-		6(2.4)	6[0.01]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Exposure to N8-GP from the different production methods is accounted from the scheduled visit where product was first dispensed.

54. 有害事象の要約 – 原薬製造工程別 – 安全性解析対象集団（3859 及び 3885 試験）

	Pivotal process N(%)	Pivotal process E[R]	Commercial process N(%)	Commercial process E[R]	Total N(%)	Total E[R]
Number of patients	254		92		254	
Patient years of exposure	824.02		54.40		878.43	
Exposure days	74076		5217		79293	
All adverse events	45(17.7)	65[0.08]	1(1.1)	1[0.02]	46(18.1)	66[0.08]
Infections and infestations	13(5.1)	19[0.02]	-		13(5.1)	19[0.02]
Cellulitis	2(0.8)	3[0.00]	-		2(0.8)	3[0.00]
Device related infection	2(0.8)	3[0.00]	-		2(0.8)	3[0.00]
Bacterial sepsis	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Anal abscess	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Catheter site infection	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Encephalitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Enteritis infectious	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Infective spondylitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Intervertebral discitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Osteomyelitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pneumonia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Sepsis syndrome	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Tonsillitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Viral infection	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Injury, poisoning and procedural complications	11(4.3)	11[0.01]	-		11(4.3)	11[0.01]
Fall	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Ankle fracture	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Extradural haematoma	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Face injury	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Femoral neck fracture	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Forearm fracture	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Head injury	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Injury	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Road traffic accident	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Toxicity to various agents	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Gastrointestinal disorders	6(2.4)	6[0.01]	1(1.1)	1[0.02]	7(2.8)	7[0.01]
Duodenal ulcer	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Abdominal hernia	-		1(1.1)	1[0.02]	1(0.4)	1[0.00]
Gastric varices	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

Summary of serious adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	E[R]	Commercial process N(%)	E[R]	Total N(%)	E[R]
Gastric varices haemorrhage	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Gastritis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pancreatitis acute	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Nervous system disorders	3(1.2)	4[0.00]	-		3(1.2)	4[0.00]
Cerebral infarction	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Cerebral microhaemorrhage	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Seizure	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Syncope	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Musculoskeletal and connective tissue disorders	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Muscle haemorrhage	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pathological fracture	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Synovitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Hepatocellular carcinoma	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Neuroma	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pancreatic carcinoma metastatic	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Renal and urinary disorders	3(1.2)	3[0.00]	-		3(1.2)	3[0.00]
Calculus urinary	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
IgA nephropathy	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Tubulointerstitial nephritis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Congenital, familial and genetic disorders	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Hydrocele	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hypertrophic cardiomyopathy	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
General disorders and administration site conditions	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]

Summary of serious adverse events by production method - trials 3859 and 3885 - safety analysis set

Continued...

	Pivotal process N(%)	E[R]	Commercial process N(%)	E[R]	Total N(%)	E[R]
Complication associated with device	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Pyrexia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Respiratory, thoracic and mediastinal disorders	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Adenoidal hypertrophy	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hypoxia	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Vascular disorders	2(0.8)	2[0.00]	-		2(0.8)	2[0.00]
Circulatory collapse	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Haemorrhage	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Blood and lymphatic system disorders	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Factor VIII inhibition	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Cardiac disorders	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Aortic valve stenosis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Eye disorders	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Cataract	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hepatobiliary disorders	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Cholecystitis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Immune system disorders	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Hypersensitivity	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Product issues	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Device dislocation	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Psychiatric disorders	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Depression	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Reproductive system and breast disorders	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]
Acquired phimosis	1(0.4)	1[0.00]	-		1(0.4)	1[0.00]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Exposure to N8-GP from the different production methods is accounted from the scheduled visit where product was first dispensed.
MedDRA version: 20.0

55. ベースラインの HIV 及び C 型肝炎の有無 – 年齢グループ別 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

	0-5 years N (%)	6-11 years N (%)	12-17 years N (%)	>=18 years N (%)	Total
Number of patients	34 (100)	34 (100)	25 (100)	177 (100)	270 (100)
Hepatitis B Antibody					
Positive	-	-	-	6 (3.39)	6 (2.22)
Negative	33 (97.06)	34 (100.00)	25 (100.00)	168 (94.92)	260 (96.30)
Limit	-	-	-	2 (1.13)	2 (0.74)
Missing	1 (2.94)	-	-	1 (0.56)	2 (0.74)
Hepatitis C Antibody					
Positive	-	-	-	120 (67.80)	120 (44.44)
Negative	33 (97.06)	34 (100.00)	25 (100.00)	56 (31.64)	148 (54.81)
Missing	1 (2.94)	-	-	1 (0.56)	2 (0.74)
Patients with hepatitis B only	-	-	-	3 (1.69)	3 (1.11)
Patients with hepatitis C only or C and B	-	-	-	120 (67.80)	120 (44.44)
Patients without hepatitis	33 (97.06)	34 (100.00)	25 (100.00)	53 (29.94)	145 (53.70)
Patients with missing hepatitis status	1 (2.94)	-	-	1 (0.56)	2 (0.74)
HIV-1/2 Antibody					
Positive	-	-	-	13 (7.34)	13 (4.81)
Negative	34 (100.00)	34 (100.00)	19 (76.00)	105 (59.32)	192 (71.11)
Missing	-	-	6 (24.00)	59 (33.33)	65 (24.07)

Patients are allocated to age groups according to the age at baseline from the first trial they entered.
The baseline viral assessment is taken from the last trial in which each patient participated and had a valid baseline assessment.

56. 有害事象の要約 – 日本人 – 治療法別– 安全性解析対象集団（3776、3859 及び 3885 試験）

	Phase 1 single dose N(%) E		Prophylaxis multiple dose N(%) E[R]		On-demand N(%) E[R,F]		Total N(%) E[R]	
Number of patients	2		15		2		19	
Patient years of exposure	0.12		34.41		6.87		41.40	
Exposure days	2		3330		505		3837	
All adverse events	1(50.0)	4	12(80.0)	178[5.17]	2(100)	28[4.08, 0.055]	15(78.9)	210[5.07]
Infections and infestations	-		10(66.7)	56[1.63]	2(100)	7[1.02, 0.014]	12(63.2)	63[1.52]
Viral upper respiratory tract infection	-		8(53.3)	14[0.41]	1(50.0)	3[0.44, 0.006]	9(47.4)	17[0.41]
Folliculitis	-		2(13.3)	2[0.06]	1(50.0)	2[0.29, 0.004]	3(15.8)	4[0.10]
Periodontitis	-		2(13.3)	3[0.09]	1(50.0)	1[0.15, 0.002]	3(15.8)	4[0.10]
Gastroenteritis	-		2(13.3)	5[0.15]		-	2(10.5)	5[0.12]
Influenza	-		2(13.3)	4[0.12]		-	2(10.5)	4[0.10]
Bronchitis	-		2(13.3)	2[0.06]		-	2(10.5)	2[0.05]
Cellulitis	-		1(6.7)	4[0.12]		-	1(5.3)	4[0.10]
Otitis media acute	-		1(6.7)	3[0.09]		-	1(5.3)	3[0.07]
Hordeolum	-		1(6.7)	2[0.06]		-	1(5.3)	2[0.05]
Rhinitis	-		1(6.7)	2[0.06]		-	1(5.3)	2[0.05]
Bacterial sepsis	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Cystitis	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Enteritis infectious	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Helicobacter gastritis	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Hepatitis C	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Impetigo	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Infective spondylitis	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Intervertebral discitis	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Localised infection	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Oral herpes	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Postoperative wound infection	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Pulpitis dental	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Streptococcal infection	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Tinea pedis	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Tonsillitis	-			-	1(50.0)	1[0.15, 0.002]	1(5.3)	1[0.02]
Urethritis	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Gastrointestinal disorders	-		8(53.3)	24[0.70]	1(50.0)	2[0.29, 0.004]	9(47.4)	26[0.63]
Dental caries	-		4(26.7)	4[0.12]		-	4(21.1)	4[0.10]
Stomatitis	-		3(20.0)	3[0.09]		-	3(15.8)	3[0.07]

Summary of adverse events by treatment type - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

	Phase 1 single dose N(%) E	Prophylaxis multiple dose N(%) E[R]		On-demand N(%) E[R,F]		Total N(%) E[R]	
Diarrhoea	-	2(13.3)	2[0.06]		-	2(10.5)	2[0.05]
Gastric varices	-	1(6.7)	2[0.06]		-	1(5.3)	2[0.05]
Barrett's oesophagus	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Chronic gastritis	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Constipation	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Dental discomfort	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Duodenitis	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Enterocolitis	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Gastric varices haemorrhage	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Gastritis	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Gastritis erosive	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Gastrooesophageal reflux disease	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Lip ulceration	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Nausea	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Perianal erythema	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Toothache	-		-	1(50.0)	1[0.15, 0.002]	1(5.3)	1[0.02]
Vomiting	-		-	1(50.0)	1[0.15, 0.002]	1(5.3)	1[0.02]
Skin and subcutaneous tissue disorders	-	8(53.3)	19[0.55]	1(50.0)	2[0.29, 0.004]	9(47.4)	21[0.51]
Eczema	-	3(20.0)	3[0.09]		-	3(15.8)	3[0.07]
Blister	-	2(13.3)	4[0.12]		-	2(10.5)	4[0.10]
Rash	-	2(13.3)	2[0.06]		-	2(10.5)	2[0.05]
Urticaria	-	2(13.3)	2[0.06]		-	2(10.5)	2[0.05]
Skin erosion	-	1(6.7)	3[0.09]		-	1(5.3)	3[0.07]
Alopecia areata	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Dry skin	-		-	1(50.0)	1[0.15, 0.002]	1(5.3)	1[0.02]
Eczema asteatotic	-		-	1(50.0)	1[0.15, 0.002]	1(5.3)	1[0.02]
Pruritus	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Purpura	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Rash pruritic	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Skin disorder	-	1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Musculoskeletal and connective tissue disorders	-	7(46.7)	10[0.29]	1(50.0)	1[0.15, 0.002]	8(42.1)	11[0.27]
Arthralgia	-	3(20.0)	3[0.09]		-	3(15.8)	3[0.07]
Musculoskeletal pain	-	2(13.3)	2[0.06]		-	2(10.5)	2[0.05]
Pain in extremity	-	2(13.3)	2[0.06]		-	2(10.5)	2[0.05]
Back pain	-		-	1(50.0)	1[0.15, 0.002]	1(5.3)	1[0.02]

Summary of adverse events by treatment type - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

	Phase 1 single dose N(%) E		Prophylaxis multiple dose N(%) E[R]		On-demand N(%) E[R,F]		Total N(%) E[R]	
Joint lock	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Myalgia	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Neck pain	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Injury, poisoning and procedural complications	-		6(40.0)	19[0.55]	1(50.0)	11[1.60, 0.022]	7(36.8)	30[0.72]
Contusion	-		3(20.0)	5[0.15]	1(50.0)	9[1.31, 0.018]	4(21.1)	14[0.34]
Laceration	-		3(20.0)	3[0.09]	-		3(15.8)	3[0.07]
Ligament sprain	-		2(13.3)	2[0.06]	-		2(10.5)	2[0.05]
Scratch	-		1(6.7)	1[0.03]	1(50.0)	1[0.15, 0.002]	2(10.5)	2[0.05]
Arthropod bite	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Compression fracture	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Epiphyseal injury	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Face injury	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Femoral neck fracture	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Joint injury	-		-		1(50.0)	1[0.15, 0.002]	1(5.3)	1[0.02]
Skin abrasion	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Tooth injury	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Traumatic haemorrhage	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Nervous system disorders	1(50.0)	1	5(33.3)	7[0.20]	1(50.0)	1[0.15, 0.002]	7(36.8)	9[0.22]
Headache	1(50.0)	1	3(20.0)	3[0.09]	1(50.0)	1[0.15, 0.002]	5(26.3)	5[0.12]
Altered state of consciousness	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Dizziness	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Epilepsy	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Tongue biting	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Respiratory, thoracic and mediastinal disorders	-		6(40.0)	11[0.32]	-		6(31.6)	11[0.27]
Oropharyngeal pain	-		2(13.3)	3[0.09]	-		2(10.5)	3[0.07]
Haemoptysis	-		1(6.7)	3[0.09]	-		1(5.3)	3[0.07]
Asthma	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Cough	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Epistaxis	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Middle lobe syndrome	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Upper respiratory tract inflammation	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]

Summary of adverse events by treatment type - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

	Phase 1 single dose N(%) E		Prophylaxis multiple dose N(%) E[R]		On-demand N(%) E[R,F]		Total N(%) E[R]	
General disorders and administration site conditions	1(50.0)	1	3(20.0)	7[0.20]	1(50.0)	1[0.15, 0.002]	5(26.3)	9[0.22]
Pyrexia	-		3(20.0)	4[0.12]	1(50.0)	1[0.15, 0.002]	4(21.1)	5[0.12]
Adverse drug reaction	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Fatigue	1(50.0)	1		-		-	1(5.3)	1[0.02]
Infusion site reaction	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Ulcer	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Metabolism and nutrition disorders	-		5(33.3)	5[0.15]		-	5(26.3)	5[0.12]
Diabetes mellitus	-		2(13.3)	2[0.06]		-	2(10.5)	2[0.05]
Hyperlipidaemia	-		2(13.3)	2[0.06]		-	2(10.5)	2[0.05]
Hyperuricaemia	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Investigations	-		2(13.3)	7[0.20]	1(50.0)	1[0.15, 0.002]	3(15.8)	8[0.19]
Alanine aminotransferase increased	-		1(6.7)	2[0.06]		-	1(5.3)	2[0.05]
C-reactive protein increased	-		1(6.7)	2[0.06]		-	1(5.3)	2[0.05]
Blood cholesterol increased	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Blood creatinine increased	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Gamma-glutamyltransferase increased	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Liver function test abnormal	-			-	1(50.0)	1[0.15, 0.002]	1(5.3)	1[0.02]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-		3(20.0)	3[0.09]		-	3(15.8)	3[0.07]
Eye naevus	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Hepatocellular carcinoma	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Nasopharyngeal neoplasm benign	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Eye disorders	-		1(6.7)	1[0.03]	1(50.0)	1[0.15, 0.002]	2(10.5)	2[0.05]
Cataract	-			-	1(50.0)	1[0.15, 0.002]	1(5.3)	1[0.02]
Conjunctivitis allergic	-		1(6.7)	1[0.03]		-	1(5.3)	1[0.02]
Hepatobiliary disorders	-		1(6.7)	1[0.03]	1(50.0)	1[0.15, 0.002]	2(10.5)	2[0.05]

Summary of adverse events by treatment type - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

	Phase 1 single dose N(%)	E	Prophylaxis multiple dose N(%)	E[R]	On-demand N(%)	E[R,F]	Total N(%)	E[R]
Hepatic fibrosis	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Hepatic function abnormal	-		-		1(50.0)	1[0.15, 0.002]	1(5.3)	1[0.02]
Immune system disorders	-		2(13.3)	2[0.06]	-		2(10.5)	2[0.05]
Food allergy	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Seasonal allergy	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Psychiatric disorders	1(50.0)	1	1(6.7)	1[0.03]	-		2(10.5)	2[0.05]
Illusion	1(50.0)	1	-		-		1(5.3)	1[0.02]
Insomnia	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Vascular disorders	-		2(13.3)	2[0.06]	-		2(10.5)	2[0.05]
Hypertension	-		2(13.3)	2[0.06]	-		2(10.5)	2[0.05]
Blood and lymphatic system disorders	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Anaemia	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Cardiac disorders	1(50.0)	1	-		-		1(5.3)	1[0.02]
Palpitations	1(50.0)	1	-		-		1(5.3)	1[0.02]
Endocrine disorders	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Adrenal insufficiency	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Renal and urinary disorders	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]
Tubulointerstitial nephritis	-		1(6.7)	1[0.03]	-		1(5.3)	1[0.02]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
[F]: Number of adverse events per exposure days (E/exposure days)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients might be included in multiple treatment types and therefore the number of patients in each row might not necessarily add up to the Total.
MedDRA version: 20.0

57. 重篤な有害事象の要約 – 日本人 – 治療法別 – 安全性解析対象集団（3776、3859 及び 3885 試験）

	Phase 1 single dose N(%) E	Prophylaxis multiple dose N(%) E[R]	On-demand N(%) E[R,F]	Total N(%) E[R]
Number of patients	2	15	2	19
Patient years of exposure	0.12	34.41	6.87	41.40
Exposure days	2	3330	505	3837
All adverse events	-	4(26.7) 11[0.32]	1(50.0) 1[0.15, 0.002]	5(26.3) 12[0.29]
Infections and infestations	-	4(26.7) 6[0.17]	-	4(21.1) 6[0.14]
Cellulitis	-	1(6.7) 2[0.06]	-	1(5.3) 2[0.05]
Bacterial sepsis	-	1(6.7) 1[0.03]	-	1(5.3) 1[0.02]
Enteritis infectious	-	1(6.7) 1[0.03]	-	1(5.3) 1[0.02]
Infective spondylitis	-	1(6.7) 1[0.03]	-	1(5.3) 1[0.02]
Intervertebral discitis	-	1(6.7) 1[0.03]	-	1(5.3) 1[0.02]
Gastrointestinal disorders	-	2(13.3) 2[0.06]	-	2(10.5) 2[0.05]
Gastric varices	-	1(6.7) 1[0.03]	-	1(5.3) 1[0.02]
Gastric varices haemorrhage	-	1(6.7) 1[0.03]	-	1(5.3) 1[0.02]
Eye disorders	-	-	1(50.0) 1[0.15, 0.002]	1(5.3) 1[0.02]
Cataract	-	-	1(50.0) 1[0.15, 0.002]	1(5.3) 1[0.02]
Injury, poisoning and procedural complications	-	1(6.7) 1[0.03]	-	1(5.3) 1[0.02]
Femoral neck fracture	-	1(6.7) 1[0.03]	-	1(5.3) 1[0.02]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	1(6.7) 1[0.03]	-	1(5.3) 1[0.02]
Hepatocellular carcinoma	-	1(6.7) 1[0.03]	-	1(5.3) 1[0.02]
Renal and urinary disorders	-	1(6.7) 1[0.03]	-	1(5.3) 1[0.02]
Tubulointerstitial nephritis	-	1(6.7) 1[0.03]	-	1(5.3) 1[0.02]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
[F]: Number of adverse events per exposure days (E/exposure days)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients might be included in multiple treatment types and therefore the number of patients in each row might not necessarily add up to the Total.
MedDRA version: 20.0

58. 有害事象の概要 – 0～5 歳の被験者 – 年齢グループ別 – 安全性解析対象集団（3885 試験）

	0-1 years N(%)	0-1 years E[R]	2-5 years N(%)	2-5 years E[R]	Total N(%)	Total E[R]
Number of patients	6		28		34	
Patient years of exposure	21.28		84.75		106.03	
Exposure days	2196		8944		11140	
All adverse events	6(100)	53[2.49]	26(92.9)	297[3.50]	32(94.1)	350[3.30]
Serious adverse events	2(33.3)	2[0.09]	8(28.6)	10[0.12]	10(29.4)	12[0.11]
Non serious adverse events	6(100)	51[2.40]	26(92.9)	287[3.39]	32(94.1)	338[3.19]
Severity						
Mild	5(83.3)	43[2.02]	22(78.6)	235[2.77]	27(79.4)	278[2.62]
Moderate	5(83.3)	8[0.38]	20(71.4)	55[0.65]	25(73.5)	63[0.59]
Severe	2(33.3)	2[0.09]	5(17.9)	7[0.08]	7(20.6)	9[0.08]
Relationship						
Probably or possibly	2(33.3)	4[0.19]	5(17.9)	8[0.09]	7(20.6)	12[0.11]
Unlikely	6(100)	49[2.30]	24(85.7)	284[3.35]	30(88.2)	333[3.14]
Missing	-		1(3.6)	5[0.06]	1(2.9)	5[0.05]
Adverse events						
Leading to withdrawal	-		2(7.1)	2[0.02]	2(5.9)	2[0.02]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.

59. 有害事象の要約 – 0～5 歳の被験者 – 年齢グループ別 – 安全性解析対象集団（3885 試験）

	0-1 years N(%)	0-1 years E[R]	2-5 years N(%)	2-5 years E[R]	Total N(%)	Total E[R]
Number of patients	6		28		34	
Patient years of exposure	21.28		84.75		106.03	
Exposure days	2196		8944		11140	
All adverse events	6(100)	53[2.49]	26(92.9)	297[3.50]	32(94.1)	350[3.30]
Infections and infestations	6(100)	23[1.08]	20(71.4)	90[1.06]	26(76.5)	113[1.07]
Viral upper respiratory tract infection	1(16.7)	3[0.14]	10(35.7)	19[0.22]	11(32.4)	22[0.21]
Upper respiratory tract infection	1(16.7)	2[0.09]	9(32.1)	14[0.17]	10(29.4)	16[0.15]
Rhinitis	3(50.0)	3[0.14]	4(14.3)	4[0.05]	7(20.6)	7[0.07]
Gastroenteritis	2(33.3)	2[0.09]	3(10.7)	6[0.07]	5(14.7)	8[0.08]
Ear infection	2(33.3)	2[0.09]	3(10.7)	3[0.04]	5(14.7)	5[0.05]
Bronchitis	1(16.7)	2[0.09]	2(7.1)	3[0.04]	3(8.8)	5[0.05]
Influenza	1(16.7)	1[0.05]	2(7.1)	4[0.05]	3(8.8)	5[0.05]
Otitis media	1(16.7)	1[0.05]	2(7.1)	2[0.02]	3(8.8)	3[0.03]
Varicella	-		3(10.7)	3[0.04]	3(8.8)	3[0.03]
Device related infection	-		2(7.1)	3[0.04]	2(5.9)	3[0.03]
Conjunctivitis	1(16.7)	1[0.05]	1(3.6)	1[0.01]	2(5.9)	2[0.02]
Molluscum contagiosum	1(16.7)	1[0.05]	1(3.6)	1[0.01]	2(5.9)	2[0.02]
Pharyngitis streptococcal	-		2(7.1)	2[0.02]	2(5.9)	2[0.02]
Viral infection	-		2(7.1)	2[0.02]	2(5.9)	2[0.02]
Viral pharyngitis	-		2(7.1)	2[0.02]	2(5.9)	2[0.02]
Enterobiasis	-		1(3.6)	5[0.06]	1(2.9)	5[0.05]
Helminthic infection	-		1(3.6)	2[0.02]	1(2.9)	2[0.02]
Cellulitis	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Conjunctivitis bacterial	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Encephalitis	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Impetigo	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Nasopharyngitis	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Otitis externa	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Pharyngitis	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Pneumonia	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Scarlet fever	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Sepsis syndrome	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Sinusitis	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Sinusitis bacterial	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Streptococcal infection	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]

Summary of adverse events by age group - patients in age group 0-5 years - trial 3885 - safety analysis set

Continued...

	0-1 years N(%)	E[R]	2-5 years N(%)	E[R]	Total N(%)	E[R]
Tonsillitis	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Tonsillitis streptococcal	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Tooth abscess	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Upper respiratory tract infection bacterial	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Viral diarrhoea	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Viral parotitis	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Respiratory, thoracic and mediastinal disorders	3(50.0)	6[0.28]	13(46.4)	51[0.60]	16(47.1)	57[0.54]
Cough	2(33.3)	2[0.09]	12(42.9)	21[0.25]	14(41.2)	23[0.22]
Epistaxis	-		4(14.3)	17[0.20]	4(11.8)	17[0.16]
Rhinorrhoea	1(16.7)	1[0.05]	3(10.7)	3[0.04]	4(11.8)	4[0.04]
Nasal congestion	1(16.7)	2[0.09]	1(3.6)	1[0.01]	2(5.9)	3[0.03]
Oropharyngeal pain	-		2(7.1)	2[0.02]	2(5.9)	2[0.02]
Asthma	-		1(3.6)	3[0.04]	1(2.9)	3[0.03]
Bronchial hyperreactivity	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Hypoxia	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Rhinitis allergic	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Sneezing	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Wheezing	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Gastrointestinal disorders	1(16.7)	1[0.05]	13(46.4)	34[0.40]	14(41.2)	35[0.33]
Vomiting	1(16.7)	1[0.05]	7(25.0)	8[0.09]	8(23.5)	9[0.08]
Diarrhoea	-		5(17.9)	7[0.08]	5(14.7)	7[0.07]
Abdominal pain	-		5(17.9)	6[0.07]	5(14.7)	6[0.06]
Constipation	-		2(7.1)	2[0.02]	2(5.9)	2[0.02]
Dental caries	-		1(3.6)	3[0.04]	1(2.9)	3[0.03]
Abdominal pain upper	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Dental necrosis	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Faeces soft	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Gastritis	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Gastrointestinal disorder	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Gastrooesophageal reflux disease	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Mouth haemorrhage	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Noninfective gingivitis	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Injury, poisoning and procedural complications	3(50.0)	5[0.23]	11(39.3)	29[0.34]	14(41.2)	34[0.32]
Fall	1(16.7)	1[0.05]	4(14.3)	6[0.07]	5(14.7)	7[0.07]

Summary of adverse events by age group - patients in age group 0-5 years - trial 3885 - safety analysis set

Continued...

	0-1 years N(%)	E[R]	2-5 years N(%)	E[R]	Total N(%)	E[R]
Limb injury	-		4(14.3)	4[0.05]	4(11.8)	4[0.04]
Head injury	-		2(7.1)	3[0.04]	2(5.9)	3[0.03]
Contusion	1(16.7)	1[0.05]	1(3.6)	1[0.01]	2(5.9)	2[0.02]
Joint injury	-		2(7.1)	2[0.02]	2(5.9)	2[0.02]
Arthropod sting	-		1(3.6)	3[0.04]	1(2.9)	3[0.03]
Arthropod bite	-		1(3.6)	2[0.02]	1(2.9)	2[0.02]
Drug administration error	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Excoriation	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Face injury	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Hand fracture	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Laceration	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Mouth injury	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Post procedural complication	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Thermal burn	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Traumatic haemorrhage	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Vaccination complication	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Wound	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Skin and subcutaneous tissue disorders	3(50.0)	8[0.38]	8(28.6)	17[0.20]	11(32.4)	25[0.24]
Rash	2(33.3)	4[0.19]	3(10.7)	3[0.04]	5(14.7)	7[0.07]
Erythema	1(16.7)	3[0.14]	2(7.1)	2[0.02]	3(8.8)	5[0.05]
Eczema	-		2(7.1)	2[0.02]	2(5.9)	2[0.02]
Miliaria	-		1(3.6)	3[0.04]	1(2.9)	3[0.03]
Dermatitis contact	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Dermatitis diaper	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Pruritus generalised	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Rash papular	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Skin irritation	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Skin lesion	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Telangiectasia	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Urticaria	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
General disorders and administration site conditions	2(33.3)	2[0.09]	6(21.4)	17[0.20]	8(23.5)	19[0.18]
Pyrexia	1(16.7)	1[0.05]	6(21.4)	15[0.18]	7(20.6)	16[0.15]
Hyperthermia	1(16.7)	1[0.05]	1(3.6)	1[0.01]	2(5.9)	2[0.02]
Injection site swelling	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]

Summary of adverse events by age group - patients in age group 0-5 years - trial 3885 - safety analysis set

Continued...

	0-1 years N(%)	E[R]	2-5 years N(%)	E[R]	Total N(%)	E[R]
Musculoskeletal and connective tissue disorders	-		8(28.6)	18[0.21]	8(23.5)	18[0.17]
Pain in extremity	-		3(10.7)	9[0.11]	3(8.8)	9[0.08]
Arthralgia	-		2(7.1)	3[0.04]	2(5.9)	3[0.03]
Joint swelling	-		2(7.1)	2[0.02]	2(5.9)	2[0.02]
Joint range of motion decreased	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Limb discomfort	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Muscle haemorrhage	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Myalgia	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Immune system disorders	1(16.7)	1[0.05]	5(17.9)	12[0.14]	6(17.6)	13[0.12]
Seasonal allergy	1(16.7)	1[0.05]	1(3.6)	1[0.01]	2(5.9)	2[0.02]
Allergic oedema	-		1(3.6)	2[0.02]	1(2.9)	2[0.02]
Allergy to animal	-		1(3.6)	2[0.02]	1(2.9)	2[0.02]
Food allergy	-		1(3.6)	2[0.02]	1(2.9)	2[0.02]
Hypersensitivity	-		1(3.6)	2[0.02]	1(2.9)	2[0.02]
Allergy to arthropod sting	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Mite allergy	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Mycotic allergy	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Ear and labyrinth disorders	1(16.7)	2[0.09]	4(14.3)	5[0.06]	5(14.7)	7[0.07]
Ear pain	1(16.7)	1[0.05]	3(10.7)	3[0.04]	4(11.8)	4[0.04]
Cerumen impaction	1(16.7)	1[0.05]	1(3.6)	1[0.01]	2(5.9)	2[0.02]
Tympanic membrane perforation	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Nervous system disorders	1(16.7)	1[0.05]	4(14.3)	6[0.07]	5(14.7)	7[0.07]
Headache	1(16.7)	1[0.05]	4(14.3)	5[0.06]	5(14.7)	6[0.06]
Post-traumatic headache	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Vascular disorders	-		5(17.9)	5[0.06]	5(14.7)	5[0.05]
Haematoma	-		2(7.1)	2[0.02]	2(5.9)	2[0.02]
Flushing	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Haemorrhage	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Vein disorder	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Blood and lymphatic system disorders	1(16.7)	1[0.05]	2(7.1)	2[0.02]	3(8.8)	3[0.03]
Anaemia	1(16.7)	1[0.05]	1(3.6)	1[0.01]	2(5.9)	2[0.02]
Leukocytosis	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]

Summary of adverse events by age group - patients in age group 0-5 years - trial 3885 - safety analysis set

Continued...

	0-1 years N(%)	E[R]	2-5 years N(%)	E[R]	Total N(%)	E[R]
Eye disorders	1(16.7)	1[0.05]	2(7.1)	2[0.02]	3(8.8)	3[0.03]
Eye pruritus	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Eye swelling	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Myopia	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Reproductive system and breast disorders	1(16.7)	1[0.05]	2(7.1)	2[0.02]	3(8.8)	3[0.03]
Acquired phimosis	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Penile adhesion	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Penis disorder	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Investigations	-		2(7.1)	3[0.04]	2(5.9)	3[0.03]
Blood alkaline phosphatase increased	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Blood creatinine increased	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Blood sodium increased	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Hepatobiliary disorders	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Hepatomegaly	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Metabolism and nutrition disorders	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Iron deficiency	1(16.7)	1[0.05]	-		1(2.9)	1[0.01]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Skin papilloma	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Product issues	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Device malfunction	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Renal and urinary disorders	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]
Pollakiuria	-		1(3.6)	1[0.01]	1(2.9)	1[0.01]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline.
MedDRA version: 20.0

60. 治験薬との因果関係が「あり」又は「可能性あり」と判定された有害事象の一覧 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	On-demand	1	Pivotal process	Gastrointestinal disorders/ Flatulence/ Flatulence	1/1/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	On-demand	2	Pivotal process	Gastrointestinal disorders/ Flatulence/ Flatulence	1/2/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	On-demand	11	Pivotal process	Infections and infestations/ Tinea infection/ Ringworm	7/79/89 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	15	Pivotal process	Nervous system disorders/ Presyncope/ Vasovagal reaction	1/141/2 days		No/ Moderate/ Possible	Dose Not Changed/ Recovered
NN7088_3776/[redacted]/ [redacted]/ NN7088_3776	Phase 1 single dose	1	Pivotal process	Nervous system disorders/ Headache/ Headache,daily	0.175/./72 hours		No/ Mild/ Possible	Na/ Recovered
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Nervous system disorders/ Headache/ Headache	3/20/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	14	Pivotal process	General disorders and administration site conditions/ Injection site reaction/ Vein irritation and induration at injection site.	1/238/.		No/ Mild/ Possible	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	21	Pivotal process	Investigations/ Alanine aminotransferase increased/ Elevated gpt	1/375/337 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	22	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Elevated gamma-gt	1/375/.		No/ Mild/ Possible	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	26	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated got	1/449/183 days		No/ Mild/ Possible	Dose Not Changed/ Recovered

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Listing of adverse events possibly or probably related to trial product- trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Injury, poisoning and procedural complications/ Product preparation error/ Error in constitution of study drug	1/3/51 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	1	Pivotal process	Gastrointestinal disorders/ Nausea/ Nausea	1/11/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Gastrointestinal disorders/ Nausea/ Nausea	2/13/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Gastrointestinal disorders/ Nausea/ Nausea	2/64/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	7	Pivotal process	Injury, poisoning and procedural complications/ Overdose/ Trial product overdose	1/96/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Investigations/ Transaminases abnormal/ Alteration of transaminase.	1/79/109 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	2	Pivotal process	Hepatobiliary disorders/ Hepatic function abnormal/ Liver dysfunction	6/33/22 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Infections and infestations/ Intervertebral discitis/ Lumber pyogenic discitis	3/60/138 days		Yes/ Severe/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	9	Pivotal process	Investigations/ Liver function test abnormal/ Abnormality of biomarkers of liverfunction	9/202/85 days		No/ Mild/ Possible	Dose Not Changed/ Recovered

Listing of adverse events possibly or probably related to trial product- trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Eruption	3/22/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	15	Pivotal process	Skin and subcutaneous tissue disorders/ Purpura/ Right leg purpura	2/94/212 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	16	Pivotal process	General disorders and adminis tration site conditions/ Pyrexia/ Fever	3/129/3 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	17	Pivotal process	Investigations/ C-reactive protein increased/ Crp test increased	2/133/72 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Investigations/ Aspartate aminotransferase ab normal/ Abnormal lab result sgpt	1/23/.		No/ Mild/ Possible	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	3	Pivotal process	Investigations/ Aspartate aminotransferase in creased/ Abnormal lab result raised sgot	1/38/177 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Gastrointestinal disorders/ Gastritis/ Gastritis	1/32/4 days		No/ Severe/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash skin	1/1/21 days		No/ Moderate/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash skin	2/123/263 days		No/ Mild/ Probable	Dose Not Changed/ Recovered

Listing of adverse events possibly or probably related to trial product- trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Mild erythema	1/9/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Mild erythema	1/10/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Mild erythema	1/11/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	2	Pivotal process	Musculoskeletal and connectiv e tissue disorders/ Arthralgia/ Pain ankle, left	15/2/1 days		No/ Moderate/ Possible	Dose Not Changed/ Recovered
	On-demand	25	Pivotal process	Investigations/ Aspartate aminotransferase in creased/ High value for got	1/149/.		No/ Mild/ Possible	Dose Not Changed/ Not Recovered
	On-demand	26	Pivotal process	Investigations/ Alanine aminotransferase incr eased/ High value for gpt	1/149/.		No/ Mild/ Possible	Dose Not Changed/ Not Recovered
	On-demand	28	Pivotal process	Investigations/ Gamma-glutamyltransferase inc reased/ Elevated gamma-gt	26/177/89 days		No/ Moderate/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Investigations/ Coagulation factor VIII level increased/ High factor viii level 30 minutes after injeciton (2.449 u/ml).	1/9/33 days		No/ Moderate/ Probable	Dose Not Changed/ Recovered

Listing of adverse events possibly or probably related to trial product- trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Metabolism and nutrition disorders/ Iron deficiency/ Iron deficiency seen on ferritine control of 28th of januray.	1/23/253 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Investigations/ Coagulation factor VIII level increased/ High factor viii level 30 minutes after injeciton (1.949 u/ml).	1/94/65 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	17	Pivotal process	Musculoskeletal and connective tissue disorders/ Arthralgia/ Pain in both wrists and hands	3/185/78 days		No/ Moderate/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	18	Pivotal process	Investigations/ Coagulation factor VIII level increased/ High factor viii level 30 minutes after injection (2.078 u/ml)	1/201/51 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	20	Pivotal process	Investigations/ Mean cell volume decreased/ Decrease of mcv	1/227/157 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	21	Pivotal process	Investigations/ Mean cell haemoglobin decreased/ Decrease of mch	1/227/73 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	24	Pivotal process	Investigations/ Serum ferritin decreased/ Low ferritine 26 ug/l	2/238/112 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	25	Pivotal process	Investigations/ Coagulation factor VIII level increased/ High factor viii level 30 minutes after injection (1.904 u/ml)	1/266/85 days		No/ Mild/ Probable	Dose Not Changed/ Recovered

Listing of adverse events possibly or probably related to trial product- trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	27	Pivotal process	Investigations/ Coagulation factor VIII level increased/ Very high and fluctuant level of fviii post infusion	1/310/181 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	29	Pivotal process	Investigations/ Coagulation factor VIII level increased/ High factor viii chromogen level 30 minutes after injeciton (2.082 u/ml).	1/376/93 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	31	Commercial process	Investigations/ Coagulation factor VIII level increased/ High factor viii chromogen level 30 minutes after injeciton (2.243 u/ml)	5/417/.		No/ Mild/ Probable	Dose Not Changed/ Missing
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Investigations/ Blood bilirubin increased/ Total bilirubin level elevated	1/38/.		No/ Mild/ Probable	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Nervous system disorders/ Dizziness/ Transient dizziness	1/1/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	6	Pivotal process	Investigations/ Transaminases increased/ Transaminitis (elevated alt)	1/145/89 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Blood and lymphatic system di sorders/ Thrombocytopenia/ Thormbocytopenia	1/94/.		No/ Mild/ Possible	Dose Not Changed/ Not Recovered

Listing of adverse events possibly or probably related to trial product- trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	8	Pivotal process	Musculoskeletal and connective tissue disorders/ Muscle haemorrhage/ Spontaneous large organised haematoma in the left thigh (probably intramuscular)	1/241/85 days		No/ Severe/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Nervous system disorders/ Headache/ Worsening of headache	1/31/143 days		No/ Moderate/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	8	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated asat = 41 u/l	1/66/25 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	15	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated asat 68u/l	1/97/28 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Nervous system disorders/ Headache/ Headache	7/147/2 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Musculoskeletal and connective tissue disorders/ Arthralgia/ Left knee pain	6/190/189 days		No/ Mild/ Possible	Dose Increased/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	8	Pivotal process	Skin and subcutaneous tissue disorders/ Pruritus/ Itching under jaw	2/14/16 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Pivotal process	Investigations/ Alanine aminotransferase increased/ Elevated gpt on core lab results	1/83/61 days		No/ Mild/ Possible	Dose Not Changed/ Recovered

Listing of adverse events possibly or probably related to trial product- trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	14	Pivotal process	Investigations/ Alanine aminotransferase increased/ Worsening of elevated gpt on central lab work	1/148/309 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	16	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated got on central lab work	1/161/85 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	19	Pivotal process	Musculoskeletal and connective tissue disorders/ Joint range of motion decreased/ Decreased rom left ankle noted on md exam	1/203/.		No/ Mild/ Possible	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Blood and lymphatic system disorders/ Factor VIII inhibition/ Factor eight inhibitor development	1/97/.		Yes/ Moderate/ Probable	Drug Withdrawn/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated asat level	1/18/21 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Investigations/ Alanine aminotransferase increased/ Elevated alat level	1/18/21 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	10	Pivotal process	Investigations/ Electrocardiogram ST segment elevation/ St elevation	28/57/.		No/ Moderate/ Possible	Not Applicable/ Not Recovered

Listing of adverse events possibly or probably related to trial product- trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	7	Pivotal process	Cardiac disorders/ Sinus arrhythmia/ Sinus arrhythmia (1)	28/57/.		No/ Mild/ Possible	Not Applicable/ Not Recovered
	Prophylaxis multiple dose	8	Pivotal process	Cardiac disorders/ Sinus bradycardia/ Sinus bradycardia (2)	28/57/.		No/ Mild/ Possible	Not Applicable/ Not Recovered
	Prophylaxis multiple dose	9	Pivotal process	Blood and lymphatic system disorders/ Neutropenia/ Neutropenia	1/30/108 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Cough/ Coughing fit	1/4/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Injury, poisoning and procedural complications/ Post procedural complication/ Worsening of venous condition due to study procedure more blood taken and more and more difficulties to proceed to the pun	1/2/64 days		No/ Moderate/ Probable	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Injury, poisoning and procedural complications/ Contusion/ Bruised hip right side	1/4/39 days		No/ Moderate/ Possible	Dose Increased/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Vascular disorders/ Haemorrhage/ Increasing haemorrhagic symptoms and signs	1/4/39 days		Yes/ Moderate/ Probable	Drug Withdrawn/ Recovered

Listing of adverse events possibly or probably related to trial product- trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Nervous system disorders/ Dizziness/ Diziness	1/167/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Investigations/ Anti factor VIII antibody test/ Inhibitor formation against fviii - first test result by central laboratory - inhibitor not confirmed by fviii-inhibitor test in the central lab	1/14/15 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	2	Pivotal process	General disorders and administration site conditions/ Injection site swelling/ Problem with i.v. injection, swollen hand	1/3/36 days		No/ Moderate/ Probable	Dose Reduced/ Recovered
	Prophylaxis multiple dose	1	Pivotal process	Vascular disorders/ Haematoma/ Multiple haematoma	3/4/31 days		No/ Moderate/ Possible	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Immune system disorders/ Hypersensitivity/ Mild type 1 allergic reaction	1/1/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Immune system disorders/ Hypersensitivity/ Severe allergic reaction	1/4/1 days		Yes/ Severe/ Probable	Drug Withdrawn/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Injury, poisoning and procedural complications/ Accidental overdose/ Accidental overdose	1/2/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	2	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash, abdomen	5/68/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered

Listing of adverse events possibly or probably related to trial product- trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash, abdomen	1/72/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash, abdomen	1/79/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Injury, poisoning and procedu ral complications/ Drug administration error/ Mesi - administration of study drug without vial adapter.	1/43/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

61. 重篤な有害事象の一覧 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	On-demand	3	Pivotal process	Injury, poisoning and procedural complications/ Extradural haematoma/ Epidural hematoma, head	15/15/9 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	10	Pivotal process	Infections and infestations/ Device related infection/ Prothesis related infection	1/117/108 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	11	Pivotal process	Infections and infestations/ Pneumonia/ Pneumonia	4/180/19 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Neuroma/ Neuroma right elbow	4/221/370 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	13	Pivotal process	Infections and infestations/ Osteomyelitis/ Osteomyelitis	6/240/.		Yes/ Severe/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	16	Pivotal process	Musculoskeletal and connective tissue disorders/ Pathological fracture/ Spontaneous fracture of the left tibia	1/286/.		Yes/ Severe/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	8	Pivotal process	Congenital, familial and genetic disorders/ Hypertrophic cardiomyopathy/ Apical hypertrophic cardiomyopathy	1/158/.		Yes/ Severe/ Unlikely	Dose Increased/ Not Recovered
	Prophylaxis multiple dose	9	Pivotal process	Cardiac disorders/ Aortic valve stenosis/ Aortic valve stenosis	2/164/.		Yes/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	10	Pivotal process	Nervous system disorders/ Cerebral microhaemorrhage/ Suspicion of micro cranial bleedings	1/168/.		Yes/ Severe/ Unlikely	Dose Increased/ Not Recovered

Listing of serious adverse events - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	11	Pivotal process	Nervous system disorders/ Cerebral infarction/ Suspicion of cranial micro infarction	1/168/.		Yes/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3776/[redacted]/ [redacted]/ NN7088_3776	Phase 1 single dose	1	Pivotal process	Infections and infestations/ Tuberculosis/ Tuberculosis	3.9666666667/./.		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovering
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Injury, poisoning and procedural complications/ Forearm fracture/ Trauma with fracture of radio and ulna of the right arm	1/7/53 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	9	Pivotal process	Congenital, familial and genetic disorders/ Hydrocele/ Hydrocele	4/276/3 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Psychiatric disorders/ Depression/ Depression	3/206/.		Yes/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	6	Pivotal process	Infections and infestations/ Anal abscess/ Perianal abscess	2/157/4 days		Yes/ Severe/ Unlikely	Dose Increased/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	6	Pivotal process	Injury, poisoning and procedural complications/ Toxicity to various agents/ Salicylic acid poisoning	2/32/2 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered

Listing of serious adverse events - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	6	Pivotal process	Product issues/ Device dislocation/ Dislocation of right hip prothesis	1/101/3 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Pancreatic carcinoma metastatic/ Pancreatic cancer metastatic	2/88/248 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Fatal
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	13	Pivotal process	Nervous system disorders/ Syncope/ Vasovagal syncope	3/234/3 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Hepatobiliary disorders/ Cholecystitis/ Cholecystitis	3/79/2 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	19	Pivotal process	Gastrointestinal disorders/ Duodenal ulcer/ Duodenal ulcer	1/259/2 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	1	Pivotal process	Eye disorders/ Cataract/ Worsening of cataract	10/5/50 days		Yes/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Infections and infestations/ Intervertebral discitis/ Lumber pyogenic discitis	3/60/138 days		Yes/ Severe/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Infections and infestations/ Infective spondylitis/ Infective spondylitis	1/2/81 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Gastrointestinal disorders/ Gastric varices/ Exacerbation of gastric varices	1/2/106 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered

Listing of serious adverse events - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	7	Pivotal process	Injury, poisoning and procedural complications/ Femoral neck fracture/ Fracture of femoral neck	1/40/214 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	25	Pivotal process	Infections and infestations/ Cellulitis/ Cellulitis	2/187/15 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	31	Pivotal process	Infections and infestations/ Cellulitis/ Cellulitis	4/203/41 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	14	Pivotal process	Infections and infestations/ Bacterial sepsis/ Septicaemia gram-negative rod	7/109/66 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	15	Pivotal process	Renal and urinary disorders/ Tubulointerstitial nephritis/ Subacute nephritis interstitial	1/110/257 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovering
	Prophylaxis multiple dose	16	Pivotal process	Gastrointestinal disorders/ Gastric varices haemorrhage/ Gastric varices ruptured	1/117/53 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Infections and infestations/ Enteritis infectious/ Enteritis infectious	2/44/14 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Hepatocellular carcinoma/ Hepatocellular carcinoma	1/135/.		Yes/ Moderate/ Unlikely	Drug Withdrawn/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Infections and infestations/ Viral infection/ Viral infection	4/12/5 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	7	Pivotal process	Renal and urinary disorders/ IgA nephropathy/ Iga nefropathy	1/81/.		Yes/ Severe/ Unlikely	Dose Not Changed/ Not Recovered

Listing of serious adverse events - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	8	Pivotal process	Gastrointestinal disorders/ Duodenal ulcer/ Ulcera duodeni	1/94/38 days		Yes/ Severe/ Unlikely	Drug With drawn/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Injury, poisoning and procedu ral complications/ Road traffic accident/ Motor vehicle accident	2/150/40 days		Yes/ Moderate/ Unlikely	Drug With drawn/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	5	Pivotal process	Injury, poisoning and procedu ral complications/ Fall/ Fall on frozen ground with rip fracture and commotio cerebri	1/15/67 days		Yes/ Severe/ Unlikely	Dose Incr eased/ Recovered
	On-demand	11	Pivotal process	Renal and urinary disorders/ Calculus urinary/ Urolithiasis	15/23/3 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	30	Pivotal process	Gastrointestinal disorders/ Pancreatitis acute/ Acute pancreatitis	1/201/26 days		Yes/ Severe/ Unlikely	Dose Incr eased/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	6	Pivotal process	Injury, poisoning and procedu ral complications/ Face injury/ Trauma on right hand side of forehead above eyebrow.	1/324/2 days		Yes/ Moderate/ Unlikely	Dose Incr eased/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	6	Pivotal process	Musculoskeletal and connectiv e tissue disorders/ Synovitis/ Synovitis ankle	1/196/2 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	8	Pivotal process	Vascular disorders/ Circulatory collapse/ Circulatory collapse relating to injestion of 'resin bomb' of mdma	13/222/1 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered

Listing of serious adverse events - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	26	Pivotal process	Injury, poisoning and procedural complications/ Ankle fracture/ Bimaleolar right ankle fracture	3/156/153 days		Yes/ Severe/ Unlikely	Drug Withdrawn/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Nervous system disorders/ Seizure/ Seizure disorder	4/39/.		Yes/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Infections and infestations/ Catheter site infection/ Possible port infection	4/8/11 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Blood and lymphatic system disorders/ Factor VIII inhibition/ Factor eight inhibitor development	1/97/.		Yes/ Moderate/ Probable	Drug Withdrawn/ Not Recovered
	Prophylaxis multiple dose	7	Pivotal process	Infections and infestations/ Bacterial sepsis/ Gram negative sepsis	././5 days		Yes/ Severe/ Unlikely	Not Applicable/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Injury, poisoning and procedural complications/ Injury/ Right sided flank pain due to injury	2/120/5 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	General disorders and administration site conditions/ Complication associated with device/ Central line infiltrate with secondary swelling	7/14/5 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	31	Commercial process	Gastrointestinal disorders/ Abdominal hernia/ Epigastric hernia	1/363/162 days		Yes/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of serious adverse events - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	14	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Hypoxia/ Severe hypoxemic asthma	2/276/6 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Injury, poisoning and procedu ral complications/ Fall/ Fall	1/108/2 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	15	Pivotal process	Infections and infestations/ Sepsis syndrome/ Septic syndrome	1/237/16 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	2	Pivotal process	Vascular disorders/ Haemorrhage/ Increasing haemorrhagic symptoms and signs	1/4/39 days		Yes/ Moderate/ Probable	Drug With drawn/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	4	Pivotal process	Injury, poisoning and procedu ral complications/ Head injury/ Head trauma	1/278/3 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Gastrointestinal disorders/ Gastritis/ Acute gastritis	3/219/2 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Infections and infestations/ Tonsillitis/ Tonsillitis acuta	2/40/10 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	15	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Adenoidal hypertrophy/ Adenoid hypertrophy	1/230/88 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered

Listing of serious adverse events - trials 3776, 3859, 4033 and 3885 - safety analysis set
Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	7	Pivotal process	Musculoskeletal and connective tissue disorders/ Muscle haemorrhage/ Left adductor muscle bleed.	1/329/16 days		Yes/ Severe/ Unlikely	Dose Increased/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Immune system disorders/ Hypersensitivity/ Severe allergic reaction	1/4/1 days		Yes/ Severe/ Probable	Drug Withdrawn/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	4	Pivotal process	General disorders and administration site conditions/ Pyrexia/ Fever	3/270/3 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	13	Pivotal process	Infections and infestations/ Cellulitis/ Cellulitus	4/212/15 days		Yes/ Moderate/ Unlikely	Dose Increased/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Infections and infestations/ Device related infection/ Hospital admission for diagnosis: bacteremia associated with intravascular line	1/116/6 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	Infections and infestations/ Device related infection/ Staphylococcus epidermidis bacteremia associated with intravascular line	2/279/4 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Reproductive system and breast disorders/ Acquired phimosis/ Paraphimosis	2/29/16 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Infections and infestations/ Encephalitis/ Meningoencephalitis	2/41/56 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

62. 治験中止に至った有害事象の一覧 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Pancreatic carcinoma metastatic/ Pancreatic cancer metastatic	2/88/248 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Fatal
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Hepatocellular carcinoma/ Hepatocellular carcinoma	1/135/.		Yes/ Moderate/ Unlikely	Drug Withdrawn/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	8	Pivotal process	Gastrointestinal disorders/ Duodenal ulcer/ Ulcera duodeni	1/94/38 days		Yes/ Severe/ Unlikely	Drug Withdrawn/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Injury, poisoning and procedural complications/ Road traffic accident/ Motor vehicle accident	2/150/40 days		Yes/ Moderate/ Unlikely	Drug Withdrawn/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	26	Pivotal process	Injury, poisoning and procedural complications/ Ankle fracture/ Bimaleolar right ankle fracture	3/156/153 days		Yes/ Severe/ Unlikely	Drug Withdrawn/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	2	Pivotal process	Vascular disorders/ Haemorrhage/ Increasing haemorrhagic symptoms and signs	1/4/39 days		Yes/ Moderate/ Probable	Drug Withdrawn/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	7	Pivotal process	Musculoskeletal and connective tissue disorders/ Joint swelling/	1/8/15 days		No/ Mild/ Unlikely	Drug Withdrawn/ Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

63. 死亡に至った有害事象の一覧 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Pancreatic carcinoma metastatic/ Pancreatic cancer metastatic	2/88/248 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Fatal

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

64. 特に注目すべき医学的事象の一覧 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Injury, poisoning and procedural complications/ Product preparation error/ Error in constitution of study drug	1/3/51 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	7	Pivotal process	Injury, poisoning and procedural complications/ Overdose/ Trial product overdose	1/96/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Pruritus allergic/ Pruritis on bilateral arms and chest, secondary to housemite dust	3/15/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Immune system disorders/ Drug hypersensitivity/ Allergy to fentanyl patch	2/7/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	46	Commercial process	Skin and subcutaneous tissue disorders/ Urticaria/ Urticaria	2/371/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	13	Pivotal process	Immune system disorders/ Food allergy/ Fruite allergy	3/260/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	6	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Ezcema	4/89/438 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of medical events of special interest - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	14	Pivotal process	Gastrointestinal disorders/ Swollen tongue/ Swollen tongue after use grazar	1/344/32 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	12	Pivotal process	Skin and subcutaneous tissue disorders/ Drug eruption/ Rash due to cortimoxazol	1/96/14 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash skin	1/1/21 days		No/ Moderate/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash skin	2/123/263 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Mild erythema	1/9/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Mild erythema	1/10/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Mild erythema	1/11/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	16	Pivotal process	Skin and subcutaneous tissue disorders/ Dermatitis contact/ Allergy (cutaneous) to self adhesive plaster (coverplast)	1/1/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered

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Listing of medical events of special interest - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	2	Pivotal process	Skin and subcutaneous tissue disorders/ Urticaria/ Allergic urticaria	6/8/260 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Skin and subcutaneous tissue disorders/ Urticaria/ Urticaria	1/154/28 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Asthma/ Asthma	2/97/178 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Allergic respiratory disease/ Allergic airway inflammation	1/143/139 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	10	Pivotal process	Skin and subcutaneous tissue disorders/ Mechanical urticaria/ Dermographism, eczema tendency	1/188/155 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Blood and lymphatic system di sorders/ Factor VIII inhibition/ Factor eight inhibitor development	1/97/.		Yes/ Moderate/ Probable	Drug With drawn/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Immune system disorders/ Allergy to arthropod sting/ Swelling and pain at sting site- right elbow. allergic reaction to wasp sting	2/49/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of medical events of special interest - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	2	Pivotal process	Vascular disorders/ Haemorrhage/ Increasing haemorrhagic symptoms and signs	1/4/39 days		Yes/ Moderate/ Probable	Drug With drawn/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	13	Pivotal process	Eye disorders/ Conjunctivitis allergic/ Allergic conjunctivitis	2/77/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	11	Pivotal process	Skin and subcutaneous tissue disorders/ Urticaria/ Urticaria	3/113/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Investigations/ Anti factor VIII antibody tes t/ Inhibitor formation against fviii - first test result by central laboratory - inhibitor not confirmed by fviii-inhibitor test in the central lab	1/14/15 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	4	Pivotal process	Eye disorders/ Eye allergy/ Eye allergie	3/49/9 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	2	Pivotal process	Immune system disorders/ Allergic oedema/ Allergic edema of face	1/155/3 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Immune system disorders/ Allergic oedema/ Allergic swelling of the upper lip	1/169/4 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Immune system disorders/ Hypersensitivity/ Mild type 1 allergic reaction	1/1/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered

Listing of medical events of special interest - trials 3776, 3859, 4033 and 3885 - safety analysis set
Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Immune system disorders/ Hypersensitivity/ Severe allergic reaction	1/4/1 days		Yes/ Severe/ Probable	Drug Withdrawn/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Injury, poisoning and procedural complications/ Accidental overdose/ Accidental overdose	1/2/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Eye disorders/ Eye pruritus/ Itchy eyes	3/41/62 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash, abdomen	5/68/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash, abdomen	1/72/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash, abdomen	1/79/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Injury, poisoning and procedural complications/ Drug administration error/ Mesi - administration of study drug without vial adapter.	1/43/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Injury, poisoning and procedural complications/ Medication error/ Medication error	1/5/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

65. アレルギー反応（広域検索）に関連する有害事象の一覧 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	20	Pivotal process	Infections and infestations/ Conjunctivitis/ Conjunctivitis	18/155/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Immune system disorders/ Seasonal allergy/ Seasonal allergy symptoms	2/125/98 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3776/[redacted]/ [redacted]/ NN7088_3776	Phase 1 single dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Pruritus/ Upper extremities itching	4.3333333333/./1 hours		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	16	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	2/302/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Nasal rash	1/6/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	23	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Flare up of eczema	8/362/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3776/[redacted]/ [redacted]/ NN7088_3776	Phase 1 single dose	2	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	7.8791666667/./24 0 hours		No/ Mild/ Unlikely	Na/ Recovered
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	10	Pivotal process	General disorders and adminis tration site conditions/ Oedema peripheral/ Edema on the left ankle	34/255/103 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	2/2/48 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Pruritus allergic/ Pruritis on bilateral arms and chest, secondary to housemite dust	3/15/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	3/33/15 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	31	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash	1/461/66 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash	1/15/14 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	11	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash on skin of corpus penis	3/51/11 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Immune system disorders/ Drug hypersensitivity/ Allergy to fentanyl patch	2/7/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Infections and infestations/ Conjunctivitis/ Conjunctivitis	2/2/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Skin efflorescences (face)	4/4/9 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Cough/ Coughing	3/14/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	13	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Cough/ Coughing	2/18/11 days	7	No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Redness of skin	1/22/77 days	8	No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	15	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Cough/ Coughing	1/77/9 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Skin rash	1/239/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	4	Pivotal process	Immune system disorders/ Allergy to chemicals/ Allergy for copper sulphate	4/279/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	15	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Dyspnoea/ Dyspnea	2/231/20 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	12	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	4/293/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Immune system disorders/ Seasonal allergy/ Deterioration of pollinosis	2/12/40 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Gastrointestinal disorders/ Stomatitis/ Stomatitis	1/65/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Asthma/ Cough variant asthma	1/133/36 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema in ankle	1/122/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash	2/68/65 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Eruption	3/22/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	26	Pivotal process	Skin and subcutaneous tissue disorders/ Rash pruritic/ Skin rash with itching behind left knee	4/179/102 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	28	Pivotal process	Skin and subcutaneous tissue disorders/ Blister/ Vesicle on right lower leg	1/185/24 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	32	Pivotal process	Skin and subcutaneous tissue disorders/ Blister/ Blister on right lower leg	2/200/55 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	33	Pivotal process	Skin and subcutaneous tissue disorders/ Skin erosion/ Erosion on right lower leg	1/207/28 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	36	Pivotal process	Skin and subcutaneous tissue disorders/ Skin erosion/ Erosion on right lower leg	2/213/14 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	39	Pivotal process	Skin and subcutaneous tissue disorders/ Blister/ Vesicle on right lower leg	1/224/22 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	41	Pivotal process	Skin and subcutaneous tissue disorders/ Skin erosion/ Erosion of right lower leg	3/238/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	43	Pivotal process	Skin and subcutaneous tissue disorders/ Pruritus/ Itching of both forearm	1/311/273 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	46	Commercial process	Skin and subcutaneous tissue disorders/ Urticaria/ Urticaria	2/371/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	16	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema	2/345/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	8	Pivotal process	Gastrointestinal disorders/ Stomatitis/ Stomatitis	3/308/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Gastrointestinal disorders/ Stomatitis/ Stomatitis	4/18/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	20	Pivotal process	Skin and subcutaneous tissue disorders/ Blister/ Blister at left ankle	6/119/14 days		No/ Mild/ Unlikely	Not Appli cable/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	12	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	6/203/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	14	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	1/281/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	6	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Ezcema	4/89/438 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	11	Pivotal process	Immune system disorders/ Seasonal allergy/ Worsening hay fever	4/274/28 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	14	Pivotal process	Gastrointestinal disorders/ Swollen tongue/ Swollen tongue after use grazar	1/344/32 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	12	Pivotal process	Skin and subcutaneous tissue disorders/ Drug eruption/ Rash due to cortimoxazol	1/96/14 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

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Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash skin	1/1/21 days		No/ Moderate/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash skin	2/123/263 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Skin and subcutaneous tissue disorders/ Photosensitivity reaction/ Sensitive for sunlight	2/195/91 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	16	Pivotal process	General disorders and adminis tration site conditions/ Oedema/ Edema feet	3/251/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	7	Pivotal process	Skin and subcutaneous tissue disorders/ Photosensitivity reaction/ Sunlight sensitivity	6/162/108 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	11	Pivotal process	General disorders and adminis tration site conditions/ Oedema peripheral/ Oedeem ankles/feet	1/183/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	6	Pivotal process	Immune system disorders/ Hypersensitivity/ Allergy	1/195/185 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Mild erythema	1/9/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Mild erythema	1/10/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered

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Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Mild erythema	1/11/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	General disorders and adminis tration site conditions/ Localised oedema/ Neck aedema sensation	3/43/199 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	23	Pivotal process	Skin and subcutaneous tissue disorders/ Blister/ Small blister	1/94/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	9	Commercial process	General disorders and adminis tration site conditions/ Oedema peripheral/ Ankle oedema both sides	5/430/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	16	Pivotal process	Skin and subcutaneous tissue disorders/ Dermatitis contact/ Allergy (cutaneous) to self adhesive plaster (coverplast)	1/1/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	9	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Recurrence of small cutaneous lesions (eczema-like, on the right calf).	4/104/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough (mostly at night, no apparent fever)	3/107/10 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	10	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Recurrence of small cutaneous lesions (eczema-like, on the left knee).	3/109/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	11	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Recurrence of small cutaneous lesions (eczema-like, on the right calf).	4/118/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	22	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Recurrence of skin lesions of both legs, eczema-like	1/245/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	2	Pivotal process	Skin and subcutaneous tissue disorders/ Urticaria/ Allergic urticaria	6/8/260 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	10	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema	1/78/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	11	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema	1/87/162 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	18	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	24/149/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	19	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Nasal obstruction/ Nasal obstruction	24/149/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	21	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	8/178/54 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	24	Pivotal process	Skin and subcutaneous tissue disorders/ Pruritus/ Itching	4/193/9 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema in the inguinal region (non-alergic)	3/94/62 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	13	Pivotal process	Skin and subcutaneous tissue disorders/ Skin erosion/ Skin erosion on right thumb	1/152/100 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	14	Pivotal process	General disorders and adminis tration site conditions/ Oedema peripheral/ Dropsy of left ankle	1/169/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	General disorders and adminis tration site conditions/ Injection site rash/ Eruption at injection region.	1/10/5 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Skin and subcutaneous tissue disorders/ Urticaria/ Urticaria	1/154/28 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema. non -allergic in nature	1/69/33 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovering
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	1/160/9 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	15	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Dry cough	2/99/16 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash to upper legs, arms and abdomen	2/14/64 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Infections and infestations/ Conjunctivitis/ Conjunctivitis	1/141/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	1/141/13 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Immune system disorders/ Seasonal allergy/ Hayfever	1/106/35 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Immune system disorders/ Seasonal allergy/ Hayfever	1/164/152 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	14	Pivotal process	Skin and subcutaneous tissue disorders/ Urticaria/ Uticaria sweat rash	1/229/66 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	20	Pivotal process	Immune system disorders/ Seasonal allergy/ Hayfever	4/274/139 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Immune system disorders/ Seasonal allergy/ Hayfever	1/91/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Pivotal process	Skin and subcutaneous tissue disorders/ Dermatitis/ Exacerbation of long term dermatitis	1/319/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	10	Pivotal process	Immune system disorders/ Seasonal allergy/ Hayfever	1/350/153 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	Infections and infestations/ Conjunctivitis/ Mild conjuctivitis	1/408/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Gastrointestinal disorders/ Mouth ulceration/ Mouth ulcer	2/174/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Immune system disorders/ Seasonal allergy/ Hayfever	4/160/56 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Pivotal process	Vascular disorders/ Circulatory collapse/ Circulatory collapse relating to injestion of 'resin bomb' of mdma	13/222/1 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Asthma/ Asthma	2/97/178 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Allergic respiratory disease/ Allergic airway inflammation	1/143/139 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	10	Pivotal process	Skin and subcutaneous tissue disorders/ Mechanical urticaria/ Dermographism, eczema tendency	1/188/155 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	20	Pivotal process	Infections and infestations/ Conjunctivitis/ Conjunctivitis	4/357/30 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	24	Pivotal process	General disorders and administration site conditions/ Local swelling/ Swelling in groin	1/400/58 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	23	Pivotal process	Immune system disorders/ Seasonal allergy/ Hayfever	1/408/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	25	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Cough/ Cough	4/136/5 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Cough/ Chronic cough	1/16/354 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Cough/ Cough	2/15/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	13	Pivotal process	Immune system disorders/ Seasonal allergy/ Seasonal allergy	3/231/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	1/7/4 days	3	No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	General disorders and adminis tration site conditions/ Local swelling/ Jaw swelling from wisdom tooth erupting	4/138/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	15	Pivotal process	General disorders and adminis tration site conditions/ Peripheral swelling/ Mild swelling of upper left arm	1/149/5 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	19	Commercial process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	4/428/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	7	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	3/114/18 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	10	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	2/124/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	30	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	1/193/24 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Rhinitis allergic/ Allergic rhinitis	3/164/35 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Skin and subcutaneous tissue disorders/ Urticaria/ Urticaria	4/187/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Rash pruritic/ Pruritic rash (non-allergic reaction)	3/197/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recoverin g
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	17	Pivotal process	Immune system disorders/ Seasonal allergy/ Seasonal allergies	3/210/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	18	Pivotal process	Immune system disorders/ Seasonal allergy/ Seasonal allergy flare	1/248/188 days		No/ Mild/ Unlikely	Dose Not Changed/ Recoverin g
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	7	Pivotal process	Immune system disorders/ Seasonal allergy/ Seasonal allergy flare	2/339/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Eye disorders/ Eye pruritus/ Itchy eyes	2/14/16 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Sneezing/ Sneezing	2/14/16 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Pivotal process	Skin and subcutaneous tissue disorders/ Pruritus/ Itching under jaw	2/14/16 days		No/ Mild/ Possible	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	General disorders and adminis tration site conditions/ Peripheral swelling/ Swellingof left index finger	4/37/5 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	11	Pivotal process	Immune system disorders/ Seasonal allergy/ Headache from increased seasonal allergies	3/190/.		No/ Mild/ Unlikely	Dose Not Changed/ Unknown
	Prophylaxis multiple dose	8	Pivotal process	Immune system disorders/ Seasonal allergy/ Seasonal allergies increased than usual intermittent rhinitis	2/113/.		No/ Mild/ Unlikely	Dose Not Changed/ Unknown
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	4/14/17 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	1/36/.		No/ Mild/ Unlikely	Dose Not Changed/ Unknown
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Commercial process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	1/299/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	13	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema	1/287/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Coughing fit	1/4/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	5	Pivotal process	Vascular disorders/ Flushing/ Cutaneous flush	1/4/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	10	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Dry cough	3/33/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	3/46/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	16	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Rough cough	4/170/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	27	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Cutaneous eruption	2/319/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	31	Commercial process	Skin and subcutaneous tissue disorders/ Urticaria/ Urticaria	1/411/12 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	11	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Asthma/ Asthma	1/75/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	Infections and infestations/ Conjunctivitis/ Left eye conjonctivitis	1/101/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	14	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Asthmatic crisis/ Asthma crisis	2/122/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	24	Pivotal process	Eye disorders/ Conjunctivitis allergic/ Allergic conjunctivitis	2/266/32 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	28	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema	2/312/13 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	7	Pivotal process	Eye disorders/ Conjunctivitis allergic/ Allergic conjunctivitis	1/183/5 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	15	Pivotal process	General disorders and administration site conditions/ Peripheral swelling/ Tumefaction of right palmar hand	1/285/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	Eye disorders/ Conjunctivitis allergic/ Allergic conjonctivitis	1/314/96 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	12	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Asthma/ Asthmatiform bronchitis	2/226/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Cough/ Cough	1/44/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Asthma/ Asthmatiform bronchitis	3/74/12 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Cough/ Cough	3/105/44 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	13	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Skin rash	2/230/11 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	15	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Asthma/ Asthma	3/276/132 days		No/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	4	Pivotal process	Infections and infestations/ Conjunctivitis/ Bilateral conjunctivitis	4/120/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	6	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Gluteal erythema	1/39/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	17	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Gluteal erythema	4/214/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	20	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Gluteal erythema	1/261/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	21	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	2/283/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	2/218/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	2/210/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	2	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	1/62/58 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Blood and lymphatic system disorders/ Eosinophilia/ Eosinophilia	1/107/92 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	10	Pivotal process	Skin and subcutaneous tissue disorders/ Pruritus generalised/ Generalised itching	3/55/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	14	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Cough/ Cough	3/110/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	22	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Cough/ Cough	1/218/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	13	Pivotal process	Eye disorders/ Conjunctivitis allergic/ Allergic conjunctivitis	2/77/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	11	Pivotal process	Skin and subcutaneous tissue disorders/ Urticaria/ Urticaria	3/113/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	14	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Cough/ Cough	3/148/16 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	13	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema	1/206/190 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	General disorders and administration site conditions/ Local swelling/ Swelling- back	1/301/43 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	9	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema right hand	1/190/93 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema	3/31/10 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	Skin and subcutaneous tissue disorders/ Dermatitis contact/ Contact dermatitis	2/157/14 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	9	Pivotal process	Infections and infestations/ Conjunctivitis/ Conjunctivitis left eye	1/147/14 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	10	Pivotal process	General disorders and adminis tration site conditions/ Oedema peripheral/ The edema in the left hand middle finger	2/170/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	11	Commercial process	Skin and subcutaneous tissue disorders/ Dermatitis/ Dermatitis (nose area)	2/389/53 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	4	Pivotal process	Eye disorders/ Eye allergy/ Eye allergie	3/49/9 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	General disorders and adminis tration site conditions/ Peripheral swelling/ Swelling on the left foot	3/118/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Caugh	2/142/7 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	2	Pivotal process	Immune system disorders/ Allergic oedema/ Allergic edema of face	1/155/3 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Immune system disorders/ Allergic oedema/ Allergic swelling of the upper lip	1/169/4 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	8	Commercial process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	3/342/8 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	4/129/5 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Commercial process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	2/352/8 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	4	Pivotal process	Infections and infestations/ Conjunctivitis/ Right eye conjunctivitis	1/155/11 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	4	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash on trunk and back	1/158/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	7	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Rhinitis allergic/ Runny nose, congestion and cough at night continues - allergic rhinitis and post nasal drip - allergy unspecified not elsewhere cla	1/158/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Immune system disorders/ Hypersensitivity/ Mild type 1 allergic reaction	1/1/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Immune system disorders/ Hypersensitivity/ Severe allergic reaction	1/4/1 days		Yes/ Severe/ Probable	Drug With drawn/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	8/4/374 days		No/ Mild/ Missing	Not Appli cable/ Recoverin g
	Prophylaxis multiple dose	7	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Patches of erythema on buttocks	13/4/.		No/ Mild/ Missing	Not Appli cable/ Not Recovered
	Prophylaxis multiple dose	8	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Small patch of eczema on left calf	13/4/.		No/ Mild/ Missing	Not Appli cable/ Not Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	17	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	2/250/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	8	Pivotal process	Skin and subcutaneous tissue disorders/ Dermatitis contact/ Contact dermatitis rash	1/253/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	12	Pivotal process	Gastrointestinal disorders/ Gingival swelling/ Swelling, left lower gum	1/142/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	4	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	4/1/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Sneezing/ Sneezing	2/2/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	6	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	3/145/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Immune system disorders/ Seasonal allergy/ Seasonal allergies, clear rhinorrhea	3/283/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	5	Commercial process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	4/351/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Commercial process	Skin and subcutaneous tissue disorders/ Erythema/ Erythema - bilateral orbits	1/379/8 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	2	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Bronchial hyperreactivity/ Reactive airway	3/1/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered With Sequelae

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

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Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema on face	2/10/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	7	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Skin rash, right knee	2/343/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Erythematous raised lesions, chest	1/264/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Eye disorders/ Eye pruritus/ Itchy eyes	3/41/62 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash, abdomen	5/68/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash, abdomen	1/72/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash, abdomen	1/79/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Immune system disorders/ Seasonal allergy/ Seasonal allergies	1/288/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	7	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	2/107/13 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	19	Commercial process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	3/374/15 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	10	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	2/178/11 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	4	Pivotal process	Eye disorders/ Eye swelling/ Slight puffiness to upper eyelid right eye	1/153/74 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough, intermittent	1/241/40 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Wheezing/ Wheezing	1/249/23 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	2/255/11 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	16	Pivotal process	Immune system disorders/ Seasonal allergy/ Seasonal allergies (symptom dry cough)	1/305/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	8	Commercial process	Respiratory, thoracic and med iastinal disorders/ Rhinitis allergic/ Allergic rhinitis	3/382/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

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Listing of adverse events - allergic reactions (broad scope) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	14	Pivotal process	Skin and subcutaneous tissue disorders/ Dermatitis contact/ Poison ivy rash	3/101/15 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	6	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Cough/ Cough	3/107/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

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66. 血栓塞栓性事象（SMQ 検索）の一覧 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	11	Pivotal process	Nervous system disorders/ Cerebral infarction/ Suspicion of cranial micro infarction	1/168/.		Yes/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

67. 稀な有害事象の一覧 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	8	Pivotal process	Congenital, familial and genetic disorders/ Hypertrophic cardiomyopathy/ Apical hypertrophic cardiomyopathy	1/158/.		Yes/ Severe/ Unlikely	Dose Increased/ Not Recovered
NN7088_3776/[redacted]/ [redacted]/ NN7088_3776	Phase 1 single dose	3	Pivotal process	Cardiac disorders/ Palpitations/ Palpitation	2.3166666667/./11 4 hours		No/ Mild/ Unlikely	Na/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	9	Pivotal process	Congenital, familial and genetic disorders/ Hydrocele/ Hydrocele	4/276/3 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Hepatobiliary disorders/ Hepatic steatosis/ Hepatic steatosis	3/258/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Hepatobiliary disorders/ Hepatic fibrosis/ Mild fibrosis of liver	1/180/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	7	Pivotal process	Blood and lymphatic system disorders/ Pancytopenia/ Pancytopenia	1/102/65 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	6	Pivotal process	Blood and lymphatic system disorders/ Thrombocytopenia/ Thrombopenie	1/149/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	13	Pivotal process	Nervous system disorders/ Syncope/ Vasovagal syncope	3/234/3 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - rare events - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Hepatobiliary disorders/ Hepatic fibrosis/ Fibrosis hepatic grade 2 / f2/	2/9/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	11	Pivotal process	Blood and lymphatic system di sorders/ Granulocytopenia/ Granulocytopenia	1/22/122 days	8	No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	Blood and lymphatic system di sorders/ Thrombocytopenia/ Thrombocytopenia	1/22/122 days	8	No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	6	Pivotal process	Gastrointestinal disorders/ Gastric varices/ Exacerbation of gastric varices	1/2/106 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	37	Pivotal process	Gastrointestinal disorders/ Gastric varices/ Exacerbation of gastric varices	2/212/249 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	15	Pivotal process	Renal and urinary disorders/ Tubulointerstitial nephritis/ Subacute nephritis interstitial	1/110/257 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovering
	Prophylaxis multiple dose	16	Pivotal process	Gastrointestinal disorders/ Gastric varices haemorrhage/ Gastric varices ruptured	1/117/53 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Hepatobiliary disorders/ Hepatic fibrosis/ Hepatic fibrosis	4/108/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	6	Pivotal process	Congenital, familial and gene tic disorders/ Thalassaemia alpha/ Alpha thalassemia trait	1/181/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered

Listing of adverse events - rare events - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	14	Pivotal process	Gastrointestinal disorders/ Swollen tongue/ Swollen tongue after use grazar	1/344/32 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	7	Pivotal process	Renal and urinary disorders/ IgA nephropathy/ Iga nefropathy	1/81/.		Yes/ Severe/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Hepatobiliary disorders/ Hepatic cirrhosis/ Cirrhosis (liver)	4/85/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	8	Pivotal process	Cardiac disorders/ Atrial fibrillation/ Atrial fibrilation	3/205/.		No/ Mild/ Unlikely	Dose Increased/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Congenital, familial and genetic disorders/ Dermoid cyst/ Dermoid cyst in hip	3/159/32 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	8	Pivotal process	Cardiac disorders/ Extrasystoles/ Extra systole, < 1 minute	3/197/91 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	9	Pivotal process	Congenital, familial and genetic disorders/ Gilbert's syndrome/ Gilbert syndrome	1/150/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Blood and lymphatic system disorders/ Thrombocytopenia/ Thormbocytopenia	1/94/.		No/ Mild/ Possible	Dose Not Changed/ Not Recovered

Listing of adverse events - rare events - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	9	Pivotal process	Congenital, familial and gene tic disorders/ Gilbert's syndrome/ Gilbert syndrome	1/14/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	7	Pivotal process	Congenital, familial and gene tic disorders/ Odontogenic cyst/ Dental cyst on l2	2/81/219 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Investigations/ Platelet count decreased/ Marked decrease in platelet count (64 10^9/l)	1/21/184 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	30	Pivotal process	Gastrointestinal disorders/ Pancreatitis acute/ Acute pancreatitis	1/201/26 days		Yes/ Severe/ Unlikely	Dose Incr eased/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	8	Pivotal process	Vascular disorders/ Circulatory collapse/ Circulatory collapse relating to injestion of 'resin bomb' of mdma	13/222/1 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Blood and lymphatic system di sorders/ Neutropenia/ Neutropenia	4/20/16 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	33	Pivotal process	Gastrointestinal disorders/ Pancreatitis/ Pancreatitis	4/209/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - rare events - trials 3776, 3859, 4033 and 3885 - safety analysis set
Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	6	Pivotal process	Cardiac disorders/ Atrioventricular block first degree/ Sinus rhythm with 1st degree a-v block. patient has been referred to cardiology to determine clinical significance and severity.	7/20/.		No/ Missing/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Cardiac disorders/ Ventricular extrasystoles/ Sinus rythum with premature vetricular complexes on ecg	6/97/.		No/ Mild/ Unlikely	Not Applicable/ Unknown
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	9	Pivotal process	Blood and lymphatic system disorders/ Neutropenia/ Neutropenia	1/30/108 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Cardiac disorders/ Sinus arrhythmia/ Sinus arrhythmia (1)	28/57/.		No/ Mild/ Possible	Not Applicable/ Not Recovered
	Prophylaxis multiple dose	8	Pivotal process	Cardiac disorders/ Sinus bradycardia/ Sinus bradycardia (2)	28/57/.		No/ Mild/ Possible	Not Applicable/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Cardiac disorders/ Ventricular extrasystoles/ Ekg read as normal rhythm with a premature ventricular complex.	1/153/800 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	19	Commercial process	Congenital, familial and genetic disorders/ Pectus carinatum/ Pectus carinatum	1/318/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

68. 投薬過誤（SMQ 検索）に関連する有害事象の一覧 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Injury, poisoning and procedu ral complications/ Product preparation error/ Error in constitution of study drug	1/3/51 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	7	Pivotal process	Injury, poisoning and procedu ral complications/ Overdose/ Trial product overdose	1/96/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Injury, poisoning and procedu ral complications/ Accidental overdose/ Accidental overdose	2/14/32 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Injury, poisoning and procedu ral complications/ Accidental overdose/ Accidental overdose	1/2/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Injury, poisoning and procedu ral complications/ Drug administration error/ Mesi - administration of study drug without vial adapter.	1/43/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Injury, poisoning and procedu ral complications/ Medication error/ Medication error	1/5/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

69. 薬剤性肝障害（SMQ 検索）に関連する有害事象の一覧 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	Hepatitis C status/ Hepatitis B status	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	21	Pivotal process	Investigations/ Alanine aminotransferase increased/ Elevated gpt	1/375/337 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	22	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Elevated gamma-gt	1/375/.		No/ Mild/ Possible	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	[redacted]/	26	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated got	1/449/183 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	14	Pivotal process	Investigations/ Alanine aminotransferase increased/ Isolated elevated alt blood result	1/213/78 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	2	Pivotal process	Investigations/ Transaminases abnormal/ Alteration of transaminase.	1/79/109 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	8	Commercial process	Investigations/ Aspartate aminotransferase increased/ Got elevation	5/361/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	5	Pivotal process	Hepatobiliary disorders / Hepatic steatosis/ Hepatic steatosis	3/258/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	4	Pivotal process	Hepatobiliary disorders / Hepatic fibrosis/ Mild fibrosis of liver	1/180/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered

Listing of adverse events - drug related hepatic disorders (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	Hepatitis C status/ Hepatitis B status	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	7	Pivotal process	Hepatobiliary disorders / Hepatomegaly/ Hepatomegalie	2/88/.	3	No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	1	Pivotal process	Hepatobiliary disorders / Hepatic fibrosis/ Fibrosis hepatic grade 2 / f2/	2/9/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	6	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated got level most probably due to simple cold	1/106/15 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	[redacted]/	2	Pivotal process	Hepatobiliary disorders / Hepatic function abnormal/ Liver dysfunction	6/33/22 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	[redacted]/	9	Pivotal process	Investigations/ Liver function test abnormal/ Abnormality of biomarkers of liverfunction	9/202/85 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	6	Pivotal process	Gastrointestinal disorders/ Gastric varices/ Exacerbation of gastric varices	1/2/106 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered

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Listing of adverse events - drug related hepatic disorders (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	Hepatitis C status/ Hepatitis B status	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	37	Pivotal process	Gastrointestinal disorders/ Gastric varices/ Exacerbation of gastric varices	2/212/249 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	7	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ High gamma-gtp	1/243/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	[redacted]/	9	Pivotal process	Investigations/ Alanine aminotransferase increased/ High gpt	1/286/85 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	12	Pivotal process	Investigations/ Alanine aminotransferase increased/ High gpt	1/331/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	16	Pivotal process	Gastrointestinal disorders/ Gastric varices haemorrhage/ Gastric varices ruptured	1/117/53 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	4	Pivotal process	Hepatobiliary disorders/ Hepatic fibrosis/ Hepatic fibrosis	4/108/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	[redacted]/	5	Pivotal process	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Hepatocellular carcinoma/ Hepatocellular carcinoma	1/135/.		Yes/ Moderate/ Unlikely	Drug Withdrawn/ Not Recovered

Listing of adverse events - drug related hepatic disorders (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	Hepatitis C status/ Hepatitis B status	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	2	Pivotal process	Investigations/ Aspartate aminotransferase abnormal/ Abnormal lab result sgpt	1/23/.		No/ Mild/ Possible	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	[redacted]/	3	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Abnormal lab result raised sgot	1/38/177 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	5	Pivotal process	Hepatobiliary disorders / Hepatic cirrhosis/ Cirrhosis (liver)	4/85/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	2	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Elevation of gamma-gt.	1/83/57 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	5	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Elevation of gamma-gt.	1/283/71 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	10	Pivotal process	Investigations/ Alanine aminotransferase increased/ Elevation of gpt(alat).	1/447/92 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	9	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Elevation of gamma-gt.	1/447/92 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	2	Pivotal process	Investigations/ Alanine aminotransferase increased/ Elevation of alat	1/22/65 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

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Listing of adverse events - drug related hepatic disorders (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	Hepatitis C status/ Hepatitis B status	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	1	Pivotal process	Investigations/ Alanine aminotransferase increased/ Elevation of gpt (alat).	1/71/49 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	1	Pivotal process	Investigations/ Alanine aminotransferase increased/ Elevation of alt.	1/16/17 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	2	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Elevation of gamma-gt.	1/16/17 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	3	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevation of got(asat).	1/79/173 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	4	Pivotal process	Investigations/ Alanine aminotransferase increased/ Elevation of gpt (alat).	1/79/173 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	5	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Elevation of gamma-gt.	1/79/173 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	7	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevation of got(asat).	5/260/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	[redacted]/	8	Pivotal process	Investigations/ Alanine aminotransferase increased/ Elevation of gpt (alat),	5/260/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered

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Listing of adverse events - drug related hepatic disorders (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	Hepatitis C status/ Hepatitis B status	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	[redacted] /	25	Pivotal process	Investigations/ Aspartate aminotransferase increased/ High value for got	1/149/.		No/ Mild/ Possible	Dose Not Changed/ Not Recovered
	On-demand	[redacted] /	26	Pivotal process	Investigations/ Alanine aminotransferase increased/ High value for gpt	1/149/.		No/ Mild/ Possible	Dose Not Changed/ Not Recovered
	On-demand	[redacted] /	28	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Elevated gamma-gt	26/177/89 days		No/ Moderate/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	[redacted] /	4	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated got (asat) 106 u/l	33/33/36 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted] /	1	Pivotal process	Investigations/ Blood bilirubin increased/ Total bilirubin level elevated	1/38/.		No/ Mild/ Probable	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	[redacted] /	3	Pivotal process	Investigations/ Alanine aminotransferase increased/ Alanine aminotransferase increased	6/13/50 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	On-demand	[redacted] /	4	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Aspartate aminotransferase increased	6/13/50 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

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Listing of adverse events - drug related hepatic disorders (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	Hepatitis C status/ Hepatitis B status	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	[redacted]/	5	Pivotal process	Investigations/ Alanine aminotransferase increased/ Alanine aminotransferase increased	1/22/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
	On-demand	[redacted]/	6	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Aspartate aminotransferase increased	1/33/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	On-demand	[redacted]/	8	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Gamma-gt elevation	1/42/51 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	[redacted]/	10	Pivotal process	Investigations/ Blood bilirubin increased/ Total bilirubin elevation	1/59/56 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	[redacted]/	9	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Gamma-gt elevation	1/59/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	[redacted]/	5	Pivotal process	Investigations/ Alanine aminotransferase increased/ Gpt elevation	1/19/50 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	[redacted]/	6	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Gamma-gt elevation	1/19/50 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	[redacted]/	8	Pivotal process	Investigations/ Alanine aminotransferase increased/ Gpt elevation	1/55/114 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

00440918 10

Listing of adverse events - drug related hepatic disorders (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	Hepatitis C status/ Hepatitis B status	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	[redacted]/	9	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Gamma-gt elevation	1/62/64 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	6	Pivotal process	Investigations/ Transaminases increased / Transaminitis (elevated alt)	1/145/89 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	7	Pivotal process	Investigations/ Blood bilirubin increased/ Elevated level of bilirubin	1/150/132 days	9	No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	5	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Raised ast 70 u/l	1/14/29 days	9	No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	6	Pivotal process	Investigations/ Alanine aminotransferase increased/ Raised alt 103 u/l	1/14/29 days	8	No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	27	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated got (asat)	3/192/15 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	28	Pivotal process	Investigations/ Alanine aminotransferase increased/ Elevated gpt (alat)	3/192/15 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	29	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Elevated gamma-gt	3/192/34 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - drug related hepatic disorders (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	Hepatitis C status/ Hepatitis B status	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	7	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Raised gamma gt 160 u/l	1/21/184 days		No/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	8	Pivotal process	Investigations/ Alanine aminotransferase increased/ Marked increase alt 590 u/l	1/21/184 days		No/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	9	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Marked increase ast 350 u/l	1/21/169 days		No/ Severe/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	25	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated got (asat) - 51 u/l	1/215/13 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	8	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated asat = 41 u/l	1/66/25 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	15	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated asat 68u/l	1/97/28 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	22	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Got (asat) elevated at 95 u/l	56/177/12 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	23	Pivotal process	Investigations/ Alanine aminotransferase increased/ Gpt (alat) 63 u/l - increased outside of normal range	56/177/12 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - drug related hepatic disorders (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	Hepatitis C status/ Hepatitis B status	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	2	Pivotal process	Investigations/ Gamma-glutamyltransferase increased/ Elevated ggt	1/53/57 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	[redacted]/	2	Pivotal process	Investigations/ Blood bilirubin increased/ Increased bilirubin	6/6/54 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	2	Pivotal process	Investigations/ Hepatic enzyme increased/ Elevated liver enzymes (ast and alt)	1/34/26 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	9	Pivotal process	Investigations/ Alanine aminotransferase increased/ Elevated gpt on core lab results	1/83/61 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	14	Pivotal process	Investigations/ Alanine aminotransferase increased/ Worsening of elevated gpt on central lab work	1/148/309 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	[redacted]/	16	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated got on central lab work	1/161/85 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	1	Pivotal process	Investigations/ Aspartate aminotransferase increased/ Elevated asat level	1/18/21 days		No/ Mild/ Possible	Dose Not Changed/ Recovered

Listing of adverse events - drug related hepatic disorders (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	Hepatitis C status/ Hepatitis B status	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	[redacted]/	2	Pivotal process	Investigations/ Alanine aminotransferase increased/ Elevated alat level	1/18/21 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	[redacted]/	6	Pivotal process	Investigations/ Blood alkaline phosphatase increased/ Elevated alkaline phosphatase	1/199/29 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	[redacted]/	7	Pivotal process	Hepatobiliary disorders / Hepatomegaly/ Hepatomegaly	2/118/221 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

70. 急性腎不全（SMQ 検索）に関連する有害事象の一覧 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Patient ID/ Age in years/ Trial ID/ Treatment	Onset or collection date	AE number	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome	Creatinine Result (umol/L)/ Ref range/ Flag
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859/ Prophylaxis multiple dose	12APR2013							69.00/ 59.00-103.00/
	26APR2013							123.00/ 59.00-103.00/ H
	20MAY2013							75.00/ 59.00-103.00/
	25JUN2013							62.00/ 59.00-103.00/
	19JUL2013							63.00/ 59.00-103.00/
	13SEP2013							86.00/ 59.00-103.00/
	03DEC2013							71.00/ 59.00-103.00/
	24JAN2014							74.00/ 59.00-103.00/
	17FEB2014							69.00/ 59.00-103.00/
	17MAR2014							79.00/ 59.00-103.00/
	14APR2014							77.00/ 59.00-103.00/
	27MAY2014							70.00/ 59.00-103.00/
	14JUL2014							71.00/ 59.00-103.00/
	24SEP2014							98.00/ 59.00-103.00/
	17DEC2014							84.00/ 59.00-103.00/
	21JAN2015							86.00/ 59.00-103.00/
	18FEB2015							82.00/ 59.00-103.00/

Listing of adverse events - acute renal failure (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID/ Treatment	Onset or collection date	AE number	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome	Creatinine Result (umol/L)/ Ref range/ Flag
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859/ Prophylaxis multiple dose	25MAY2015							83.00/ 59.00-103.00/
	13AUG2015							88.00/ 59.00-103.00/
	02SEP2015	35	Investigations/ Blood creatinine increased/ Creatinin level increased	1/210/10 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered	
	18NOV2015							66.00/ 59.00-103.00/
	29JAN2016							90.00/ 59.00-103.00/
	16MAY2016							90.00/ 59.00-103.00/
	27JUL2016							78.00/ 59.00-103.00/
	07OCT2016							94.00/ 59.00-103.00/
	11JAN2017							92.00/ 59.00-103.00/
	24MAR2017							85.00/ 59.00-103.00/
	28JUN2017							89.00/ 59.00-103.00/
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859/ Prophylaxis multiple dose	18MAR2013							74.00/ 59.00-103.00/
	08APR2013							75.00/ 59.00-103.00/
	02MAY2013							79.00/ 59.00-103.00/
	03JUN2013							72.00/ 59.00-103.00/

Listing of adverse events - acute renal failure (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID/ Treatment	Onset or collection date	AE number	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome	Creatinine Result (umol/L)/ Ref range/ Flag
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859/ Prophylaxis multiple dose	27JUN2013							72.00/ 59.00-103.00/
	26AUG2013							80.00/ 59.00-103.00/
	18NOV2013							74.00/ 59.00-103.00/
	09JAN2014							73.00/ 59.00-103.00/
	06FEB2014							73.00/ 59.00-103.00/
	06MAR2014							78.00/ 59.00-103.00/
	03APR2014							68.00/ 59.00-103.00/
	01MAY2014							78.00/ 59.00-103.00/
	19JUN2014							83.00/ 59.00-103.00/
	14AUG2014							72.00/ 59.00-103.00/
	09OCT2014							80.00/ 59.00-103.00/
	04DEC2014							74.00/ 59.00-103.00/
	26DEC2014	15	Renal and urinary disorders/ Tubulointerstitial nephritis/ Subacute nephritis interstitial	1/110/257 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovering	
	26JAN2015							655.00/ 59.00-103.00/ H

Listing of adverse events - acute renal failure (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID/ Treatment	Onset or collection date	AE number	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome	Creatinine Result (umol/L)/ Ref range/ Flag
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859/ Prophylaxis multiple dose	22APR2013							120.00/ 59.00-103.00/ H
	03MAY2013							126.00/ 59.00-103.00/ H
	31MAY2013							136.00/ 59.00-103.00/ H
	24JUN2013							131.00/ 59.00-103.00/ H
	22JUL2013							140.00/ 59.00-103.00/ H
	16SEP2013							133.00/ 59.00-103.00/ H
	11NOV2013							122.00/ 59.00-103.00/ H
	06JAN2014							131.00/ 59.00-103.00/ H
	03MAR2014							129.00/ 59.00-103.00/ H
	31MAR2014							134.00/ 59.00-103.00/ H
	28APR2014	13	Investigations/ Blood creatinine increased/ Elevated creatinine 162 umol/l	1/85/65 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered	162.00/ 59.00-103.00/ H

Listing of adverse events - acute renal failure (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID/ Treatment	Onset or collection date	AE number	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome	Creatinine Result (umol/L)/ Ref range/ Flag
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859/ Prophylaxis multiple dose	02JUN2014							130.00/ 59.00-103.00/ H
	30JUN2014							141.00/ 59.00-103.00/ H
	11AUG2014							149.00/ 59.00-103.00/ H
	06OCT2014							150.00/ 59.00-103.00/ H
	08DEC2014							123.00/ 59.00-103.00/ H
	26JAN2015							140.00/ 59.00-103.00/ H
	16MAR2015							159.00/ 59.00-103.00/ H
	11MAY2015	20	Investigations/ Blood creatinine increased/ Elevated creatinine	1/139/31 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered	154.00/ 59.00-103.00/ H
	01JUN2015							130.00/ 59.00-103.00/ H
	29JUN2015							141.00/ 59.00-103.00/ H
	17AUG2015							141.00/ 59.00-103.00/ H
	12OCT2015							144.00/ 59.00-103.00/ H

Listing of adverse events - acute renal failure (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID/ Treatment	Onset or collection date	AE number	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome	Creatinine Result (umol/L)/ Ref range/ Flag
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859/ Prophylaxis multiple dose	30NOV2015							146.00/ 59.00-103.00/ H
	18JAN2016							153.00/ 59.00-103.00/ H
	14MAR2016							145.00/ 59.00-103.00/ H
	16MAY2016							170.00/ 59.00-103.00/ H
	18MAY2016	26	Investigations/ Blood creatinine increased/ Elevated creatinine	3/192/15 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered	
	04JUL2016							156.00/ 59.00-103.00/ H
	22AUG2016							119.00/ 59.00-103.00/ H
	15SEP2016							110.00/ 59.00-103.00/ H
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885/ Prophylaxis multiple dose	28FEB2014							19.00/ 21.00-36.00/ L
	31MAR2014							24.00/ 21.00-36.00/
	25JUL2014							21.00/ 21.00-36.00/
	15SEP2014							26.00/ 21.00-36.00/

Listing of adverse events - acute renal failure (SMQ) - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID/ Treatment	Onset or collection date	AE number	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome	Creatinine Result (umol/L)/ Ref range/ Flag
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885/ Prophylaxis multiple dose	27MAR2015	3	Investigations/ Blood creatinine increase d/ Elevated creatinine level	1/106/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered	42.00/ 27.00-42.00/
	25SEP2015							24.00/ 27.00-42.00/ L
	19FEB2016							28.00/ 27.00-42.00/
	02SEP2016							28.00/ 27.00-42.00/
	17FEB2017							29.00/ 28.00-52.00/

ED: exposure days. Duration: duration of event. Days since latest dose: days from latest exposure to onset of event, both days included.
Relationship: relationship as reported by investigator
Flag: values above reference range are marked with H and values below reference range are marked with L
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

nn7088/nn7088-filing/sum_20180910_er
10SEP2018:18:46:55 - l_teae_renal.sas/l_274600220_teae_renal_smq04_re.txt

71. 治験薬による病原体感染の疑いに関連する有害事象の一覧 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

There is no data to display

nn7088/nn7088-filing/sum_20180910_er
10SEP2018:16:56:42 - l_teae.sas/l_274600230_teae_cq04_ti.txt

72. 注射部位反応に関連する有害事象の要約 – 安全性解析対象集団（3776、3859、4033 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3776/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	14	Pivotal process	General disorders and administration site conditions/ Injection site reaction/ Vein irritation and induration at injection site.	1/238/.		No/ Mild/ Possible	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	10	Pivotal process	General disorders and administration site conditions/ Vessel puncture site haematoma/ Hematoma due to puncture on stenum and crista iliaca	1/108/5 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	General disorders and administration site conditions/ Infusion site reaction/ Infusion site reaction	2/66/23 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	General disorders and administration site conditions/ Injection site erythema/ Injection site erythema with small bullae	2/8/11 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	General disorders and administration site conditions/ Injection site rash/ Eruption at injection region.	1/10/5 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	General disorders and administration site conditions/ Vessel puncture site pain/ Pain in left anticubital associated with blood draw	1/1/3 days		No/ Mild/ Missing	/ Recovered

Listing of adverse events - injection site reactions - trials 3776, 3859, 4033 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	2	Pivotal process	General disorders and administration site conditions/ Injection site swelling/ Problem with i.v. injection, swollen hand	1/3/36 days		No/ Moderate/ Probable	Dose Reduced/ Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

73. 有害事象の一覧 – 日本人 – 安全性解析対象集団（3776、3859 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3776/[redacted]/ [redacted]/ NN7088_3776	Phase 1 single dose	1	Pivotal process	Psychiatric disorders/ Illusion/ Optical illusion	0.2375/./164 hours		No/ Mild/ Unlikely	Na/ Recovered
	Phase 1 single dose	3	Pivotal process	Cardiac disorders/ Palpitations/ Palpitation	2.3166666667/./114 hours		No/ Mild/ Unlikely	Na/ Recovered
	Phase 1 single dose	4	Pivotal process	General disorders and administration site conditions/ Fatigue/ Fatigue	2.6083333333/./107 hours		No/ Mild/ Unlikely	Na/ Recovered
	Phase 1 single dose	5	Pivotal process	Nervous system disorders/ Headache/ Headache	2.6083333333/./107 hours		No/ Mild/ Unlikely	Na/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Immune system disorders/ Seasonal allergy/ Deterioration of pollinosis	2/12/40 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Eye naevus/ Conjunctival nevus	2/12/40 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	1	Pivotal process	Infections and infestations/ Bronchitis/ Acute bronchitis	1/21/32 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Infections and infestations/ Folliculitis/ Purulent folliculitis	4/39/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Infections and infestations/ Hordeolum/ Hordeolum	1/60/9 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Gastrointestinal disorders/ Stomatitis/ Stomatitis	1/65/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Infections and infestations/ Hordeolum/ Hordeolum	3/111/16 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	10	Pivotal process	Musculoskeletal and connectiv e tissue disorders/ Musculoskeletal pain/ Right shoulder pain	1/127/15 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Asthma/ Cough variant asthma	1/133/36 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	1	Pivotal process	Eye disorders/ Cataract/ Worsening of cataract	10/5/50 days		Yes/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	2	Pivotal process	Hepatobiliary disorders/ Hepatic function abnormal/ Liver dysfunction	6/33/22 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	On-demand	3	Pivotal process	Infections and infestations/ Periodontitis/ Apical periodontitis	3/38/309 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	4	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Oropharyngeal pain/ Pain pharynx	1/77/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	1	Pivotal process	Metabolism and nutrition diso rders/ Hyperlipidaemia/ Hyper lipemia	1/112/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	2	Pivotal process	Skin and subcutaneous tissue disorders/ Alopecia areata/ Alopecia areata	2/113/563 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema in ankle	1/122/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	6	Pivotal process	Nervous system disorders/ Epilepsy/ Worsening of epilepsy	1/253/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Injury, poisoning and procedural complications/ Contusion/ Contusion of lower right leg	3/292/12 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Musculoskeletal and connective tissue disorders/ Pain in extremity/ Left plantar region pain	4/381/81 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Oropharyngeal pain/ Pharynx pain	1/385/2 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Commercial process	Injury, poisoning and procedural complications/ Contusion/ Contusion of right knee	4/424/2 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Infections and infestations/ Intervertebral discitis/ Lumber pyogenic discitis	3/60/138 days		Yes/ Severe/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	General disorders and administration site conditions/ Infusion site reaction/ Infusion site reaction	2/66/23 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash	2/68/65 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Infections and infestations/ Hepatitis C/ Aggravation of chronic hepatitis c	1/94/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	6	Pivotal process	Musculoskeletal and connective tissue disorders/ Musculoskeletal pain/ Buttock pain	1/100/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	5	Pivotal process	Nervous system disorders/ Headache/ Occipital headache	1/112/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	9	Pivotal process	Metabolism and nutrition disorders/ Hyperuricaemia/ Hyperuricemia	4/129/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	7	Pivotal process	Blood and lymphatic system disorders/ Anaemia/ Anemia	3/131/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	8	Pivotal process	General disorders and administration site conditions/ Pyrexia/ Fever	3/131/31 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	1	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	1/101/17 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	2	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	4/146/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	3	Pivotal process	Skin and subcutaneous tissue disorders/ Dry skin/ Dry skin	6/155/113 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	4	Pivotal process	Injury, poisoning and procedural complications/ Joint injury/ Trauma of left elbow	1/160/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	5	Pivotal process	Musculoskeletal and connective tissue disorders/ Back pain/ Back pain	2/166/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	On-demand	7	Pivotal process	Gastrointestinal disorders/ Toothache/ Toothache	5/177/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	6	Pivotal process	Injury, poisoning and procedural complications/ Contusion/ Bruise	1/179/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	8	Pivotal process	Injury, poisoning and procedural complications/ Contusion/ Bruise	1/195/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	9	Pivotal process	Investigations/ Liver function test abnormal/ Abnormality of biomarkers of liverfunction	9/202/85 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	On-demand	10	Pivotal process	Injury, poisoning and procedural complications/ Contusion/ Bruise	6/205/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	11	Pivotal process	Injury, poisoning and procedural complications/ Contusion/ Bruise	6/208/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	12	Pivotal process	Injury, poisoning and procedural complications/ Contusion/ Bruise	5/213/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	13	Pivotal process	Injury, poisoning and procedural complications/ Contusion/ Bruise	3/217/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	16	Pivotal process	Infections and infestations/ Tonsillitis/ Tonsillitis	2/246/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	15	Pivotal process	Nervous system disorders/ Headache/ Headache	8/249/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	17	Pivotal process	Injury, poisoning and procedural complications/ Scratch/ Scratch	1/282/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	18	Pivotal process	Injury, poisoning and procedural complications/ Contusion/ Bruise	1/283/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	19	Pivotal process	Injury, poisoning and procedural complications/ Contusion/ Bruise	4/284/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	20	Pivotal process	Injury, poisoning and procedural complications/ Contusion/ Bruise	1/306/23 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	On-demand	21	Pivotal process	General disorders and administration site conditions/ Pyrexia/ Fever	1/307/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	22	Pivotal process	Gastrointestinal disorders/ Vomiting/ Vomit	1/307/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	23	Pivotal process	Infections and infestations/ Folliculitis/ Folliculitis	9/329/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	On-demand	25	Pivotal process	Infections and infestations/ Folliculitis/ Folliculitis	5/403/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	On-demand	26	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema asteatotic/ Dry eczema	5/403/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	On-demand	27	Commercial process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	3/422/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Eruption	3/22/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Gastrointestinal disorders/ Dental caries/ Dental caries	1/29/15 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	3/64/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	4/102/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Gastrointestinal disorders/ Dental discomfort/ Uncomfortable feeling of tooth	3/108/218 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	9	Pivotal process	Infections and infestations/ Postoperative wound infection / Superificial infection on surgical site	3/61/83 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Injury, poisoning and procedu ral complications/ Compression fracture/ Exacerbation of compression fracture	1/1/.		No/ Moderate/ Missing	/ Not Recovered
	Prophylaxis multiple dose	4	Pivotal process	General disorders and adminis tration site conditions/ Adverse drug reaction/ Gastrointestinal symptoms by antibiotic	4/1/51 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Infections and infestations/ Infective spondylitis/ Infective spondylitis	1/2/81 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Gastrointestinal disorders/ Gastric varices/ Exacerbation of gastric varices	1/2/106 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	8	Pivotal process	Gastrointestinal disorders/ Perianal erythema/ Redness around anus	3/4/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Infections and infestations/ Folliculitis/ Folliculitis	1/16/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Injury, poisoning and procedural complications/ Femoral neck fracture/ Fracture of femoral neck	1/40/214 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	10	Pivotal process	Gastrointestinal disorders/ Gastrooesophageal reflux disease/ Reflux esophagitis	1/82/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	11	Pivotal process	Gastrointestinal disorders/ Duodenitis/ Duodenitis	1/82/764 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	Injury, poisoning and procedural complications/ Contusion/ Bruise	4/93/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	15	Pivotal process	Skin and subcutaneous tissue disorders/ Purpura/ Right leg purpura	2/94/212 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	13	Pivotal process	Musculoskeletal and connective tissue disorders/ Pain in extremity/ Pain of the right arm	2/95/208 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	14	Pivotal process	Musculoskeletal and connective tissue disorders/ Arthralgia/ Pain of right elbow	1/98/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	16	Pivotal process	General disorders and administration site conditions/ Pyrexia/ Fever	3/129/3 days		No/ Mild/ Possible	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	17	Pivotal process	Investigations/ C-reactive protein increased/ Crp test increased	2/133/72 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	18	Pivotal process	Infections and infestations/ Cellulitis/ Cellulitis	2/140/44 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	19	Pivotal process	General disorders and adminis tration site conditions/ Pyrexia/ Fever	3/143/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	20	Pivotal process	General disorders and adminis tration site conditions/ Ulcer/ Right leg ulcer	1/162/37 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	22	Pivotal process	Injury, poisoning and procedu ral complications/ Laceration/ Cut on left foot fifth toe	1/163/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	21	Pivotal process	Vascular disorders/ Hypertension/ Exacerbation of hypertension	2/167/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	23	Pivotal process	Injury, poisoning and procedu ral complications/ Contusion/ Bruise	1/171/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	24	Pivotal process	Injury, poisoning and procedu ral complications/ Skin abrasion/ Brush burn	1/171/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	27	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Epistaxis/ Epistaxis	2/171/77 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	26	Pivotal process	Skin and subcutaneous tissue disorders/ Rash pruritic/ Skin rash with itching behind left knee	4/179/102 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	28	Pivotal process	Skin and subcutaneous tissue disorders/ Blister/ Vesicle on right lower leg	1/185/24 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	25	Pivotal process	Infections and infestations/ Cellulitis/ Cellulitis	2/187/15 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	29	Pivotal process	Infections and infestations/ Cellulitis/ Cellulitis	1/192/22 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	30	Pivotal process	Musculoskeletal and connectiv e tissue disorders/ Joint lock/ Locking of right knee	3/195/16 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	32	Pivotal process	Skin and subcutaneous tissue disorders/ Blister/ Blister on right lower leg	2/200/55 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	31	Pivotal process	Infections and infestations/ Cellulitis/ Cellulitis	4/203/41 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	33	Pivotal process	Skin and subcutaneous tissue disorders/ Skin erosion/ Erosion on right lower leg	1/207/28 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	35	Pivotal process	Investigations/ Blood creatinine increased/ Creatinin level increased	1/210/10 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	40	Pivotal process	Injury, poisoning and procedu ral complications/ Scratch/ Scrach of flank	2/210/149 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	34	Pivotal process	Gastrointestinal disorders/ Chronic gastritis/ Chronic gastritis	2/212/249 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	37	Pivotal process	Gastrointestinal disorders/ Gastric varices/ Exacerbation of gastric varices	2/212/249 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	36	Pivotal process	Skin and subcutaneous tissue disorders/ Skin erosion/ Erosion on right lower leg	2/213/14 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	38	Pivotal process	Musculoskeletal and connectiv e tissue disorders/ Neck pain/ Pain of around neck	3/216/39 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	39	Pivotal process	Skin and subcutaneous tissue disorders/ Blister/ Vesicle on right lower leg	1/224/22 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	41	Pivotal process	Skin and subcutaneous tissue disorders/ Skin erosion/ Erosion of right lower leg	3/238/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	42	Pivotal process	Investigations/ C-reactive protein increased/ Crp level increased	1/293/73 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	43	Pivotal process	Skin and subcutaneous tissue disorders/ Pruritus/ Itching of both forearm	1/311/273 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	44	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	3/334/23 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	45	Commercial process	Infections and infestations/ Bronchitis/ Acute pharynx bronhitis	1/351/31 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	46	Commercial process	Skin and subcutaneous tissue disorders/ Urticaria/ Urticaria	2/371/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Gastrointestinal disorders/ Dental caries/ Tooth caries	1/28/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Infections and infestations/ Oral herpes/ Oral herpes	1/80/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Infections and infestations/ Influenza/ Influenza	3/85/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Injury, poisoning and procedu ral complications/ Laceration/ Small cut	1/91/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Injury, poisoning and procedu ral complications/ Traumatic haemorrhage/ Traumatic subcutaneous bleeding	1/132/13 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Investigations/ Gamma-glutamyltransferase inc reased/ High gamma-gtp	1/243/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	13	Pivotal process	Immune system disorders/ Food allergy/ Fruite allergy	3/260/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	14	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	3/260/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Pivotal process	Metabolism and nutrition diso rders/ Hyperlipidaemia/ Worsening of hyperlipidemia	1/265/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	9	Pivotal process	Investigations/ Alanine aminotransferase incr eased/ High gpt	1/286/85 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	10	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	4/304/17 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	11	Pivotal process	Investigations/ Blood cholesterol increased/ High tc(total chloresterol)	1/331/73 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	Investigations/ Alanine aminotransferase increased/ High gpt	1/331/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	16	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema	2/345/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Gastrointestinal disorders/ Gastritis/ Gastritis	3/66/267 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	1	Pivotal process	Injury, poisoning and procedural complications/ Tooth injury/ Tooth injury	2/106/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Middle lobe syndrome/ Middle lobe lingular syndrome	4/166/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	4	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Haemoptysis/ Sputum bloody	1/181/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Infections and infestations/ Helicobacter gastritis/ Helicobacter pylori gastritis	1/200/122 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Haemoptysis/ Sputum bloody	3/262/59 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Haemoptysis/ Sputum bloody	4/288/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	8	Pivotal process	Gastrointestinal disorders/ Stomatitis/ Stomatitis	3/308/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Pivotal process	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Nasopharyngeal neoplasm benign/ Nasopharynx posterior wall tumor(benign)	2/343/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	10	Pivotal process	Gastrointestinal disorders/ Barrett's oesophagus/ Short segment barrett esophagus	1/351/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	11	Pivotal process	Gastrointestinal disorders/ Gastritis erosive/ Verrucous gastritis	1/351/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	12	Pivotal process	Injury, poisoning and procedural complications/ Ligament sprain/ Sprain(right ankle)	3/389/15 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	13	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Cold	3/392/13 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	10	Pivotal process	Metabolism and nutrition disorders/ Diabetes mellitus/ Diabetes mellitus aggravated	1/63/197 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Infections and infestations/ Tinea pedis/ Secondary infection of tinea pedis	4/6/128 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	1	Pivotal process	Vascular disorders/ Hypertension/ Hypertension	3/10/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Infections and infestations/ Periodontitis/ Apical periodontitis	2/15/106 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Gastrointestinal disorders/ Stomatitis/ Stomatitis	4/18/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Nervous system disorders/ Headache/ Headache	3/37/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Gastrointestinal disorders/ Nausea/ Nausea	3/37/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Nervous system disorders/ Dizziness/ Dizziness	3/37/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Pivotal process	Infections and infestations/ Pulpitis dental/ Acute suppurative pulpitis	6/66/92 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Cold	3/74/20 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	11	Pivotal process	Musculoskeletal and connective tissue disorders/ Arthralgia/ Gonalgia	5/79/137 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	Psychiatric disorders/ Insomnia/ Insomnia	5/79/64 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	17	Pivotal process	Infections and infestations/ Periodontitis/ Chronic suppurative apical periodontitis	6/89/85 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	18	Pivotal process	Gastrointestinal disorders/ Dental caries/ Dental caries	6/101/29 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	13	Pivotal process	Gastrointestinal disorders/ Diarrhoea/ Diarrhea	1/104/44 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	14	Pivotal process	Infections and infestations/ Bacterial sepsis/ Septicaemia gram-negative rod	7/109/66 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	15	Pivotal process	Renal and urinary disorders/ Tubulointerstitial nephritis/ Subacute nephritis interstitial	1/110/257 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovering
	Prophylaxis multiple dose	19	Pivotal process	Gastrointestinal disorders/ Lip ulceration/ Lip ulceration	1/110/32 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	23	Pivotal process	Endocrine disorders/ Adrenal insufficiency/ Adrenal insufficiency	1/110/9 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	16	Pivotal process	Gastrointestinal disorders/ Gastric varices haemorrhage/ Gastric varices ruptured	1/117/53 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	20	Pivotal process	Skin and subcutaneous tissue disorders/ Blister/ Blister at left ankle	6/119/14 days		No/ Mild/ Unlikely	Not Applicable/ Recovered
	Prophylaxis multiple dose	21	Pivotal process	Nervous system disorders/ Altered state of consciousness/ Consciousness disturbed	8/119/24 days		No/ Mild/ Unlikely	Not Applicable/ Recovered
	Prophylaxis multiple dose	24	Pivotal process	General disorders and administration site conditions/ Pyrexia/ Fever	16/119/2 days		No/ Mild/ Unlikely	Not Applicable/ Recovered
	Prophylaxis multiple dose	22	Pivotal process	Skin and subcutaneous tissue disorders/ Skin disorder/ Disorder skin at buttocks	17/119/17 days		No/ Mild/ Unlikely	Not Applicable/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	3	Pivotal process	Nervous system disorders/ Headache/ Headache	3/43/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Infections and infestations/ Enteritis infectious/ Enteritis infectious	2/44/14 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	6	Pivotal process	Metabolism and nutrition disorders/ Diabetes mellitus/ Diabetes	1/106/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	4	Pivotal process	Hepatobiliary disorders/ Hepatic fibrosis/ Hepatic fibrosis	4/108/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	5	Pivotal process	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Hepatocellular carcinoma/ Hepatocellular carcinoma	1/135/.		Yes/ Moderate/ Unlikely	Drug With drawn/ Not Recovered
	Prophylaxis multiple dose	7	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	2/138/9 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Musculoskeletal and connective tissue disorders/ Myalgia/ Exercised induced muscle pain	5/8/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	17	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	3/242/23 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	13	Pivotal process	Eye disorders/ Conjunctivitis allergic/ Allergic conjunctivitis	2/77/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	1	Pivotal process	Infections and infestations/ Rhinitis/ Rhinitis	2/12/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Gastrointestinal disorders/ Diarrhoea/ Diarrhea	3/32/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	4	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	1/35/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Infections and infestations/ Streptococcal infection/ Strepto coccal infection	1/37/15 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Musculoskeletal and connectiv e tissue disorders/ Arthralgia/ Right ankle pain	1/47/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	2/55/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Pivotal process	Nervous system disorders/ Tongue biting/ Tongue biting	3/71/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Pivotal process	Infections and infestations/ Rhinitis/ Rhinitis	4/82/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	10	Pivotal process	Injury, poisoning and procedu ral complications/ Laceration/ Cut on left finger	1/97/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	11	Pivotal process	Skin and subcutaneous tissue disorders/ Urticaria/ Urticaria	3/113/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	4/119/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	14	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	3/148/16 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	15	Pivotal process	Infections and infestations/ Urethritis/ Urethritis	3/168/94 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	16	Pivotal process	Infections and infestations/ Gastroenteritis/ Gastroenteritis	5/168/92 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	18	Pivotal process	Infections and infestations/ Cystitis/ Cystitis	1/261/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	19	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Oropharyngeal pain/ Sore throat	2/297/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	20	Pivotal process	Injury, poisoning and procedu ral complications/ Ligament sprain/ Sprains of left ankle	1/299/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	21	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	1/346/9 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	8	Pivotal process	Injury, poisoning and procedu ral complications/ Contusion/ Bruise of head	1/116/22 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	14	Pivotal process	Infections and infestations/ Otitis media acute/ Acute otitis media(right)	4/226/19 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Pivotal process	Infections and infestations/ Gastroenteritis/ Acute gastroenteritis	4/140/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Infections and infestations/ Gastroenteritis/ Gastroenteritis	4/14/5 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Upper respiratory tract infla mmation/ Acute upper respiratory inflamation	3/23/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Infections and infestations/ Gastroenteritis/ Gastroenteritis	1/37/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Infections and infestations/ Influenza/ Influenza a	2/45/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Gastrointestinal disorders/ Enterocolitis/ Acute enterocolitis	1/58/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Infections and infestations/ Influenza/ Influenza	3/61/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	10	Pivotal process	Gastrointestinal disorders/ Constipation/ Constipation	1/148/40 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	11	Pivotal process	Infections and infestations/ Impetigo/ Impetigo	1/158/5 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	Infections and infestations/ Localised infection/ Left index finger suppuration	3/193/14 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	13	Pivotal process	Skin and subcutaneous tissue disorders/ Eczema/ Eczema	1/206/190 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	15	Pivotal process	Injury, poisoning and procedu ral complications/ Epiphyseal injury/ Proximal phalange epiphyseal injury in the fifth toe (left)	3/240/79 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	17	Pivotal process	Gastrointestinal disorders/ Dental caries/ Dental caries	1/299/48 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	18	Pivotal process	Infections and infestations/ Periodontitis/ Periodontitis	1/299/56 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	16	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Common cold	4/300/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	19	Pivotal process	Injury, poisoning and procedural complications/ Arthropod bite/ Insect bite	3/308/25 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	20	Pivotal process	Infections and infestations/ Otitis media acute/ Acute otitis media(right)	2/312/18 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	21	Pivotal process	Infections and infestations/ Otitis media acute/ Acute otitis media(right)	4/330/9 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	22	Commercial process	Infections and infestations/ Gastroenteritis/ Acute gastroenteritis	2/347/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	23	Commercial process	Injury, poisoning and procedural complications/ Face injury/ Facial injury	1/353/38 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	24	Commercial process	Infections and infestations/ Influenza/ Influenza a	3/364/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

74. 重篤な有害事象の一覧 – 日本人 – 安全性解析対象集団（3776、3859 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	On-demand	1	Pivotal process	Eye disorders/ Cataract/ Worsening of cataract	10/5/50 days		Yes/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Infections and infestations/ Intervertebral discitis/ Lumber pyogenic discitis	3/60/138 days		Yes/ Severe/ Possible	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Infections and infestations/ Infective spondylitis/ Infective spondylitis	1/2/81 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Gastrointestinal disorders/ Gastric varices/ Exacerbation of gastric varices	1/2/106 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Injury, poisoning and procedural complications/ Femoral neck fracture/ Fracture of femoral neck	1/40/214 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	25	Pivotal process	Infections and infestations/ Cellulitis/ Cellulitis	2/187/15 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	31	Pivotal process	Infections and infestations/ Cellulitis/ Cellulitis	4/203/41 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	14	Pivotal process	Infections and infestations/ Bacterial sepsis/ Septicaemia gram-negative rod	7/109/66 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	15	Pivotal process	Renal and urinary disorders/ Tubulointerstitial nephritis/ Subacute nephritis interstitial	1/110/257 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovering
	Prophylaxis multiple dose	16	Pivotal process	Gastrointestinal disorders/ Gastric varices haemorrhage/ Gastric varices ruptured	1/117/53 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered

Listing of serious adverse events - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Infections and infestations/ Enteritis infectious/ Enteritis infectious	2/44/14 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Hepatocellular carcinoma/ Hepatocellular carcinoma	1/135/.		Yes/ Moderate/ Unlikely	Drug Withdrawn/ Not Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

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75. 治験中止に至った有害事象の一覧 – 日本人 – 安全性解析対象集団（3776、3859 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Neoplasms benign, malignant a nd unspecified (incl cysts an d polyps)/ Hepatocellular carcinoma/ Hepatocellular carcinoma	1/135/.		Yes/ Moderate/ Unlikely	Drug With drawn/ Not Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
MedDRA version: 20.0

nn7088/nn7088-filing/sum_20180910_er
10SEP2018:16:56:44 - l_teae.sas/l_274600270_teae_jap_withd.txt

76. 基本語が更新された有害事象の一覧 – 安全性解析対象集団

Patient ID/ Age in years/ Trial ID	Treatment	AE number	As reported in CTR System organ class/ Preferred term/ Original MedDRA version	As reported in submission with MedDRA 20.0 System organ class/ Preferred term/ Investigator description
NN7088_3776/[redacted]/ [redacted]/ NN7088_3776	Phase 1 single dose	2	Infections and infestations/ Nasopharyngitis/ Meddra14.0	Infections and infestations/ Viral upper respiratory tract infection/ COMMON COLD

nn7088/nn7088-filing/sum_20180910_er
10SEP2018:16:56:32 - l_pt_update.sas/l_274600280_pt_update.txt

77. N8-GP の曝露状況一覧 – 日本人 – 安全性解析対象集団（3776、3859 及び 3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	Patient years of exposure	Exposure days
NN7088_3776/[redacted]/ [redacted]/ NN7088_3776	[redacted]	0.04	1
NN7088_3776/[redacted]/ [redacted]/ NN7088_3776		0.08	1
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		1.46	180
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		1.46	60
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		5.01	459
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		1.45	141
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		5.41	445
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		1.77	161
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		4.04	378
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		4.07	390

Listing of exposure to N8-GP - Japanese patients - trials 3776, 3859 and 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	Patient years of exposure	Exposure days
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	[redacted]	4.73	435
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		1.69	119
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		1.52	140
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		0.54	60
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		0.06	5
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		0.05	6
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		0.62	62
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885		3.72	405
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885		3.70	389

78. N8-GP の曝露状況一覧 – 2 歳未満 – 安全性解析対象集団（3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	Patient years of exposure	Exposure days
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3.24	343
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3.23	337
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3.69	386
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3.47	359
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3.73	391
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	3.92	380

Patients are allocated to age groups according to the age at baseline from the first trial they entered.

79. 有害事象の一覧 – 2 歳未満 – 安全性解析対象集団（3885 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Injury, poisoning and procedural complications/ Post procedural complication/ Worsening of venous condition due to study procedure more blood taken and more and more difficulties to proceed to the pun	1/2/64 days		No/ Moderate/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Infections and infestations/ Gastroenteritis/ Gastroenteritis	2/42/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Injury, poisoning and procedural complications/ Fall/ Fall	1/108/2 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Blood and lymphatic system disorders/ Anaemia/ Anemia	1/108/71 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Infections and infestations/ Conjunctivitis/ Bilateral conjunctivitis	4/120/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Infections and infestations/ Rhinitis/ Rhinitis	4/278/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Commercial process	Infections and infestations/ Ear infection/ Otitis	2/297/31 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Commercial process	Infections and infestations/ Scarlet fever/ Scarlatina	3/315/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	10	Commercial process	Metabolism and nutrition disorders/ Iron deficiency/ Hypoferitinemia	5/343/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered

Listing of adverse events - patients with age < 2 years - trial 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	2	Pivotal process	Gastrointestinal disorders/ Vomiting/ Vomitting	1/1/1 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Infections and infestations/ Gastroenteritis/ Gastroenteritis	1/2/10 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Nasal congestion/ Nasal congestion	1/33/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Gluteal erythema	1/39/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Infections and infestations/ Nasopharyngitis/ Rhinopharyngitis	3/70/31 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Pivotal process	General disorders and adminis tration site conditions/ Hyperthermia/ Hyperthermia	3/78/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Rhinorrhoea/ Rhinorrhea	1/96/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	10	Pivotal process	Ear and labyrinth disorders/ Ear pain/ Otalgia	4/108/11 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	11	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Nasal congestion/ Nasal congestion	1/129/11 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	12	Pivotal process	Infections and infestations/ Otitis media/ Serous otitis	4/140/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	13	Pivotal process	Infections and infestations/ Influenza/ Flue	2/206/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - patients with age < 2 years - trial 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ NN7088_3885	Prophylaxis multiple dose	14	Pivotal process	Infections and infestations/ Rhinitis/ Rhinitis	1/209/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	16	Pivotal process	Infections and infestations/ Bronchitis/ Bronchitis	4/214/5 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	17	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Gluteal erythema	4/214/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	18	Pivotal process	Infections and infestations/ Bronchitis/ Bronchitis	4/222/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	19	Pivotal process	Ear and labyrinth disorders/ Cerumen impaction/ Cerumen accumulation	4/222/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	15	Pivotal process	Infections and infestations/ Sepsis syndrome/ Septic syndrome	1/237/16 days		Yes/ Severe/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	20	Pivotal process	Skin and subcutaneous tissue disorders/ Erythema/ Gluteal erythema	1/261/8 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	21	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Cough/ Cough	2/283/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	22	Pivotal process	Reproductive system and breas t disorders/ Penile adhesion/ Prepuce adherence	2/283/105 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Infections and infestations/ Tonsillitis/ Tonsilititis acuta	4/15/12 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - patients with age < 2 years - trial 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	2	Pivotal process	Injury, poisoning and procedural complications/ Wound/ Wound of eyelid and periocular area	1/372/1 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	2	Pivotal process	Injury, poisoning and procedural complications/ Contusion/ Bruises on the back	1/129/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	3	Pivotal process	Injury, poisoning and procedural complications/ Excoriation/ Excoriation of the face	1/130/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Cold	1/143/4 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Cold	4/167/6 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Infections and infestations/ Viral upper respiratory tract infection/ Cold	2/229/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Infections and infestations/ Rhinitis/ Rhinitis	2/306/6 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Commercial process	Respiratory, thoracic and mediastinal disorders/ Cough/ Cough	3/342/8 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ [redacted]/ NN7088_3885	Prophylaxis multiple dose	1	Pivotal process	Infections and infestations/ Ear infection/ Left ear infection	1/32/15 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered

Listing of adverse events - patients with age < 2 years - trial 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Infections and infestations/ Sinusitis/ Possible sinus infection	4/127/16 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Infections and infestations/ Upper respiratory tract infection/ Upper respiratory infection	1/152/10 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash on trunk and back	1/158/2 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Respiratory, thoracic and mediastinal disorders/ Rhinitis allergic/ Runny nose, congestion and cough at night continues - allergic rhinitis and post nasal drip - allergy unspecified not elsewhere cla	1/158/7 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Pivotal process	General disorders and administration site conditions/ Pyrexia/ Fever the morning of 12aug2015 (99.4)	2/208/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Pivotal process	Infections and infestations/ Upper respiratory tract infection/ Upper respiratory infection	1/262/3 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
NN7088_3885/[redacted]/ NN7088_3885	Prophylaxis multiple dose	5	Pivotal process	Infections and infestations/ Molluscum contagiosum/ Moluscum contagiosium	3/148/272 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	1	Pivotal process	Eye disorders/ Eye pruritus/ Itchy eyes	3/41/62 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	2	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash, abdomen	5/68/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered

Listing of adverse events - patients with age < 2 years - trial 3885 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3885/[redacted]/ NN7088_3885	Prophylaxis multiple dose	3	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash, abdomen	1/72/1 days		No/ Mild/ Possible	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash, abdomen	1/79/1 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Nervous system disorders/ Headache/ Headache	1/225/2 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Immune system disorders/ Seasonal allergy/ Seasonal allergies	1/288/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	8	Pivotal process	Skin and subcutaneous tissue disorders/ Telangiectasia/ Facial telangiectasia	4/317/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered

ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

80. N8-GP の曝露状況一覧 – 65 歳以上 – 安全性解析対象集団（3859 及び 4033 試験）

Patient ID/ Age in years/ Trial ID	Treatment	Patient years of exposure	Exposure days
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	[redacted]	1.59	162
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		4.60	337
NN7088_3859/[redacted]/ [redacted]/ NN7088_4033		0.10	5
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859		4.33	318
NN7088_3859/[redacted]/ [redacted]/ NN7088_4033		0.08	4

Patients are allocated to age groups according to the age at baseline from the first trial they entered.

81. 有害事象の一覧 – 65 歳以上 – 安全性解析対象集団（3859 及び 4033 試験）

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Gastrointestinal disorders/ Abdominal pain/ Abdominal pain	2/88/.	2,3	No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	2	Pivotal process	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Neoplasm malignant/ Suspicion of malignant tumor	2/88/.	3	No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	3	Pivotal process	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Pancreatic carcinoma metastatic/ Pancreatic cancer metastatic	2/88/248 days		Yes/ Moderate/ Unlikely	Dose Not Changed/ Fatal
	Prophylaxis multiple dose	5	Pivotal process	Musculoskeletal and connective tissue disorders/ Bone pain/ Bone pain	2/88/.	3	No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	7	Pivotal process	Hepatobiliary disorders/ Hepatomegaly/ Hepatomegalie	2/88/.	3	No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	6	Pivotal process	Blood and lymphatic system disorders/ Thrombocytopenia/ Thrombopenie	1/149/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	1	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash skin	1/1/21 days		No/ Moderate/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	17	Pivotal process	Eye disorders/ Eye irritation/ Irritated eye	1/92/9 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Eye disorders/ Corneal disorder/ Roughening cornea	1/92/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered

Listing of adverse events - patients with age >=65 years - trials 3859 and 4033 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	5	Pivotal process	Skin and subcutaneous tissue disorders/ Rash/ Rash skin	2/123/263 days		No/ Mild/ Probable	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	6	Pivotal process	Cardiac disorders/ Pericarditis/ Pericarditis	3/176/15 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Skin and subcutaneous tissue disorders/ Photosensitivity reaction/ Sensitive for sunlight	2/195/91 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	8	Pivotal process	General disorders and adminis tration site conditions/ Fatigue/ Tiredness	2/195/134 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	9	Pivotal process	Gastrointestinal disorders/ Abdominal discomfort/ Upper abdominal discomfort	2/195/91 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	10	Pivotal process	Vascular disorders/ Hypertension/ Hypertension	1/211/120 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	11	Pivotal process	Vascular disorders/ Hypertension/ Hypertension	3/251/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	16	Pivotal process	General disorders and adminis tration site conditions/ Oedema/ Edema feet	3/251/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	13	Pivotal process	Gastrointestinal disorders/ Diaphragmatic hernia/ Hernia diafragmatica	1/264/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	18	Pivotal process	Eye disorders/ Cataract/ Cataract	3/325/.		No/ Mild/ Unlikely	Dose Not Changed/ Not Recovered

Listing of adverse events - patients with age >=65 years - trials 3859 and 4033 - safety analysis set

Continued...

Patient ID/ Age in years/ Trial ID	Treatment	AE number	Production method	System organ class/ Preferred term/ Investigator description	Days since latest dose /ED /Duration	Related to diagnosis	Serious/ Severity/ Relationship	Action/ Outcome
NN7088_3859/[redacted]/ [redacted]/ NN7088_3859	Prophylaxis multiple dose	2	Pivotal process	Blood and lymphatic system di sorders/ Anaemia/ Anemia	4/67/27 days		No/ Mild/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	4	Pivotal process	Respiratory, thoracic and med iastinal disorders/ Dyspnoea exertional/ Dyspneu d'effort	4/67/51 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	5	Pivotal process	Hepatobiliary disorders/ Hepatic cirrhosis/ Cirrhosis (liver)	4/85/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	6	Pivotal process	Infections and infestations/ Influenza/ Flu	6/155/11 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	7	Pivotal process	Skin and subcutaneous tissue disorders/ Photosensitivity reaction/ Sunlight sensitivity	6/162/108 days		No/ Moderate/ Unlikely	Dose Not Changed/ Recovered
	Prophylaxis multiple dose	11	Pivotal process	General disorders and adminis tration site conditions/ Oedema peripheral/ Oedeem ankles/feet	1/183/.		No/ Moderate/ Unlikely	Dose Not Changed/ Not Recovered
	Prophylaxis multiple dose	8	Pivotal process	Cardiac disorders/ Atrial fibrillation/ Atrial fibrilation	3/205/.		No/ Mild/ Unlikely	Dose Increased/ Not Recovered

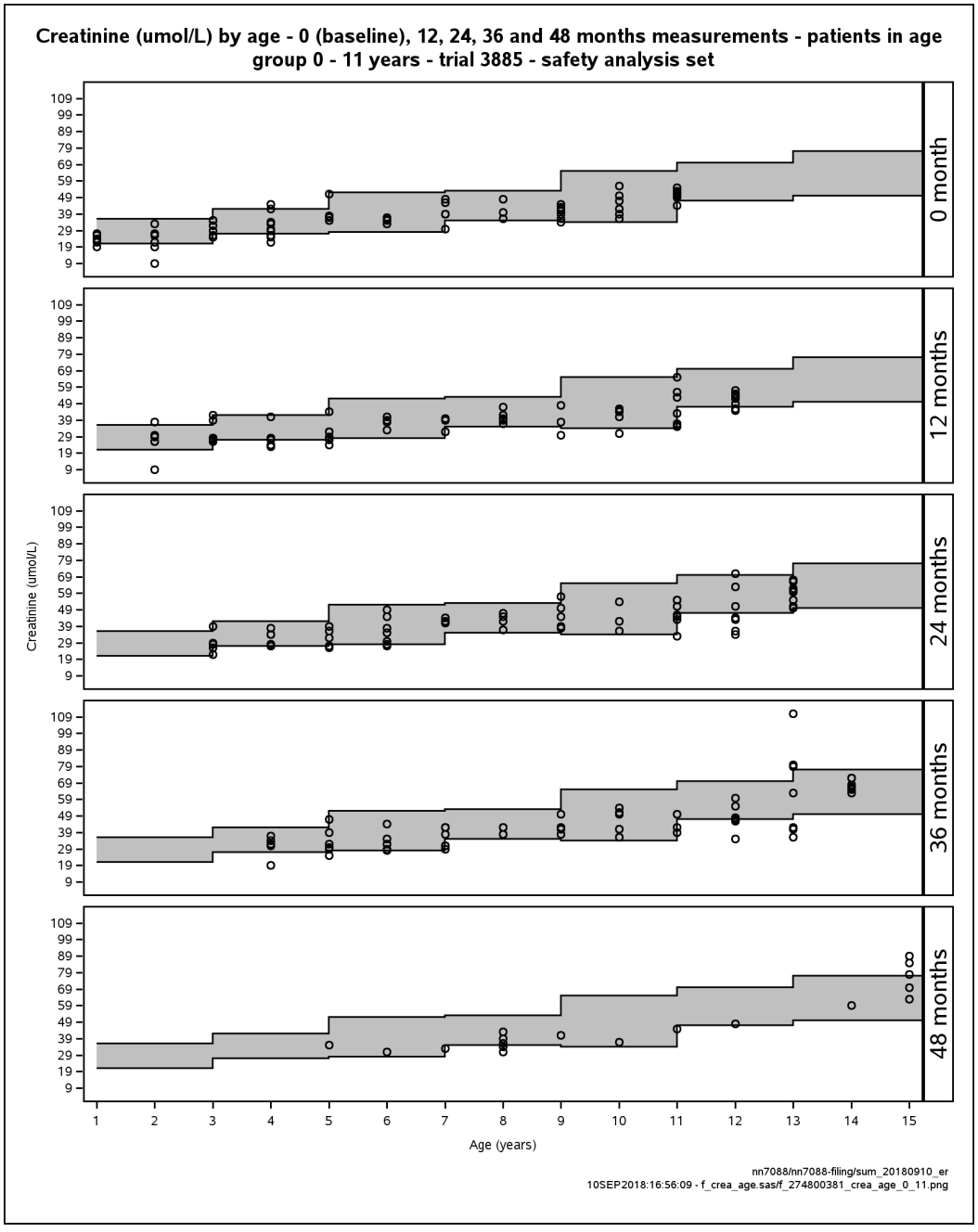
ED: exposure days
Days since latest dose: days from latest exposure to onset of event, both days included
Duration: duration of event
Relationship: relationship as reported by investigator
An exposure day is a day when the patient received at least one dose of N8-GP.
Patients are allocated to age groups according to the age at baseline from the first trial they entered.
MedDRA version: 20.0

82. FVIII インヒビター発生 – 安全性解析対象集団（3859、3860、4033 及び 3885 試験）

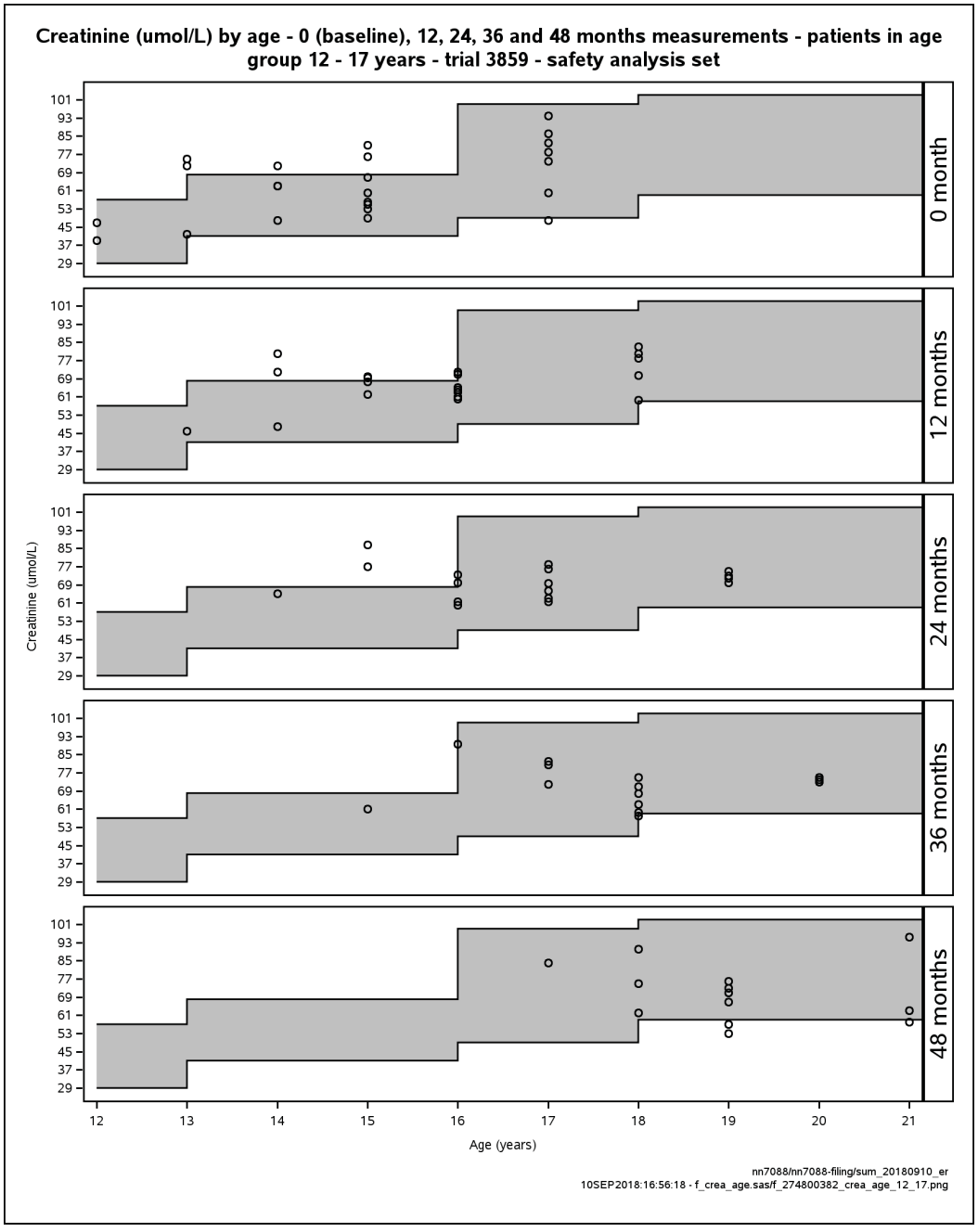
	Total
Number of patients	270
Number of patients at risk	235
Number of patients with confirmed inhibitory antibodies	1
Rate of inhibitory antibodies	
Estimated rate	0.004
Upper 97.5% confidence limit	0.023

The number of patients at risk are patients who have a minimum of 50 exposure days to N8-GP or who have confirmed inhibitory antibodies against FVIII regardless the number of exposure days.
Two patients (NN70883776/490402 and NN7088_3885/552003) are excluded from the analysis since the patients
were tested positive for inhibitory antibodies against FVIII at inclusion before first dose of N8-GP.
Estimates are based on exact calculations for a binomial distribution.

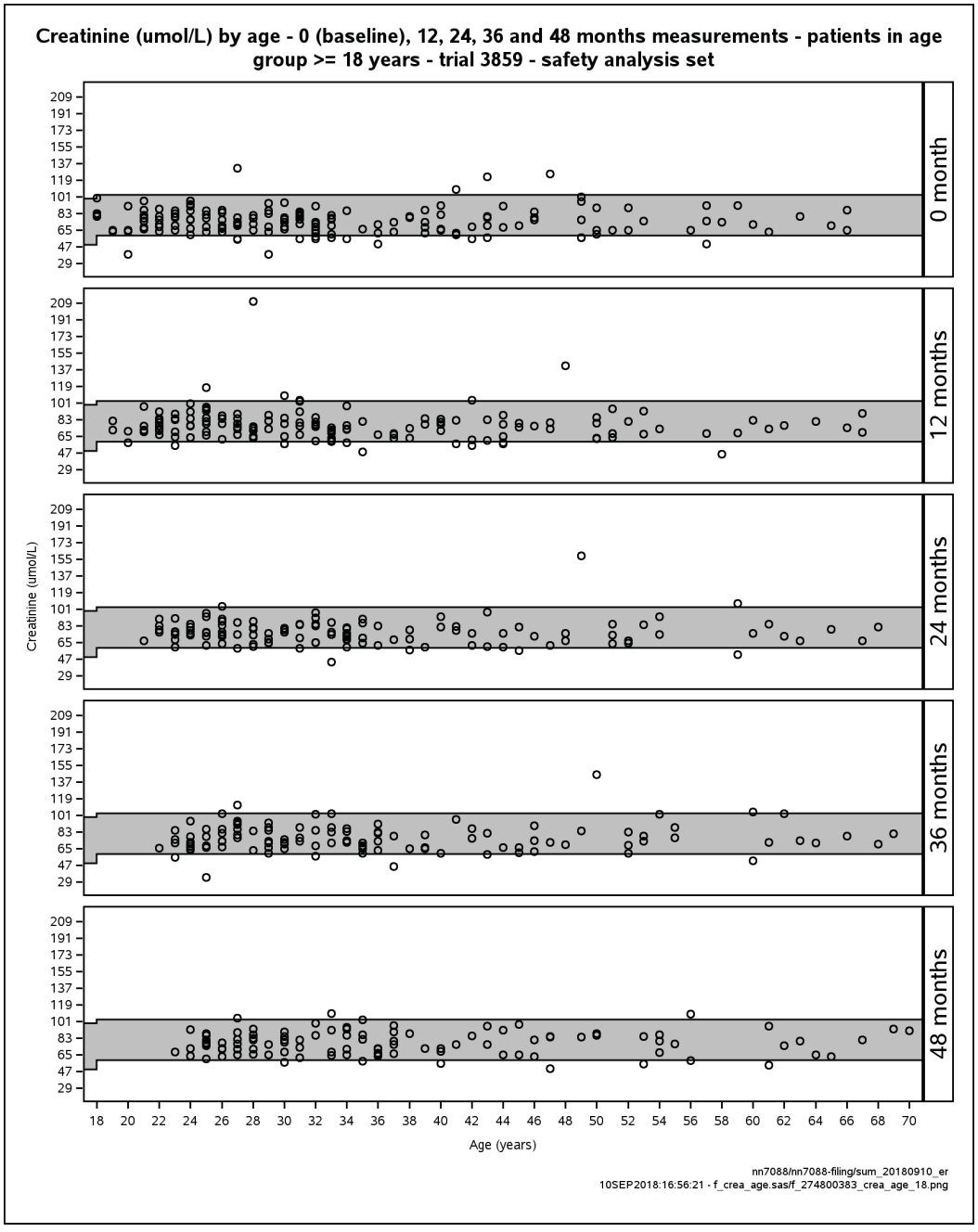
nn7088/nn7088-filing/sum_20180910_er
10SEP2018:16:57:12 - t_inhib.sas/t_274700100_inhib_overall.txt



83. 年齢別のクレアチニン（umol/L）－0（ベースライン）、12、24、36 及び 48 ヵ月時点 – 0～11 歳 – 安全性解析対象集団（3885 試験）



84. 年齢別のクレアチニン（umol/L）－0（ベースライン）、12、24、36 及び 48 ヵ月時点 – 12～17 歳 – 安全性解析対象集団（3859 試験）



85. 年齢別のクレアチニン（umol/L）－0（ベースライン）、12、24、36 及び 48 ヵ月時点 – 18 歳以上 – 安全性解析対象集団（3859 試験）

86. NNMQ「アレルギー反応」（広域検索）に含まれる基本語一覧

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Acquired epidermolysis bullosa	10056508	Infantile asthma	10049585
Acute generalised exanthematous pustulosis	10048799	Infusion site dermatitis	10065458
Acute kidney injury	10069339	Infusion site eczema	10074850
Acute prerenal failure	10001017	Infusion site hypersensitivity	10065471
Acute respiratory failure	10001053	Infusion site photosensitivity reaction	10065486
Administration site dermatitis	10075096	Infusion site rash	10059830
Administration site eczema	10075099	Infusion site recall reaction	10076085
Administration site hypersensitivity	10075102	Infusion site urticaria	10065490
Administration site photosensitivity reaction	10075961	Infusion site vasculitis	10074851
Administration site rash	10071156	Injection site dermatitis	10022056
Administration site recall reaction	10075964	Injection site eczema	10066221
Administration site urticaria	10075109	Injection site hypersensitivity	10022071
Administration site vasculitis	10075969	Injection site photosensitivity reaction	10053396
Airway remodelling	10075289	Injection site rash	10022094
Allergic bronchitis	10052613	Injection site recall reaction	10066797
Allergic colitis	10059447	Injection site urticaria	10022107
Allergic cough	10053779	Injection site vasculitis	10067995
Allergic cystitis	10051394	Instillation site hypersensitivity	10073612
Allergic eosinophilia	10075185	Instillation site rash	10073622
Allergic gastroenteritis	10075308	Instillation site urticaria	10073627
Allergic hepatitis	10071198	Interstitial granulomatous dermatitis	10067972
Allergic keratitis	10057380	Interstitial lung disease	10022611
Allergic myocarditis	10001715	Intestinal angioedema	10076229
Allergic oedema	10060934	Iodine allergy	10052098
Allergic otitis externa	10075072	Irregular breathing	10076213
Allergic otitis media	10061557	Jugular vein distension	10059865
Allergic pharyngitis	10050639	Kaposi's varicelliform eruption	10051891
Allergic reaction to excipient	10078853	Kounis syndrome	10069167
Allergic respiratory disease	10063532	Laryngeal dyspnoea	10052390
Allergic respiratory symptom	10063527	Laryngeal obstruction	10059639
Allergic sinusitis	10049153	Laryngeal oedema	10023845
Allergic transfusion reaction	10066173	Laryngitis allergic	10064866
Allergy alert test positive	10075479	Laryngospasm	10023891
Allergy test positive	10056352	Laryngotracheal oedema	10023893
Allergy to chemicals	10061626	Leukotriene increased	10064663
Allergy to fermented products	10054929	Limbal swelling	10070492
Allergy to immunoglobulin therapy	10074079	Lip exfoliation	10064482
Allergy to surgical sutures	10077279	Lip oedema	10024558
Allergy to vaccine	10055048	Lip swelling	10024570
Alpha tumour necrosis factor increased	10059982	Local swelling	10024770
Alveolitis	10001889	Localised oedema	10048961
Alveolitis allergic	10001890	Mast cell degranulation present	10076606
Anaphylactic reaction	10002198	Mechanical urticaria	10068773
Anaphylactic shock	10002199	Medical device site dermatitis	10075572
Anaphylactic transfusion reaction	10067113	Medical device site eczema	10075575
Anaphylactoid reaction	10002216	Medical device site hypersensitivity	10075579
Anaphylactoid shock	10063119	Medical device site photosensitivity reaction	10076137
Anaphylaxis treatment	10002222	Medical device site rash	10075585
Angioedema	10002424	Medical device site recall reaction	10076140

Listing of preferred terms used for NNMQ allergic reactions (broad scope)

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Anti-insulin antibody increased	10053815	Medical device site urticaria	10075588
Anti-insulin antibody positive	10053814	Mesenteric panniculitis	10063031
Anti-insulin receptor antibody increased	10068226	Mouth swelling	10075203
Anti-insulin receptor antibody positive	10068225	Mouth ulceration	10028034
Anti-neutrophil cytoplasmic antibody positive vasculitis	10050894	Mucocutaneous rash	10056671
Antiallergic therapy	10064059	Mucocutaneous ulceration	10028084
Antibody test abnormal	10061425	Mucosa vesicle	10028103
Antibody test positive	10061427	Mucosal erosion	10061297
Antiendomysial antibody positive	10065514	Mucosal exfoliation	10064486
Anuria	10002847	Mucosal necrosis	10067993
Application site dermatitis	10003036	Mucosal ulceration	10028124
Application site eczema	10050099	Multiple allergies	10028164
Application site hypersensitivity	10063683	Myocardial depression	10069140
Application site photosensitivity reaction	10058730	Nasal crease	10078581
Application site rash	10003054	Nasal obstruction	10028748
Application site recall reaction	10076024	Nasal oedema	10028750
Application site urticaria	10050104	Necrotising panniculitis	10062579
Application site vasculitis	10076027	Neonatal anuria	10049778
Arthritis allergic	10061430	Neonatal multi-organ failure	10050401
Aspirin-exacerbated respiratory disease	10075084	Neonatal respiratory failure	10028975
Asthma	10003553	Nephritis allergic	10029120
Asthma late onset	10003559	Neurodermatitis	10029263
Asthma-chronic obstructive pulmonary disease overlap syndrome	10077005	Neutralising antibodies positive	10064980
Asthmatic crisis	10064823	Nikolsky's sign	10029415
Atopy	10003645	Nipple oedema	10059012
Auricular swelling	10003800	Nipple swelling	10058680
Blepharitis allergic	10005149	Nodular rash	10075807
Blister	10005191	Non-neutralising antibodies positive	10064982
Blister rupture	10073385	Noninfective conjunctivitis	10074701
Blood immunoglobulin A abnormal	10005584	Obstructive airways disorder	10061877
Blood immunoglobulin A increased	10005586	Occupational asthma	10070836
Blood immunoglobulin D increased	10063244	Occupational dermatitis	10030012
Blood immunoglobulin E abnormal	10005589	Ocular hyperaemia	10030041
Blood immunoglobulin E increased	10005591	Oculomucocutaneous syndrome	10030081
Blood immunoglobulin G abnormal	10005594	Oculorespiratory syndrome	10067317
Blood immunoglobulin G increased	10005596	Oedema	10030095
Blood immunoglobulin M abnormal	10005599	Oedema genital	10030104
Blood immunoglobulin M increased	10005601	Oedema mouth	10030110
Blood pressure decreased	10005734	Oedema mucosal	10030111
Blood pressure diastolic decreased	10005737	Oedema neonatal	10061317
Blood pressure immeasurable	10005748	Oedema peripheral	10030124
Blood pressure systolic decreased	10005758	Oral allergy syndrome	10068355
Breast oedema	10006294	Oral mucosal blistering	10030995
Breast swelling	10006312	Oral mucosal exfoliation	10064487

Listing of preferred terms used for NNMQ allergic reactions (broad scope)

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Bromoderma	10006404	Oral papule	10031010
Bronchial hyperreactivity	10066091	Orbital oedema	10031051
Bronchial oedema	10056695	Organ failure	10053159
Bronchospasm	10006482	Oropharyngeal blistering	10067950
Bullous impetigo	10006563	Oropharyngeal oedema	10078783
Caffeine allergy	10074895	Oropharyngeal spasm	10031111
Capillaritis	10068406	Oropharyngeal swelling	10031118
Cardiac arrest	10007515	Palatal oedema	10056998
Cardio-respiratory arrest	10007617	Palatal swelling	10074403
Cardio-respiratory distress	10049874	Palisaded neutrophilic granulomatous dermatitis	10068809
Cardiovascular insufficiency	10065929	Palpable purpura	10056872
Catheter site dermatitis	10073992	Panniculitis	10033675
Catheter site eczema	10073995	Pathergy reaction	10074332
Catheter site hypersensitivity	10073998	Pemphigoid	10034277
Catheter site rash	10052271	Pemphigus	10034280
Catheter site urticaria	10052272	Penile exfoliation	10064485
Catheter site vasculitis	10074014	Penile oedema	10066774
Cerebral hypoperfusion	10065384	Penile swelling	10034319
Charcot-Leyden crystals	10008413	Perineal rash	10075364
Chest discomfort	10008469	Perinephric oedema	10078818
Choking	10008589	Periorbital oedema	10034545
Choking sensation	10008590	Peripheral oedema neonatal	10049779
Chronic eosinophilic rhinosinusitis	10071399	Peripheral swelling	10048959
Chronic hyperplastic eosinophilic sinusitis	10071380	Perivascular dermatitis	10064986
Circulatory collapse	10009192	Pharyngeal oedema	10034829
Circumoral oedema	10052250	Photosensitivity reaction	10034972
Conjunctival oedema	10010726	Pneumonitis	10035742
Conjunctivitis	10010741	Prerenal failure	10072370
Conjunctivitis allergic	10010744	Propofol infusion syndrome	10063181
Contact stomatitis	10067510	Prurigo	10037083
Contrast media allergy	10066973	Pruritus	10037087
Contrast media reaction	10010836	Pruritus allergic	10063438
Corneal exfoliation	10064489	Pruritus generalised	10052576
Corneal oedema	10011033	Pulmonary eosinophilia	10037382
Cough	10011224	Radioallergosorbent test positive	10037789
Cutaneous vasculitis	10011686	Rash	10037844
Cyanosis	10011703	Rash erythematous	10037855
Cytokine release syndrome	10052015	Rash follicular	10037857
Cytokine storm	10050685	Rash generalised	10037858
Dennie-Morgan fold	10062918	Rash macular	10037867
Dermatitis	10012431	Rash maculo-papular	10037868
Dermatitis acneiform	10012432	Rash maculovesicular	10050004
Dermatitis allergic	10012434	Rash morbilliform	10037870
Dermatitis atopic	10012438	Rash neonatal	10037871
Dermatitis bullous	10012441	Rash papulosquamous	10037879
Dermatitis contact	10012442	Rash pruritic	10037884
Dermatitis exfoliative	10012455	Rash pustular	10037888
Dermatitis exfoliative generalised	10012456	Rash rubelliform	10057984
Dermatitis herpetiformis	10012468	Rash scarlatiniform	10037890
Dermatitis infected	10012470	Rash vesicular	10037898
Dermatitis psoriasiform	10058675	Reaction to azo-dyes	10037973
Device allergy	10072867	Reaction to colouring	10037974
Dialysis membrane reaction	10076665	Reaction to drug excipients	10064787
Diastolic hypotension	10066077	Reaction to preservatives	10064788
Distributive shock	10070559	Reactive airways dysfunction syndrome	10070832
Documented hypersensitivity to administered product	10076470	Red man syndrome	10038192
Drug cross-reactivity	10076743	Renal failure	10038435
Drug eruption	10013687	Renal failure neonatal	10038447
Drug hypersensitivity	10013700	Respiratory arrest	10038669
Drug provocation test	10074350	Respiratory distress	10038687

Listing of preferred terms used for NNMQ allergic reactions (broad scope)

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Drug reaction with eosinophilia and systemic symptoms	10073508	Respiratory failure	10038695
Dyspnoea	10013968	Respiratory tract oedema	10070774
Ear swelling	10014025	Reversible airways obstruction	10062109
Eczema	10014184	Rhinitis allergic	10039085
Eczema infantile	10014198	Rhinitis perennial	10039094
Eczema nummular	10014201	Scleral oedema	10057431
Eczema vaccinatum	10066042	Scleritis allergic	10051126
Eczema vesicular	10058681	Scrotal oedema	10039755
Eczema weeping	10055182	Scrotal swelling	10039759
Encephalitis allergic	10056387	Seasonal allergy	10048908
Encephalopathy allergic	10014627	Sensation of foreign body	10061549
Endotracheal intubation	10067450	Septal panniculitis	10056876
Eosinophil count abnormal	10061125	Serum sickness	10040400
Eosinophil count increased	10014945	Serum sickness-like reaction	10040402
Eosinophil percentage abnormal	10058133	Shock	10040560
Eosinophil percentage increased	10052222	Shock symptom	10040581
Eosinophilia	10014950	Skin erosion	10040840
Eosinophilia myalgia syndrome	10014952	Skin exfoliation	10040844
Eosinophilic bronchitis	10065563	Skin necrosis	10040893
Eosinophilic granulomatosis with polyangiitis	10078117	Skin oedema	10058679
Eosinophilic oesophagitis	10064212	Skin reaction	10040914
Eosinophilic pneumonia	10014962	Skin swelling	10053262
Eosinophilic pneumonia acute	10052832	Skin test positive	10040934
Eosinophilic pneumonia chronic	10052833	Sneezing	10041232
Epidermal necrosis	10059284	Soft tissue swelling	10076991
Epidermolysis	10053177	Solar urticaria	10041307
Epidermolysis bullosa	10014989	Solvent sensitivity	10041316
Epiglottic oedema	10015029	Staphylococcal scalded skin syndrome	10041929
Erythema	10015150	Status asthmaticus	10041961
Erythema multiforme	10015218	Stevens-Johnson syndrome	10042033
Erythema nodosum	10015226	Stoma site hypersensitivity	10074509
Exfoliative rash	10064579	Stoma site rash	10059071
Eye allergy	10015907	Stomatitis	10042128
Eye oedema	10052139	Streptokinase antibody increased	10053797
Eye pruritus	10052140	Stridor	10042241
Eye swelling	10015967	Suffocation feeling	10042444
Eyelid oedema	10015993	Swelling	10042674
Face oedema	10016029	Swelling face	10042682
Fixed eruption	10016741	Swollen tongue	10042727
Flushing	10016825	Symmetrical drug-related intertriginous and flexural exanthema	10078325
Gastrointestinal oedema	10058061	Tachypnoea	10043089
Generalised erythema	10051576	Throat tightness	10043528
Generalised oedema	10018092	Tongue exfoliation	10064488
Genital rash	10018175	Tongue oedema	10043967
Genital swelling	10067639	Toxic epidermal necrolysis	10044223
Genital ulceration	10018180	Toxic skin eruption	10057970
Giant papillary conjunctivitis	10018258	Tracheal obstruction	10044291
Gingival oedema	10049305	Tracheal oedema	10044296
Gingival swelling	10018291	Tracheostomy	10044320
Gleich's syndrome	10066837	Transplantation associated food allergy	10075008
Grey syndrome neonatal	10018723	Type I hypersensitivity	10045240
HLA marker study positive	10067937	Type II hypersensitivity	10054000
HLA-B*1502 assay positive	10074771	Type III immune complex mediated reaction	10053614
HLA-B*5801 assay positive	10074774	Type IV hypersensitivity reaction	10053613
Haemolytic transfusion reaction	10067122	Upper airway obstruction	10067775

Listing of preferred terms used for NNMQ allergic reactions (broad scope)

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Haemorrhagic urticaria	10059499	Urticaria	10046735
Hand dermatitis	10058898	Urticaria cholinergic	10046740
Henoch-Schonlein purpura	10019617	Urticaria chronic	10052568
Henoch-Schonlein purpura nephritis	10069440	Urticaria contact	10046742
Heparin-induced thrombocytopenia	10062506	Urticaria papular	10046750
Hepatic congestion	10019645	Urticaria physical	10046751
Hepatojugular reflux	10051448	Urticaria pigmentosa	10046752
Hepatorenal failure	10019845	Urticaria vesiculosa	10046755
Hereditary angioedema	10019860	Urticarial vasculitis	10048820
Hypersensitivity	10020751	Vaccination site dermatitis	10069477
Hypersensitivity vasculitis	10020764	Vaccination site eczema	10076161
Hyperventilation	10020910	Vaccination site exfoliation	10069489
Hypoperfusion	10058558	Vaccination site hypersensitivity	10068880
Hypopharyngeal synechiae	10077469	Vaccination site photosensitivity reaction	10076186
Hypotension	10021097	Vaccination site rash	10069482
Idiopathic angioedema	10073257	Vaccination site recall reaction	10076188
Idiopathic urticaria	10021247	Vaccination site urticaria	10069622
Immediate post-injection reaction	10067142	Vaccination site vasculitis	10076191
Immune complex level increased	10064650	Vaccination site vesicles	10069623
Immune thrombocytopenic purpura	10074667	Vaginal exfoliation	10064483
Immune tolerance induction	10070581	Vaginal oedema	10063818
Immune-mediated adverse reaction	10077665	Vaginal ulceration	10046943
Immunoglobulins abnormal	10021497	Vasculitic rash	10047111
Immunoglobulins increased	10021500	Vessel puncture site rash	10077117
Immunology test abnormal	10061214	Vessel puncture site vesicles	10077813
Implant site dermatitis	10063855	Visceral oedema	10065768
Implant site hypersensitivity	10063858	Vulval oedema	10047763
Implant site photosensitivity	10073415	Vulval ulceration	10047768
Implant site rash	10063786	Vulvovaginal rash	10071588
Implant site urticaria	10063787	Vulvovaginal swelling	10071211
Incision site dermatitis	10073168	Vulvovaginal ulceration	10050181
Incision site rash	10073411	Wheezing	10047924

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87. SMQ「塞栓および血栓」に含まれる基本語一覧

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Acute aortic syndrome	10074337	Mesenteric vein thrombosis	10027402
Acute myocardial infarction	10000891	Mesenteric venous occlusion	10027403
Administration site thrombosis	10075968	Microembolism	10073734
Adrenal thrombosis	10075178	Monoparesis	10027925
Amaurosis	10001902	Monoplegia	10027926
Amaurosis fugax	10001903	Myocardial infarction	10028596
Angiogram abnormal	10060956	Myocardial necrosis	10028602
Angiogram cerebral abnormal	10052906	Obstetrical pulmonary embolism	10029925
Angiogram peripheral abnormal	10057517	Obstructive shock	10073708
Angioplasty	10002475	Ophthalmic vein thrombosis	10074349
Aortic bypass	10057617	Optic nerve infarction	10030936
Aortic embolus	10002897	Ovarian vein thrombosis	10072059
Aortic surgery	10061651	Paget-Schroetter syndrome	10050216
Aortic thrombosis	10002910	Pancreatic infarction	10068239
Aortogram abnormal	10057794	Papillary muscle infarction	10033697
Application site thrombosis	10076026	Paradoxical embolism	10066059
Arterectomy	10071026	Paraneoplastic thrombosis	10079251
Arterectomy with graft replacement	10003140	Paraparesis	10033885
Arterial bypass occlusion	10077766	Paraplegia	10033892
Arterial bypass operation	10056418	Paresis	10033985
Arterial bypass thrombosis	10077765	Pelvic venous thrombosis	10034272
Arterial graft	10061655	Penile artery occlusion	10068035
Arterial occlusive disease	10062599	Penile vein thrombosis	10034324
Arterial stent insertion	10061657	Percutaneous coronary intervention	10065608
Arterial therapeutic procedure	10052949	Peripheral arterial occlusive disease	10062585
Arterial thrombosis	10003178	Peripheral arterial reocclusion	10069379
Arteriogram abnormal	10061659	Peripheral artery angioplasty	10057518
Arteriogram carotid abnormal	10003195	Peripheral artery bypass	10072561
Arteriotomy	10078636	Peripheral artery occlusion	10057525
Arteriovenous fistula occlusion	10058562	Peripheral artery stent insertion	10072562
Arteriovenous fistula thrombosis	10003192	Peripheral artery thrombosis	10072564
Arteriovenous graft thrombosis	10053182	Peripheral embolism	10061340
Artificial blood vessel occlusion	10078895	Peripheral endarterectomy	10072560
Atherectomy	10063025	Peripheral revascularisation	10053351
Atherosclerotic plaque rupture	10076604	Phlebectomy	10048874
Atrial thrombosis	10048632	Pituitary infarction	10035092
Axillary vein thrombosis	10003880	Placental infarction	10064620
Basal ganglia infarction	10069020	Pneumatic compression therapy	10059829
Basal ganglia stroke	10071043	Popliteal artery entrapment syndrome	10071642
Basilar artery occlusion	10048963	Portal shunt procedure	10077479
Basilar artery thrombosis	10063093	Portal vein cavernous transformation	10073979
Blindness transient	10005184	Portal vein occlusion	10058989
Bone infarction	10049824	Portal vein thrombosis	10036206
Brachiocephalic artery occlusion	10069694	Portosplenomesenteric venous thrombosis	10077623
Brachiocephalic vein occlusion	10076837	Post procedural myocardial infarction	10066592
Brachiocephalic vein thrombosis	10063363	Post procedural pulmonary embolism	10063909
Brain stem embolism	10074422	Post procedural stroke	10066591
Brain stem infarction	10006147	Post thrombotic syndrome	10048591
Brain stem stroke	10068644	Postinfarction angina	10058144
Brain stem thrombosis	10062573	Postoperative thrombosis	10050902
Budd-Chiari syndrome	10006537	Postpartum thrombosis	10077022
Capsular warning syndrome	10067744	Postpartum venous thrombosis	10036300
Cardiac ventricular thrombosis	10053994	Precerebral artery occlusion	10036511
Carotid angioplasty	10071260	Precerebral artery thrombosis	10074717
Carotid arterial embolus	10007684	Profundaplasty	10078867

Listing of preferred terms used for SMQ embolic and thrombotic events

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Carotid artery bypass	10053003	Prosthetic vessel implantation	10068628
Carotid artery occlusion	10048964	Pulmonary artery occlusion	10078201
Carotid artery stent insertion	10066102	Pulmonary artery therapeutic procedure	10063731
Carotid artery thrombosis	10007688	Pulmonary artery thrombosis	10037340
Carotid endarterectomy	10007692	Pulmonary embolism	10037377
Catheter site thrombosis	10079523	Pulmonary endarterectomy	10072893
Catheterisation venous	10052698	Pulmonary infarction	10037410
Cavernous sinus thrombosis	10007830	Pulmonary microemboli	10037421
Central venous catheterisation	10053377	Pulmonary thrombosis	10037437
Cerebellar artery occlusion	10053633	Pulmonary vein occlusion	10068690
Cerebellar artery thrombosis	10008023	Pulmonary veno-occlusive disease	10037458
Cerebellar embolism	10067167	Pulmonary venous thrombosis	10037459
Cerebellar infarction	10008034	Quadriparesis	10049680
Cerebral artery embolism	10008088	Quadriplegia	10037714
Cerebral artery occlusion	10008089	Renal artery angioplasty	10057493
Cerebral artery thrombosis	10008092	Renal artery occlusion	10048988
Cerebral congestion	10076929	Renal artery thrombosis	10038380
Cerebral hypoperfusion	10065384	Renal embolism	10063544
Cerebral infarction	10008118	Renal infarct	10038470
Cerebral infarction foetal	10008119	Renal vascular thrombosis	10072226
Cerebral ischaemia	10008120	Renal vein embolism	10038547
Cerebral microembolism	10078311	Renal vein occlusion	10056293
Cerebral septic infarct	10070671	Renal vein thrombosis	10038548
Cerebral thrombosis	10008132	Retinal artery embolism	10038826
Cerebral vascular occlusion	10076895	Retinal artery occlusion	10038827
Cerebral venous thrombosis	10008138	Retinal artery thrombosis	10038831
Cerebrospinal thrombotic tamponade	10052173	Retinal infarction	10051742
Cerebrovascular accident	10008190	Retinal vascular thrombosis	10062108
Cerebrovascular accident prophylaxis	10049165	Retinal vein occlusion	10038907
Cerebrovascular disorder	10008196	Retinal vein thrombosis	10038908
Cerebrovascular insufficiency	10058842	SI QIII TIII pattern	10068479
Cerebrovascular operation	10051902	Shunt occlusion	10040621
Cerebrovascular stenosis	10061751	Shunt thrombosis	10059054
Choroidal infarction	10057403	Silent myocardial infarction	10049768
Coeliac artery occlusion	10069696	Spinal artery embolism	10049440
Collateral circulation	10069729	Spinal artery thrombosis	10071316
Compression garment application	10079209	Spinal cord infarction	10058571
Coronary angioplasty	10050329	Splenic artery thrombosis	10074600
Coronary arterial stent insertion	10052086	Splenic embolism	10068677
Coronary artery bypass	10011077	Splenic infarction	10041648
Coronary artery embolism	10011084	Splenic thrombosis	10074601
Coronary artery occlusion	10011086	Splenic vein occlusion	10068122
Coronary artery reocclusion	10053261	Splenic vein thrombosis	10041659
Coronary artery thrombosis	10011091	Stoma site thrombosis	10074515
Coronary bypass thrombosis	10059025	Stress cardiomyopathy	10066286
Coronary endarterectomy	10011101	Stroke in evolution	10059613
Coronary revascularisation	10049887	Subclavian artery embolism	10042332
Coronary vascular graft occlusion	10075162	Subclavian artery occlusion	10069695
Deep vein thrombosis	10051055	Subclavian artery thrombosis	10042334
Deep vein thrombosis postoperative	10066881	Subclavian vein occlusion	10079164
Device embolisation	10074896	Subclavian vein thrombosis	10049446
Device occlusion	10064685	Superior mesenteric artery syndrome	10054156
Device related thrombosis	10077455	Superior sagittal sinus thrombosis	10042567
Diplegia	10013033	Superior vena cava occlusion	10058988
Directional Doppler flow tests abnormal	10013048	Superior vena cava syndrome	10042569

Listing of preferred terms used for SMQ embolic and thrombotic events

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Disseminated intravascular coagulation	10013442	Surgical vascular shunt	10058408
Disseminated intravascular coagulation in newborn	10013443	Testicular infarction	10043337
Embolia cutis medicamentosa	10058729	Thalamic infarction	10064961
Embolic cerebral infarction	10060839	Thrombectomy	10043530
Embolic pneumonia	10065680	Thromboangiitis obliterans	10043540
Embolic stroke	10014498	Thromboembolectomy	10064958
Embolism	10061169	Thrombolysis	10043568
Embolism arterial	10014513	Thrombophlebitis	10043570
Embolism venous	10014522	Thrombophlebitis migrans	10043581
Endarterectomy	10014648	Thrombophlebitis neonatal	10043586
Femoral artery embolism	10068365	Thrombophlebitis superficial	10043595
Foetal cerebrovascular disorder	10053601	Thrombosed varicose vein	10043605
Graft thrombosis	10051269	Thrombosis	10043607
Haemorrhagic cerebral infarction	10019005	Thrombosis corpora cavernosa	10067270
Haemorrhagic infarction	10019013	Thrombosis in device	10062546
Haemorrhagic stroke	10019016	Thrombosis mesenteric vessel	10043626
Haemorrhagic transformation stroke	10055677	Thrombosis prophylaxis	10043634
Haemorrhoids thrombosed	10019023	Thrombotic cerebral infarction	10067347
Hemiparesis	10019465	Thrombotic microangiopathy	10043645
Hemiplegia	10019468	Thrombotic stroke	10043647
Heparin-induced thrombocytopenia	10062506	Thrombotic thrombocytopenic purpura	10043648
Hepatic artery embolism	10019635	Thyroid infarction	10043742
Hepatic artery occlusion	10051991	Transient ischaemic attack	10044390
Hepatic artery thrombosis	10019636	Transverse sinus thrombosis	10044457
Hepatic infarction	10019680	Truncus coeliacus thrombosis	10062363
Hepatic vascular thrombosis	10074494	Tumour embolism	10045168
Hepatic vein embolism	10078810	Tumour thrombosis	10068067
Hepatic vein occlusion	10058991	Ultrasonic angiogram abnormal	10061604
Hepatic vein thrombosis	10019713	Ultrasound Doppler abnormal	10045413
Homans' sign positive	10051031	Umbilical cord occlusion	10076714
Hypothenar hammer syndrome	10063518	Umbilical cord thrombosis	10071652
Iliac artery embolism	10021338	Vaccination site thrombosis	10076190
Iliac artery occlusion	10064601	Vascular access site thrombosis	10078675
Iliac vein occlusion	10058992	Vascular graft	10067740
Implant site thrombosis	10063868	Vascular graft occlusion	10049060
Incision site vessel occlusion	10076839	Vascular graft thrombosis	10069922
Infarction	10061216	Vascular operation	10049071
Inferior vena cava syndrome	10070911	Vascular pseudoaneurysm thrombosis	10078269
Inferior vena caval occlusion	10058987	Vascular stent insertion	10063382
Infusion site thrombosis	10065489	Vascular stent occlusion	10077143
Injection site thrombosis	10022104	Vascular stent thrombosis	10063934
Inner ear infarction	10070754	Vasodilation procedure	10058794
Instillation site thrombosis	10073625	Vena cava embolism	10047193
Intestinal infarction	10022657	Vena cava filter insertion	10048932
Intra-aortic balloon placement	10052989	Vena cava filter removal	10074397
Intracardiac mass	10066087	Vena cava thrombosis	10047195
Intracardiac thrombus	10048620	Venogram abnormal	10047209
Intracranial venous sinus thrombosis	10061251	Venoocclusive disease	10062173
Intraoperative cerebral artery occlusion	10056382	Venoocclusive liver disease	10047216
Ischaemic cerebral infarction	10060840	Venous angioplasty	10077826
Ischaemic stroke	10061256	Venous occlusion	10058990
Jugular vein occlusion	10076835	Venous operation	10062175
Jugular vein thrombosis	10023237	Venous recanalisation	10068605
Lacunar infarction	10051078	Venous repair	10052964
Left atrial appendage occlusion	10075476	Venous stent insertion	10063389
Leriche syndrome	10024242	Venous thrombosis	10047249

Listing of preferred terms used for SMQ embolic and thrombotic events

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Mahler sign	10075428	Venous thrombosis in pregnancy	10067030
May-Thurner syndrome	10069727	Venous thrombosis limb	10061408
Medical device site thrombosis	10076145	Venous thrombosis neonatal	10064602
Mesenteric arterial occlusion	10027394	Vertebral artery occlusion	10048965
Mesenteric arteriosclerosis	10065560	Vertebral artery thrombosis	10057777
Mesenteric artery embolism	10027395	Vessel puncture site occlusion	10076838
Mesenteric artery stenosis	10027396	Vessel puncture site thrombosis	10070649
Mesenteric artery stent insertion	10071261	Visceral venous thrombosis	10077829
Mesenteric artery thrombosis	10027397	Visual acuity reduced transiently	10047532
Mesenteric vascular insufficiency	10027401	Visual midline shift syndrome	10066856
Mesenteric vascular occlusion	10074583		

SMQ: Standardised MedDRA querie
SMQ code: 20000081
MedDRA version: 20.0

88. NNMQ「稀な有害事象」に含まれる基本語一覧

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
11-beta-hydroxylase deficiency	10000002	Hand-foot-genital syndrome	10072361
17,20-desmolase deficiency	10000013	Harlequin foetus	10019163
17-alpha-hydroxylase deficiency	10000014	Hartnup disease	10019165
18q minus syndrome	10068533	Heart alternation	10058155
2-Hydroxyglutaric aciduria	10078971	Heart block congenital	10019263
20,22-desmolase deficiency	10000020	Heart disease congenital	10019273
21-hydroxylase deficiency	10000021	Heart rate abnormal	10019300
3-hydroxyacetyl-coenzyme A dehydrogenase deficiency	10072273	Heart rate decreased	10019301
5-alpha-reductase deficiency	10000029	Heart rate increased	10019303
ABO haemolytic disease of newborn	10000205	Heart rate irregular	10019304
Aase syndrome	10063429	Hemihypertrophy	10019463
Abdominal transposition	10000098	Hemimegalencephaly	10078100
Abdominal wall anomaly	10000101	Hemivertebra	10019477
Abnormal palmar/plantar creases	10000162	Henoch-Schonlein purpura nephritis	10069440
Acardia	10075721	Hepatectomy	10061997
Accelerated idioventricular rhythm	10049003	Hepatic arteriovenous malformation	10019633
Accessory auricle	10000361	Hepatic atrophy	10019637
Accessory breast	10049786	Hepatic calcification	10065274
Accessory cardiac pathway	10067618	Hepatic cirrhosis	10019641
Accessory carpal bone	10000362	Hepatic encephalopathy	10019660
Accessory kidney	10048781	Hepatic encephalopathy prophylaxis	10066599
Accessory liver lobe	10052752	Hepatic failure	10019663
Accessory muscle	10000364	Hepatic fibrosis	10019668
Accessory navicular syndrome	10062626	Hepatic hydrothorax	10067365
Accessory salivary gland	10000368	Hepatic infiltration eosinophilic	10064668
Accessory spleen	10068059	Hepatic lesion	10061998
Acetylcholinesterase deficiency	10071435	Hepatic necrosis	10019692
Achromotrichia congenital	10049864	Hepatic steato-fibrosis	10077215
Acquired amegakaryocytic thrombocytopenia	10076747	Hepatic steatosis	10019708
Acral peeling skin syndrome	10078538	Hepatitis	10019717
Acrodermatitis enteropathica	10000596	Hepatitis acute	10019727
Acrokeratosis verruciformis	10069445	Hepatitis cholestatic	10019754
Activated PI3 kinase delta syndrome	10078281	Hepatitis chronic active	10019755
Acute focal bacterial nephritis	10071736	Hepatitis chronic persistent	10019759
Acute generalised exanthematous pustulosis	10048799	Hepatitis fulminant	10019772
Acute graft versus host disease in liver	10066263	Hepatitis toxic	10019795
Acute hepatic failure	10000804	Hepatitis virus-associated nephropathy	10068610
Acute kidney injury	10069339	Hepato-lenticular degeneration	10019819
Acute motor axonal neuropathy	10076658	Hepatobiliary disease	10062000
Acute motor-sensory axonal neuropathy	10076657	Hepatocellular foamy cell syndrome	10053244
Acute on chronic liver failure	10077305	Hepatocellular injury	10019837
Acute phosphate nephropathy	10069688	Hepatopulmonary syndrome	10052274
Acute prerenal failure	10001017	Hepatorenal failure	10019845
Acute yellow liver atrophy	10070815	Hepatorenal syndrome	10019846
Adactyly	10049207	Hepatotoxicity	10019851
Adams-Oliver syndrome	10079369	Hereditary angioedema	10019860
Adams-Stokes syndrome	10001115	Hereditary areflexic dystasia	10063449
Adenine phosphoribosyl transferase deficiency	10072609	Hereditary cerebral degeneration	10061204
Adenomatous polyposis coli	10056981	Hereditary choroidal dystrophy	10019864
Adrenal insufficiency neonatal	10001368	Hereditary disorder	10061205

Listing of preferred terms used for NNMQ rare events

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Adrenogenital syndrome	10061630	Hereditary fructose intolerance	10019878
Adrenoleukodystrophy	10051260	Hereditary haemochromatosis	10057873
Adult polyglucosan body disease	10077946	Hereditary haemolytic anaemia	10060893
Aglossia	10001501	Hereditary haemorrhagic telangiectasia	10019883
Agonal rhythm	10054015	Hereditary hypophosphataemic rickets	10077943
Agranulocytosis	10001507	Hereditary leiomyomatosis renal cell carcinoma	10067944
Aicardi's syndrome	10054935	Hereditary motor and sensory neuropathy	10077306
Alagille syndrome	10053870	Hereditary motor neurone disease	10071328
Albinism	10001557	Hereditary multiple osteochondromas	10079019
Albright's disease	10052032	Hereditary neuropathic amyloidosis	10019889
Alcoholic pancreatitis	10056977	Hereditary neuropathy with liability to pressure palsies	10069382
Alcoholic pancreopathy	10076384	Hereditary non-polyposis colorectal cancer syndrome	10051922
Alkaptonuria	10001689	Hereditary optic atrophy	10019895
Allan-Herndon-Dudley syndrome	10078821	Hereditary palmoplantar keratoderma	10072537
Allergic hepatitis	10071198	Hereditary pancreatitis	10056976
Alpers' disease	10062943	Hereditary papillary renal carcinoma	10067943
Alpha-1 anti-trypsin deficiency	10001806	Hereditary retinal dystrophy	10019899
Alport's syndrome	10001843	Hereditary sideroblastic anaemia	10019902
Alstroem syndrome	10068783	Hereditary spastic paraplegia	10019903
Alternating hemiplegia of childhood	10077948	Hereditary spherocytosis	10019904
Alveolar capillary dysplasia	10077023	Hereditary stomatocytosis	10053589
Amblyopia congenital	10001908	Hermansky-Pudlak syndrome	10071775
Amegakaryocytic thrombocytopenia	10076744	Hermaphroditism	10019906
Aminoaciduria	10001939	Hernia congenital	10019912
Amniotic band syndrome	10064100	Heterochromia iridis	10066799
Amyotrophic lateral sclerosis gene carrier	10052653	Heterotaxia	10067265
Anal atresia	10002120	Hexokinase deficiency anaemia	10020022
Anaphylactic reaction	10002198	High arched palate	10020046
Anaphylactic shock	10002199	Hollow visceral myopathy	10060811
Anaphylactic transfusion reaction	10067113	Holoprosencephaly	10056304
Anaphylactoid reaction	10002216	Holt-Oram syndrome	10050469
Anaphylactoid shock	10063119	Homocystinaemia	10048707
Androgen insensitivity syndrome	10056292	Homocystinuria	10020365
Anencephaly	10002320	Hooded prepuce	10072135
Angelman's syndrome	10049004	Huntington's disease	10070668
Angioedema	10002424	Hydranencephaly	10073472
Angiotensin converting enzyme inhibitor foetopathy	10051098	Hydrocele	10020488
Aniridia	10002532	Hydronephrosis	10020524
Ankyloglossia congenital	10049244	Hydroureter	10020533
Annular pancreas	10071757	Hydroxyprolinaemia	10053148
Anodontia	10002583	Hyper IgD syndrome	10072010
Anomalous arrangement of pancreaticobiliary duct	10064902	Hyper IgE syndrome	10051040
Anomalous atrioventricular excitation	10002611	Hyper IgM syndrome	10066130

Listing of preferred terms used for NNMQ rare events

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Anomalous pulmonary venous connection	10058079	Hyperbilirubinaemia	10020578
Anomaly of external ear congenital	10062339	Hyperexplexia	10058271
Anomaly of middle ear congenital	10060957	Hyperinsulinism syndrome	10077858
Anomaly of orbit, congenital	10002633	Hypermethioninaemia	10051245
Anophthalmos	10002640	Hypermethioniuria	10051231
Anorchism	10002641	Hyperprolinaemia	10058509
Anorectal agenesis	10056271	Hypersplenism congenital	10049282
Anotia	10002654	Hypertelorism of orbit	10020771
Anterior chamber cleavage syndrome	10059199	Hyperthermia malignant	10020844
Anterior displaced anus	10071651	Hypertrophic cardiomyopathy	10020871
Antithrombin III deficiency	10002832	Hypocalvaria	10073670
Anuria	10002847	Hypochondroplasia	10020967
Aorta hypoplasia	10049209	Hypodontia	10055001
Aortic valve atresia	10066801	Hypomelanosis of Ito	10075301
Aorticopulmonary septal defect	10063732	Hyponatriuria	10077515
Apert's syndrome	10002943	Hypophosphatasia	10049933
Aphakia congenital	10002947	Hypopituitarism foetal	10021068
Aplasia	10002961	Hypoplastic left heart syndrome	10021076
Aplasia cutis congenita	10002963	Hypoplastic nasal cartilage	10074970
Aplastic anaemia	10002967	Hypoplastic right heart syndrome	10064962
Arachnodactyly	10063847	Hypospadias	10021093
Arcuate foramen	10067850	Hypotelorism of orbit	10057855
Arginase deficiency	10062695	Hypothalamic hamartoma	10078217
Argininosuccinate lyase deficiency	10058299	Hypoxanthine-guanine phosphoribosyl transferase deficiency	10075774
Argininosuccinate synthetase deficiency	10058298	Ichthyosis	10021198
Arnold-Chiari malformation	10003101	Icterus index increased	10021209
Arrhythmia	10003119	Idiopathic angioedema	10073257
Arrhythmia neonatal	10003124	Idiopathic neutropenia	10051645
Arrhythmia supraventricular	10003130	IgA nephropathy	10021263
Arrhythmogenic right ventricular dysplasia	10058093	IgM nephropathy	10077209
Arteriovenous malformation	10003193	Ileal atresia	10021298
Ascites	10003445	Immunodeficiency congenital	10021450
Ash leaf macule	10076367	Immunotactoid glomerulonephritis	10067871
Aspartate-glutamate-transporter deficiency	10079140	Imperforate hymen	10021529
Aspartylglucosaminuria	10068220	Imperforate oesophagus	10021530
Asphyxiating thoracic dystrophy	10057621	Inborn error in primary bile acid synthesis	10070882
Aspiration bone marrow abnormal	10003506	Inborn error of bilirubin metabolism	10062017
Asplenia	10053622	Inborn error of lipid metabolism	10072272
Asterixis	10003547	Inborn error of metabolism	10062018
Asymptomatic gene carrier	10061662	Infantile cortical hyperostosis	10073206
Ataxia telangiectasia	10003594	Infantile genetic agranulocytosis	10052210
Atrial conduction time prolongation	10064191	Infantile septic granulomatosis	10048708
Atrial fibrillation	10003658	Inferior vena cava syndrome	10070911
Atrial flutter	10003662	Inherited cardiac conduction disorder	10070294
Atrial parasystole	10071666	Iniencephaly	10022034
Atrial septal defect	10003664	Interferon gamma receptor deficiency	10057605
Atrial tachycardia	10003668	Interruption of aortic arch	10022599

Listing of preferred terms used for NNMQ rare events

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Atrioventricular block	10003671	Intestinal angioedema	10076229
Atrioventricular block complete	10003673	Intestinal atresia	10062022
Atrioventricular block first degree	10003674	Intestinal malrotation	10064024
Atrioventricular block second degree	10003677	Intestinal neuronal dysplasia	10073659
Atrioventricular conduction time shortened	10068180	Intestinal sepsis	10075622
Atrioventricular dissociation	10069571	Intestinal transposition	10022712
Atrioventricular node dispersion	10077893	Intestinal varices	10071502
Atrioventricular septal defect	10063836	Intestinal varices haemorrhage	10078058
Auditory neuropathy spectrum disorder	10072198	Intracranial arterial fenestration	10077285
Autoimmune aplastic anaemia	10071576	Intracranial lipoma	10072288
Autoimmune hepatitis	10003827	Iris coloboma	10052642
Autoimmune lymphoproliferative syndrome	10069521	Ischaemic hepatitis	10023025
Autoimmune nephritis	10077087	Ischaemic pancreatitis	10066127
Autoimmune pancreatitis	10069002	Jaundice	10023126
Autosomal chromosome anomaly	10060975	Jaundice cholestatic	10023129
Azotaemia	10003885	Jaundice hepatocellular	10023136
Azygos lobe	10069490	Johanson-Blizzard syndrome	10074947
B-lymphocyte abnormalities	10053775	Joubert syndrome	10078574
B-lymphocyte count abnormal	10078589	Junctional ectopic tachycardia	10074640
B-lymphocyte count decreased	10051313	Juvenile Paget's disease	10078977
Bacterascites	10068547	Kabuki make-up syndrome	10063935
Baltic myoclonic epilepsy	10054895	Kaufman-McKusick syndrome	10052312
Band neutrophil count decreased	10057950	Kearns-Sayre syndrome	10048804
Band neutrophil percentage decreased	10059130	Kenny-Caffey syndrome	10073228
Baraitser Rodeck Garner syndrome	10076038	Keratitis-ichthyosis-deafness syndrome	10048786
Barakat syndrome	10075281	Keratolysis exfoliativa congenital	10052290
Barth syndrome	10078537	Keratosis follicular	10023369
Bartter's syndrome	10050839	Kidney duplex	10023416
Basal cell naevus syndrome	10062804	Kidney malformation	10023430
Baseline foetal heart rate variability disorder	10074638	Kidney malrotation	10067877
Basophil count abnormal	10060978	Kimmerle's anomaly	10076416
Basophil count decreased	10004167	Kinematic imbalances due to suboccipital strain	10062992
Basophil percentage decreased	10052219	Kleefstra syndrome	10079365
Basophilopenia	10075813	Klinefelter's syndrome	10023463
Becker's muscular dystrophy	10059117	Klippel-Feil syndrome	10023464
Beckwith-Wiedemann syndrome	10050344	Klippel-Trenaunay syndrome	10051452
Benign congenital hypotonia	10051900	Kounis syndrome	10069167
Benign familial haematuria	10060876	Krabbe's disease	10023492
Benign familial neonatal convulsions	10067866	Kyphosis congenital	10048576
Benign familial pemphigus	10004265	LDLR mutation	10075640
Berdon's syndrome	10064596	Labial tie	10076772
Beta ketothiolase deficiency	10067728	Lacrimal punctum agenesis	10023636
Bezold-Jarisch reflex	10076999	Laevocardia	10071015
Bickerstaff's encephalitis	10076985	Lafora's myoclonic epilepsy	10054030
Bicuspid aortic valve	10004552	Lamin A/C gene mutation	10075979
Bicuspid pulmonary valve	10063730	Langer-Giedion syndrome	10050638
Bicytopenia	10058956	Laron syndrome	10075492
Bifascicular block	10057393	Larsen syndrome	10073856
Biliary cirrhosis	10004659	Laryngeal cleft	10069115
Biliary cirrhosis primary	10004661	Laryngeal oedema	10023845
Biliary fibrosis	10004664	Laryngeal web	10023871
Biliary hamartoma	10074610	Laryngo-onycho-cutaneous syndrome	10062987

Listing of preferred terms used for NNMQ rare events

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Bilirubin excretion disorder	10061009	Laryngocele	10023885
Biopsy bone marrow abnormal	10004738	Laryngomalacia	10060786
Biotinidase deficiency	10071434	Laryngotracheal oedema	10023893
Birt-Hogg-Dube syndrome	10067736	Laurence-Moon-Bardet-Biedl syndrome	10056715
Birth mark	10004950	Leber's congenital amaurosis	10070667
Bladder agenesis	10056655	Lecithin-cholesterol acyltransferase deficiency	10077917
Blau syndrome	10071755	Left ventricle outflow tract obstruction	10065930
Blepharophimosis congenital	10049241	Left-to-right cardiac shunt	10077834
Blindness congenital	10005176	Lenegre's disease	10071710
Bloch-Sulzberger syndrome	10077624	Lens abnormality, congenital	10024202
Blood count abnormal	10064198	Leukodystrophy	10024381
Blood disorder	10061590	Leukopenia	10024384
Blood incompatibility haemolytic anaemia of newborn	10056369	Leukopenia neonatal	10050504
Bloom syndrome	10073032	Li-Fraumeni syndrome	10066795
Bone marrow disorder	10061729	Lichen spinulosus	10024436
Bone marrow failure	10065553	Liddle's syndrome	10052313
Bone marrow infiltration	10075173	Limb hypoplasia congenital	10048575
Bone marrow myelogram abnormal	10057528	Limb malformation	10024500
Bone marrow necrosis	10058822	Limb reduction defect	10024503
Bone marrow toxicity	10051779	Lip oedema	10024558
Brachycephaly	10053682	Lip swelling	10024570
Brachydactyly	10072883	Lipid proteinosis	10051661
Bradyarrhythmia	10049765	Lipidosis	10024585
Bradycardia	10006093	Lipodermoid tumour	10073484
Bradycardia foetal	10006094	Lipomeningocele	10050084
Bradycardia neonatal	10056471	Lissencephaly	10048911
Brain malformation	10048409	Liver and small intestine transplant	10052280
Branchial cleft sinus	10006162	Liver dialysis	10076640
Branchial cyst	10006164	Liver disorder	10024670
Branchio-oto-renal syndrome	10071135	Liver injury	10067125
Branchiogenic syndrome	10058169	Liver operation	10062040
Breast malformation	10006271	Liver sarcoidosis	10068664
Bronchogenic cyst	10064585	Liver transplant	10024714
Brugada syndrome	10059027	Long QT syndrome	10024803
Bruton's agammaglobulinaemia	10060360	Long QT syndrome congenital	10057926
Bulbospinal muscular atrophy congenital	10068597	Long-chain acyl-coenzyme A dehydrogenase deficiency	10072653
Bundle branch block	10006578	Loss of consciousness	10024855
Bundle branch block bilateral	10006579	Low set ears	10024929
Bundle branch block left	10006580	Lown-Ganong-Levine syndrome	10024984
Bundle branch block right	10006582	Lowry-Wood syndrome	10062600
Buried penis syndrome	10067131	Lumbarisation	10063410
C3 glomerulopathy	10077827	Lupoid hepatic cirrhosis	10025129
CANDLE syndrome	10073960	Lupus hepatitis	10067737
CHARGE syndrome	10064063	Lupus nephritis	10025140
Camptodactyly congenital	10049028	Lupus pancreatitis	10067750
Camptomelia	10078297	Lymphangiectasia intestinal congenital	10054722
Canavan disease	10067608	Lymphocyte count abnormal	10025252
Cancer gene carrier	10052648	Lymphocyte count decreased	10025256
Carbamoyl phosphate synthetase deficiency	10058297	Lymphocyte percentage abnormal	10063337
Carbohydrate metabolism disorder	10061023	Lymphocyte percentage decreased	10052231
Carcinogenic effect in offspring	10007268	Lymphocytopenia neonatal	10025279
Cardiac arrest	10007515	Lymphopenia	10025327
Cardiac arrest neonatal	10007516	Lysinuric protein intolerance	10058300
Cardiac death	10049993	Lysosomal acid lipase deficiency	10077267
Cardiac fibrillation	10061592	MELAS syndrome	10053872
Cardiac flutter	10052840	MLASA syndrome	10078801

Listing of preferred terms used for NNMQ rare events

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Cardiac lymphangioma	10055010	MYH9-related disease	10079437
Cardiac malposition	10007585	Macrocephaly	10050183
Cardiac septal defect	10064021	Macrocheilia	10025378
Cardiac telemetry abnormal	10053450	Macrocornea	10059253
Cardio-respiratory arrest	10007617	Macrodactyly	10025386
Cardio-respiratory arrest neonatal	10007618	Macrogenia	10025387
Carney complex	10076601	Macroglossia	10025391
Carnitine palmitoyltransferase deficiency	10050215	Macrognathia	10052658
Carnitine-acylcarnitine translocase deficiency	10078729	Macrostomia	10025395
Carpus curvus	10007700	Macrotia	10025396
Cartilage-hair hypoplasia	10069596	Macular dystrophy congenital	10025412
Cataract congenital	10007747	Majeed's syndrome	10072223
Caudal regression syndrome	10059387	Malformation biliary	10025523
Central bradycardia	10078310	Malformation venous	10025532
Central core disease	10057620	Mandibulofacial dysostosis	10051456
Central nervous system dermoid tumour	10007942	Maple syrup disease	10026817
Cerebellar dysplasia	10072942	Marcus Gunn syndrome	10064583
Cerebellar hypoplasia	10008033	Marfan's syndrome	10026829
Cerebral arteriovenous malformation haemorrhagic	10008086	Maxillonasal dysplasia	10075843
Cerebral atrophy congenital	10052236	Mayer-Rokitansky-Kuster-Hauser syndrome	10065148
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy	10065551	Medium-chain acyl-coenzyme A dehydrogenase deficiency	10072654
Cerebral dysgenesis	10056467	Megakaryocytes decreased	10027119
Cerebral palsy	10008129	Meier-Gorlin syndrome	10070612
Cerebrohepatorenal syndrome	10053684	Melkersson-Rosenthal syndrome	10027166
Cerebrovascular arteriovenous malformation	10056371	Membranous lipodystrophy	10065127
Cervical auricle	10008227	Meningocele	10027266
Cervical rib	10008299	Meningomyelocele	10027287
Chediak-Higashi syndrome	10008415	Menkes' syndrome	10027294
Chiari network	10069393	Mesangioproliferative glomerulonephritis	10066453
Chimerism	10068051	Mesenteric fibrosis	10027398
Choanal atresia	10008587	Mesoblastic nephroma	10070665
Choanal stenosis	10074053	Mesonephric duct cyst	10027405
Cholaemia	10048611	Metabolic myopathy	10068836
Cholangiectasis congenital	10053630	Metachromatic leukodystrophy	10067609
Cholangitis	10008604	Metamyelocyte count decreased	10050984
Choledochal cyst	10008625	Metaphyseal dysplasia	10066147
Cholestasis	10008635	Metatarsus primus varus	10027489
Cholestatic liver injury	10067969	Methylenetetrahydrofolate reductase deficiency	10070309
Cholestatic pruritus	10064190	Methylenetetrahydrofolate reductase gene mutation	10074753
Chondrodystrophy	10008723	Methylmalonic aciduria	10059521
Chondroectodermal dysplasia	10008724	Mevalonate kinase deficiency	10072221
Chordee	10008746	Mevalonic aciduria	10072219
Chorioretinal degeneration congenital	10008763	Microcephaly	10027534
Choroidal coloboma	10057402	Microcheilia	10027535
Chromosomal deletion	10061764	Microcolon	10073456
Chromosomal mutation	10061765	Microcornea	10057414
Chronic autoimmune glomerulonephritis	10073016	Microencephaly	10068320
Chronic graft versus host disease in liver	10072160	Microgenia	10027541
Chronic granulomatous disease	10008906	Microglossia	10027542
Chronic hepatic failure	10057573	Micrognathia	10027543

Listing of preferred terms used for NNMQ rare events

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Chronic hepatitis	10008909	Micropenis	10071706
Chronic infantile neurological cutaneous and articular syndrome	10064568	Microphthalmos	10027548
Chronic inflammatory demyelinating polyradiculoneuropathy	10057645	Microscopic polyangiitis	10063344
Chronotropic incompetence	10068627	Microstomia	10027553
Circulatory collapse	10009192	Microtia	10027555
Circumoral oedema	10052250	Microvillous inclusion disease	10068494
Citrate transporter deficiency	10077947	Miller Fisher syndrome	10049567
Cleft foot	10075491	Minimal hepatic encephalopathy	10076204
Cleft lip	10009259	Mismatch repair cancer syndrome	10077888
Cleft lip and palate	10009260	Mitochondrial DNA deletion	10051403
Cleft palate	10009269	Mitochondrial DNA depletion	10059396
Cleft uvula	10053507	Mitochondrial DNA duplication	10052640
Cleidocranial dysostosis	10075994	Mitochondrial DNA mutation	10052641
Clinodactyly	10058668	Mitochondrial encephalomyopathy	10058799
Cloacal exstrophy	10067424	Mitochondrial enzyme deficiency	10067729
Clostridial infection	10061043	Mitochondrial hepatopathy	10062938
Clostridial sepsis	10078496	Mitochondrial myopathy	10027710
Clostridium bacteraemia	10058852	Mitochondrial neurogastrointestinal encephalopathy	10065271
Clostridium colitis	10058305	Mitral valve atresia	10066800
Clostridium difficile colitis	10009657	Mitral valve hypoplasia	10049211
Clostridium difficile infection	10054236	Mittendorf dot	10076031
Clostridium test positive	10070027	Mixed liver injury	10066758
Coagulation factor mutation	10065442	Mobile caecum syndrome	10074307
Coarctation of the aorta	10009807	Moebius II syndrome	10027802
Cobb syndrome	10068841	Molybdenum cofactor deficiency	10069687
Cockayne's syndrome	10009835	Monoblast count decreased	10058772
Cohen syndrome	10049066	Monocyte count abnormal	10061293
Collodion baby	10009926	Monocyte count decreased	10027878
Coloboma	10009934	Monocyte percentage decreased	10052229
Colour blindness	10010050	Monocytopenia	10027905
Coma hepatic	10010075	Monopodia	10049214
Combined immunodeficiency	10010099	Morning glory syndrome	10027974
Complement deficiency disease	10075551	Morton's syndrome	10079320
Conduction disorder	10010276	Mosaicism	10068052
Congenital Eustachian tube anomaly	10062331	Mount-Reback syndrome	10065658
Congenital HIV infection	10010504	Mouth swelling	10075203
Congenital Horner's syndrome	10074554	Muckle-Wells syndrome	10064569
Congenital abdominal hernia	10067183	Mucolipidosis	10072939
Congenital absence of bile ducts	10010317	Mucolipidosis type I	10072927
Congenital absence of cranial vault	10010318	Mucolipidosis type II	10072928
Congenital absence of vertebra	10010320	Mucolipidosis type III	10072929
Congenital acrochordon	10050730	Mucolipidosis type IV	10072930
Congenital adrenal gland hypoplasia	10049057	Mucopolysaccharidosis	10028093
Congenital anaemia	10010329	Mucopolysaccharidosis I	10056886
Congenital androgen deficiency	10063469	Mucopolysaccharidosis II	10056889
Congenital anomalies of ear ossicles	10010341	Mucopolysaccharidosis III	10056890
Congenital anomaly	10010356	Mucopolysaccharidosis IV	10028095
Congenital anomaly in offspring	10063726	Mucopolysaccharidosis V	10056891
Congenital anomaly of adrenal gland	10062341	Mucopolysaccharidosis VI	10056892

Listing of preferred terms used for NNMQ rare events

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Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Congenital anomaly of inner ear	10062340	Mucopolysaccharidosis VII	10056893
Congenital aortic anomaly	10061052	Muir-Torre syndrome	10063042
Congenital aortic atresia	10010368	Multiple carboxylase deficiency	10028176
Congenital aortic dilatation	10058150	Multiple cardiac defects	10028178
Congenital aortic stenosis	10010369	Multiple congenital abnormalities	10028182
Congenital aortic valve incompetence	10010370	Multiple cutaneous and uterine leiomyomatosis	10077859
Congenital aortic valve stenosis	10010371	Multiple endocrine neoplasia	10051747
Congenital aplastic anaemia	10053138	Multiple endocrine neoplasia Type 1	10073150
Congenital aqueductal stenosis	10066084	Multiple endocrine neoplasia Type 2	10073149
Congenital arterial malformation	10062325	Multiple endocrine neoplasia Type 2A	10073148
Congenital arteriovenous fistula	10010374	Multiple endocrine neoplasia Type 2B	10073151
Congenital astigmatism	10074992	Multiple epiphyseal dysplasia	10028197
Congenital aural fistula	10054215	Multiple gastrointestinal atresias	10028210
Congenital benign neoplasm	10073493	Multiple lentigines syndrome	10062901
Congenital bladder anomaly	10061053	Multiple organ dysfunction syndrome	10077361
Congenital bladder diverticulum	10010381	Muscular dystrophy	10028356
Congenital bladder neck obstruction	10010382	Mutagenic effect	10028400
Congenital bowing of long bones	10054064	Myeloblast count decreased	10050961
Congenital brain damage	10010390	Myeloblast percentage decreased	10052225
Congenital bronchiectasis	10010391	Myelocyte count decreased	10050986
Congenital bronchomalacia	10010392	Myelocyte percentage decreased	10052227
Congenital calyceal diverticulum	10057510	Myelodysplastic syndrome	10028533
Congenital cardiovascular anomaly	10061054	Myelodysplastic syndrome transformation	10067387
Congenital carnitine deficiency	10062698	Myelofibrosis	10028537
Congenital central diabetes insipidus	10073008	Myeloid maturation arrest	10028560
Congenital central hypoventilation syndrome	10066131	Myeloid metaplasia	10028561
Congenital central nervous system anomaly	10010411	Myeloperoxidase deficiency	10074767
Congenital cerebellar agenesis	10048784	Myocardial bridging	10052289
Congenital cerebral cyst	10054954	Myoclonic epilepsy and ragged-red fibres	10069825
Congenital cerebral haemangioma	10048924	Myotonia congenita	10028655
Congenital cerebrovascular anomaly	10062327	Myotonic dystrophy	10068871
Congenital choroid plexus cyst	10048785	N-acetylglutamate synthase deficiency	10071092
Congenital choroidal anomaly	10057886	Naevus anaemicus	10069365
Congenital chylothorax	10078770	Naevus flammeus	10067193
Congenital clavicular agenesis	10010416	Naevus spider congenital	10050896
Congenital claw toe	10010417	Nail-patella syndrome	10063431
Congenital cleft hand	10010418	Nasopharyngeal atresia	10069701
Congenital coagulopathy	10063563	Neonatal alloimmune thrombocytopenia	10075149
Congenital condyloma	10066944	Neonatal anuria	10049778
Congenital corneal anomaly	10061059	Neonatal haemochromatosis	10078355

Listing of preferred terms used for NNMQ rare events

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Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Congenital coronary artery malformation	10061060	Neonatal leukaemia	10028958
Congenital cranial nerve paralysis	10069774	Neonatal lupus erythematosus	10057887
Congenital cutis laxa	10057042	Neonatal tachycardia	10049775
Congenital cyst	10062328	Nephritic syndrome	10065673
Congenital cystic disease of liver	10010427	Nephritis	10029117
Congenital cystic kidney disease	10010428	Nephritis allergic	10029120
Congenital cystic lung	10010429	Nephritis haemorrhagic	10029132
Congenital cytomegalovirus infection	10010430	Nephritis radiation	10029140
Congenital deformity of clavicle	10010434	Nephropathy toxic	10029155
Congenital dermal sinus	10048728	Nephrotic syndrome	10029164
Congenital diaphragmatic anomaly	10061061	Netherton's syndrome	10062909
Congenital diaphragmatic eventration	10010438	Neural tube defect	10052046
Congenital diaphragmatic hernia	10010439	Neurofibromatosis	10029268
Congenital disorder of glycosylation	10075892	Neuroleptic malignant syndrome	10029282
Congenital dysfibrinogenaemia	10051123	Neuronal ceroid lipofuscinosis	10074607
Congenital dyskeratosis	10062759	Neuronal migration disorder	10076677
Congenital ectodermal dysplasia	10010452	Neuropathy, ataxia, retinitis pigmentosa syndrome	10062940
Congenital ectopic bladder	10010453	Neutropenia	10029354
Congenital ectopic pancreas	10056987	Neutropenia neonatal	10029358
Congenital elevation of scapula	10010455	Neutropenic colitis	10062959
Congenital emphysema	10010456	Neutropenic infection	10059482
Congenital endocrine anomaly	10062329	Neutropenic sepsis	10049151
Congenital epiblepharon	10056531	Neutrophil count abnormal	10061313
Congenital epiglottal anomaly	10062330	Neutrophil count decreased	10029366
Congenital eye disorder	10059159	Neutrophil percentage decreased	10052223
Congenital eye naevus	10051050	Niemann-Pick disease	10029403
Congenital eyelid malformation	10061146	Nijmegen breakage syndrome	10067857
Congenital facial nerve hypoplasia	10049449	Nodal arrhythmia	10029458
Congenital fallopian tube anomaly	10061062	Nodal rhythm	10029470
Congenital fibrosarcoma	10065859	Nodular regenerative hyperplasia	10051081
Congenital flaccid paralysis	10010474	Non-alcoholic fatty liver	10029530
Congenital flat feet	10010475	Non-alcoholic steatohepatitis	10053219
Congenital floppy infant	10053153	Non-cirrhotic portal hypertension	10077259
Congenital foot malformation	10062332	Non-compaction cardiomyopathy	10079253
Congenital gastric anomaly	10061063	Nonketotic hyperglycinaemia	10070639
Congenital gastrointestinal vessel anomaly	10062342	Nonreassuring foetal heart rate pattern	10074641
Congenital generalised lipodystrophy	10053547	Noonan syndrome	10029748
Congenital genital malformation	10062333	Norrie's disease	10069760
Congenital genital malformation female	10010481	Obstructive uropathy	10029984
Congenital genital malformation male	10059492	Ocular albinism	10065276
Congenital genitourinary abnormality	10062334	Ocular icterus	10058117
Congenital great vessel anomaly	10061080	Oculoauriculovertebral dysplasia	10051934

Listing of preferred terms used for NNMQ rare events

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Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Congenital haematological disorder	10072107	Oculocerebrorenal syndrome	10051707
Congenital hair disorder	10061064	Oculodentodigital dysplasia	10063691
Congenital hand malformation	10062335	Oculomucocutaneous syndrome	10030081
Congenital hearing disorder	10010493	Oculopharyngeal dystrophy	10052181
Congenital heart valve disorder	10064086	Oculorespiratory syndrome	10067317
Congenital heart valve incompetence	10077594	Odontogenic cyst	10063413
Congenital hemiparesis	10071359	Oedema due to hepatic disease	10049631
Congenital hepatic fibrosis	10056533	Oedema mouth	10030110
Congenital hepatitis B infection	10010496	Oedematous pancreatitis	10052400
Congenital hepatobiliary anomaly	10061065	Oesophageal atresia	10030146
Congenital hepatomegaly	10051130	Oesophageal cyst	10079063
Congenital herpes simplex infection	10019949	Oesophageal varices haemorrhage	10030210
Congenital hiatus hernia	10010501	Olfacto genital dysplasia	10053142
Congenital high airway obstruction syndrome	10074187	Olfactory nerve agenesis	10072941
Congenital hydrocele renalis	10051147	Oliguria	10030302
Congenital hydrocephalus	10010506	Olmsted syndrome	10068842
Congenital hydronephrosis	10050975	Omenn syndrome	10069097
Congenital hypercoagulation	10070954	Opitz-G/BBB syndrome	10079435
Congenital hyperextension of knee	10048954	Optic nerve hypoplasia	10062942
Congenital hyperextension of spine	10048953	Oral-facial-digital syndrome type II	10078419
Congenital hyperthyroidism	10062264	Ornithine transcarbamoylase deficiency	10052450
Congenital hypertrichosis	10010507	Oropharyngeal oedema	10078783
Congenital hypogammaglobulinaemia	10060747	Oropharyngeal swelling	10031118
Congenital hypoparathyroidism	10051315	Oroticaciduria congenital	10052773
Congenital hypothyroidism	10010510	Os trigonum	10069805
Congenital infection	10062343	Osteogenesis imperfecta	10031243
Congenital inguinal hernia	10068321	Osteopathia striata	10073776
Congenital intestinal malformation	10061067	Osteopetrosis	10031280
Congenital intestinal obstruction	10073207	Osteopoikilosis	10031281
Congenital intrinsic factor deficiency	10070440	Osteoporosis-pseudoglioma syndrome	10052452
Congenital iris anomaly	10057411	Ota's naevus	10051713
Congenital jaw malformation	10062336	Otocephaly	10058118
Congenital joint malformation	10062337	Ovarian agenesis	10033120
Congenital knee deformity	10061068	Ovarian hypoplasia	10079495
Congenital knee dislocation	10010520	PHACES syndrome	10068032
Congenital kyphoscoliosis	10048890	Pacemaker generated arrhythmia	10053486
Congenital labia pudendi adhesions	10050268	Pacemaker syndrome	10051994
Congenital lacrimal gland anomaly	10010523	Pachydermoperiostosis	10051686
Congenital lacrimal passage anomaly	10062338	Pachygyria	10048910
Congenital large intestinal atresia	10010526	Palpitations	10033557
Congenital laryngeal stridor	10010527	Pancreas divisum	10069419
Congenital lenticonus	10064660	Pancreas infection	10051741
Congenital limb hyperextension	10049011	Pancreatic abscess	10048984
Congenital lip fistula	10010532	Pancreatic haemorrhage	10033625
Congenital lymphoedema	10010535	Pancreatic necrosis	10058096
Congenital malaria	10010538	Pancreatic phlegmon	10056975
Congenital malignant neoplasm	10073492	Pancreatic pseudocyst	10033635
Congenital megacolon	10010539	Pancreatic pseudocyst drainage	10033636
Congenital megaureter	10010540	Pancreatitis	10033645

Listing of preferred terms used for NNMQ rare events

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Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Congenital melanocytic naevus	10072036	Pancreatitis acute	10033647
Congenital melanosis	10010541	Pancreatitis bacterial	10065191
Congenital methaemoglobinaemia	10010543	Pancreatitis chronic	10033649
Congenital mitochondrial cytopathy	10057954	Pancreatitis fungal	10065190
Congenital mitral valve incompetence	10010547	Pancreatitis haemorrhagic	10033650
Congenital mitral valve stenosis	10010548	Pancreatitis helminthic	10065189
Congenital monorchidism	10069505	Pancreatitis mumps	10033653
Congenital multiplex arthrogryposis	10051643	Pancreatitis necrotising	10033654
Congenital muscle absence	10010550	Pancreatitis relapsing	10033657
Congenital musculoskeletal anomaly	10062344	Pancreatitis viral	10065192
Congenital myopathy	10062547	Pancreatorenal syndrome	10056277
Congenital myopia	10069153	Pancytopenia	10033661
Congenital naevus	10067248	Panmyelopathy	10050026
Congenital nail disorder	10010557	Parachute mitral valve	10064192
Congenital neoplasm	10078557	Paranasal sinus aplasia	10074401
Congenital nephrogenic diabetes insipidus	10068304	Paraneoplastic glomerulonephritis	10076749
Congenital nephrotic syndrome	10060737	Paraneoplastic nephrotic syndrome	10075626
Congenital neurological degeneration	10010558	Parasystole	10033929
Congenital neurological disorder	10062345	Parenteral nutrition associated liver disease	10074151
Congenital neuropathy	10062346	Parkes-Weber syndrome	10075554
Congenital night blindness	10010559	Paroxysmal arrhythmia	10050106
Congenital nose malformation	10062347	Paroxysmal atrioventricular block	10077503
Congenital nystagmus	10010562	Patent ductus arteriosus	10034130
Congenital oculomotor apraxia	10053877	Pearson's syndrome	10062941
Congenital oesophageal anomaly	10061069	Pectus carinatum	10034203
Congenital oesophageal stenosis	10010564	Pectus excavatum	10034204
Congenital oesophageal web	10010565	Pelizaeus-Merzbacher disease	10067610
Congenital optic nerve anomaly	10061528	Pelvi-ureteric obstruction	10034232
Congenital oral malformation	10061070	Pelvic fibrosis	10034244
Congenital osteodystrophy	10010582	Pelvic kidney	10034259
Congenital ovarian anomaly	10061071	Penile torsion	10070235
Congenital oxalosis	10068593	Penoscrotal fusion	10064951
Congenital pancreatic anomaly	10061072	Penoscrotal transposition	10067287
Congenital perforated nasal septum	10010588	Perinephritis	10072058
Congenital pharyngeal anomaly	10061073	Periodontal congenital anomaly	10057476
Congenital pigmentation disorder	10010593	Periorbital oedema	10034545
Congenital pneumonia	10010594	Peripancreatic varices	10073215
Congenital poikiloderma	10052465	Peritoneal dialysis	10034660
Congenital pseudarthrosis	10061573	Periventricular nodular heterotopia	10066854
Congenital pulmonary artery anomaly	10061074	Perry syndrome	10079207
Congenital pulmonary hypertension	10050701	Persistent cloaca	10069442
Congenital pulmonary valve atresia	10052644	Persistent foetal circulation	10034708
Congenital pulmonary valve disorder	10061075	Persistent left superior vena cava	10064193
Congenital pyelocaliectasis	10049938	Persistent pupillary membrane	10070872
Congenital renal cyst	10010607	Persistent urogenital sinus	10059800
Congenital renal disorder	10066875	Peutz-Jeghers syndrome	10034764
Congenital retinoblastoma	10073470	Phakomatosis	10048734
Congenital rubella infection	10010619	Phalangeal agenesis	10054879

Listing of preferred terms used for NNMQ rare events

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Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Congenital salivary gland anomaly	10010620	Phalangeal hypoplasia	10049212
Congenital scleral disorder	10061530	Pharyngeal oedema	10034829
Congenital scoliosis	10050694	Phenylketonuria	10034872
Congenital scrotal hypertrophy	10048800	Phimosis	10034878
Congenital skin dimples	10072978	Phytosterolaemia	10063985
Congenital skin disorder	10067769	Pierre Robin syndrome	10035009
Congenital small intestinal atresia	10010626	Pilonidal cyst congenital	10054019
Congenital spinal cord anomaly	10061076	Plagiocephaly	10048586
Congenital spinal fusion	10010629	Plasma cell disorder	10062081
Congenital spinal stenosis	10077379	Plasma cells absent	10035230
Congenital spondylolisthesis	10010633	Plasmablast count decreased	10058774
Congenital spondylolysis	10010634	Platelet count decreased	10035528
Congenital syphilis	10010641	Platelet glycoprotein gene mutation	10071024
Congenital syphilitic encephalitis	10010643	Platelet maturation arrest	10035537
Congenital syphilitic meningitis	10010644	Platelet production decreased	10035540
Congenital syphilitic osteochondritis	10054002	Platelet toxicity	10059440
Congenital teratoma	10052012	Platonychia	10072590
Congenital thrombocyte disorder	10058896	Platybasia	10057115
Congenital thrombocytopenia	10077833	Platyspondylia	10068629
Congenital thymus absence	10048801	Poland's syndrome	10036007
Congenital thyroid disorder	10076602	Polycystic liver disease	10048834
Congenital tongue anomaly	10061077	Polydactyly	10036063
Congenital torticollis	10010650	Polymicrogyria	10073489
Congenital toxoplasmosis	10010652	Porencephaly	10036172
Congenital tracheomalacia	10010654	Porokeratosis	10036175
Congenital trichomegaly	10073654	Porphyria	10036181
Congenital tricuspid valve atresia	10049767	Porphyria acute	10036182
Congenital tricuspid valve incompetence	10067887	Porphyria non-acute	10036186
Congenital tricuspid valve stenosis	10010656	Porphyrin metabolism disorder	10061356
Congenital tuberculosis	10010657	Porphyrinuria	10036193
Congenital umbilical hernia	10010658	Portal fibrosis	10074726
Congenital ureteric anomaly	10061078	Portal hypertension	10036200
Congenital ureterocele	10056434	Portal hypertensive colopathy	10079446
Congenital ureterovesical junction anomaly	10068133	Portal hypertensive enteropathy	10068923
Congenital urethral anomaly	10062349	Portal hypertensive gastropathy	10050897
Congenital urinary tract obstruction	10010663	Portal tract inflammation	10075331
Congenital uterine anomaly	10061079	Portal vein cavernous transformation	10073979
Congenital vaginal cyst	10063457	Portal vein dilatation	10073209
Congenital varicella infection	10010668	Portal venous system anomaly	10076609
Congenital varicocele	10074459	Portopulmonary hypertension	10067281
Congenital vas deferens absence	10010670	Post infection glomerulonephritis	10074480
Congenital vesicoureteric reflux	10010672	Post streptococcal glomerulonephritis	10036303
Congenital visual acuity reduced	10059157	Postauricular fistula	10036329
Congenital vitreous anomaly	10061085	Posterior segment of eye anomaly congenital	10053202
Congenital white blood cell disorder	10061086	Potter's syndrome	10036462
Conjoined twins	10010688	Prader-Willi syndrome	10036476
Conjunctivitis gonococcal neonatal	10010749	Preauricular cyst	10036509

Listing of preferred terms used for NNMQ rare events

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Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Constricted ear deformity	10071233	Preduodenal portal vein	10059798
Continuous haemodiafiltration	10066338	Prerenal failure	10072370
Cor biloculare	10010967	Preternatural anus	10064917
Cor triatriatum	10010972	Primary cerebellar degeneration	10036686
Corneal dystrophy	10011005	Primary ciliary dyskinesia	10069713
Corneal opacity congenital	10011037	Primary familial brain calcification	10078822
Cornelia de Lange syndrome	10077707	Primary familial hypomagnesaemia	10076626
Corrected transposition of great vessels	10011120	Primary hypercholesterolaemia	10077965
Cortical dysplasia	10070666	Primary immunodeficiency syndrome	10064859
Costello syndrome	10067380	Primary insulin like growth factor-1 deficiency	10071079
Cowden's disease	10051906	Primary myelofibrosis	10077161
Craniofacial deformity	10074180	Progeria	10036794
Craniofacial dysostosis	10066946	Progressive cerebellar degeneration	10036801
Craniolacunia	10072116	Progressive external ophthalmoplegia	10036802
Craniorachischisis	10011321	Progressive familial intrahepatic cholestasis	10076033
Craniosynostosis	10049889	Prominent epicanthal folds	10065273
Craniotabes	10065419	Promyelocyte count decreased	10050987
Cri du Chat syndrome	10011385	Protein C deficiency	10051298
Crigler-Najjar syndrome	10011386	Protein S deficiency	10051292
Cryopyrin associated periodic syndrome	10068850	Proteus syndrome	10074067
Cryptogenic cirrhosis	10063075	Protuberant ear	10071232
Cryptophthalmos	10011497	Proximal focal femoral deficiency	10078473
Cryptorchism	10011498	Pseudocholinesterase deficiency	10062674
Cullen's sign	10059029	Pseudohermaphroditism	10037122
Cutaneous vasculitis	10011686	Pseudohermaphroditism female	10037123
Cutaneovisceral angiomatosis with thrombocytopenia	10069098	Pseudohermaphroditism male	10037124
Cyclic neutropenia	10053176	Pseudohypoparathyroidism	10037126
Cyclopia	10057648	Pseudomembranous colitis	10037128
Cystathionine beta-synthase deficiency	10071093	Pseudotruncus arteriosus	10050053
Cystic angiomatosis	10079371	Pseudoxanthoma elasticum	10037150
Cystic eyeball, congenital	10011761	Pterygium colli	10051972
Cystic fibrosis	10011762	Pulmonary aplasia	10037322
Cystic fibrosis carrier	10052656	Pulmonary arteriovenous fistula	10037332
Cystic fibrosis gastrointestinal disease	10079428	Pulmonary artery atresia	10037337
Cystic fibrosis hepatic disease	10068289	Pulmonary artery stenosis congenital	10037339
Cystic fibrosis lung	10011763	Pulmonary hypoplasia	10037407
Cystic fibrosis pancreatic	10011766	Pulmonary lymphangiectasia	10073661
Cystic fibrosis related diabetes	10068271	Pulmonary malformation	10037419
Cystic lymphangioma	10058949	Pulmonary renal syndrome	10068513
Cystinosis	10011777	Pulmonary sequestration	10059160
Cystinuria	10011778	Pulmonary valve stenosis congenital	10037451
Cytogenetic abnormality	10067477	Pulseless electrical activity	10058151
Cytomegalovirus nephritis	10079095	Pure white cell aplasia	10068043
Cytomegalovirus pancreatitis	10049566	Pyloric stenosis	10037621
Cytopenia	10066274	Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome	10072222

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Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
DNA mismatch repair protein gene mutation	10078672	Pyruvate carboxylase deficiency	10077944
Dacryostenosis congenital	10011850	Pyruvate kinase deficiency anaemia	10037682
Dandy-Walker syndrome	10048411	Radiation hepatitis	10051015
Deaf mutism	10011875	Radiation leukopenia	10067354
Deafness congenital	10011882	Radioulnar synostosis	10037798
Defect conduction intraventricular	10012118	Rathke's cleft cyst	10058969
Deficiency of bile secretion	10071634	Rebound tachycardia	10067207
Deficiency of the interleukin-1 receptor antagonist	10072224	Rectal atresia	10038031
Deficiency of the interleukin-36 receptor antagonist	10079451	Red blood cell enzymes abnormal	10049191
Delta-beta thalassaemia	10012236	Refsum's disease	10038275
Demyelinating polyneuropathy	10061811	Renal and liver transplant	10052279
Dent's disease	10069199	Renal aplasia	10064655
Dentatorubral-pallidoluysian atrophy	10075298	Renal arteriovenous malformation	10038368
Dentinogenesis imperfecta	10054013	Renal dysplasia	10038433
Dentofacial anomaly	10012331	Renal failure	10038435
Denys-Drash syndrome	10070179	Renal failure neonatal	10038447
Dermatitis bullous	10012441	Renal fusion anomaly	10068033
Dermatitis exfoliative	10012455	Renal hypoplasia	10049102
Dermatitis exfoliative generalised	10012456	Renal impairment	10062237
Dermatofibrosis lenticularis disseminata	10056878	Renal impairment neonatal	10049776
Dermatoglyphic anomaly	10061455	Renal malposition	10072019
Dermoid cyst	10012522	Renal vessel congenital anomaly	10038552
Developmental glaucoma	10012565	Reperfusion arrhythmia	10058156
Developmental hip dysplasia	10073767	Reproductive tract hypoplasia, male	10057858
Dextrocardia	10012592	Respiratory sinus arrhythmia magnitude abnormal	10079117
DiGeorge's syndrome	10012979	Respiratory sinus arrhythmia magnitude decreased	10079116
Diabetic foetopathy	10059116	Respiratory sinus arrhythmia magnitude increased	10079115
Diabetic hepatopathy	10071265	Respiratory tract malformation	10038733
Dialysis	10061105	Retinal anomaly congenital	10038821
Dialysis membrane reaction	10076665	Retinal arteriovenous malformation	10038824
Diaphragmatic aplasia	10012711	Retinal coloboma	10052643
Diastematomyelia	10012750	Retinitis pigmentosa	10038914
Diencephalic syndrome of infancy	10012774	Retinopathy congenital	10050706
Diethylstilboestrol syndrome	10012780	Retinoschisis congenital	10038938
Differential white blood cell count abnormal	10012785	Retrograde p-waves	10071187
Dihydropyrimidine dehydrogenase deficiency	10052622	Retrograde portal vein flow	10067338
Dilatation intrahepatic duct congenital	10013003	Retroperitoneal fibrosis	10038979
Disorder of sex development	10070597	Retroperitonitis	10078424
Disseminated intravascular coagulation	10013442	Rett syndrome	10077709
Distichiasis	10066128	Reye's syndrome	10039012
Diverticulitis Meckel's	10013542	Reynold's syndrome	10070953
Diverticulum of pharynx, congenital	10013568	Rhesus haemolytic disease of newborn	10039037
Dolichocolon	10063917	Rhythm idioventricular	10039111
Double cortex syndrome	10073490	Rib hypoplasia	10048893

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Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Double heterozygous sickling disorders	10013609	Rib synostosis	10076624
Double outlet right ventricle	10013611	Right aortic arch	10067407
Double ureter	10013613	Right ventricle outflow tract obstruction	10064195
Dowling-Degos disease	10068651	Right-to-left cardiac shunt	10076605
Drug reaction with eosinophilia and systemic symptoms	10073508	Riley-Day syndrome	10039179
Drug-induced liver injury	10072268	Rippling muscle disease	10069417
Duane's syndrome	10013799	Rotor's syndrome	10039234
Dubin-Johnson syndrome	10013800	Rubinstein-Taybi syndrome	10039281
Dubowitz syndrome	10059589	Sacral hypoplasia	10056659
Duchenne muscular dystrophy	10013801	Sacralisation	10064932
Duchenne muscular dystrophy gene carrier	10052655	Sarcosinaemia	10059299
Ductus arteriosus premature closure	10049996	Scan bone marrow abnormal	10053504
Ductus arteriosus stenosis foetal	10013808	Scaphocephaly	10049426
Ductus venosus agenesis	10068665	Schimke immunoosseous dysplasia	10048699
Duodenal atresia	10013812	Schinzel-Giedion syndrome	10063540
Duodenal varices	10051010	Schizencephaly	10073487
Duplex appendix	10078212	Scimitar syndrome	10051951
Dyschondrosteosis	10071437	Sclerotylosis	10070504
Dysgnathia	10074336	Sebaceous naevus	10039785
Dysmorphism	10066054	Sensory neuropathy hereditary	10040037
Dysmyelination	10067601	Septate hymen	10068484
Dysplastic naevus syndrome	10013960	Septo-optic dysplasia	10067159
ECG P wave inverted	10057526	Septum pellucidum agenesis	10062267
Eagle Barrett syndrome	10051025	Serotonin syndrome	10040108
Ear malformation	10014016	Sertoli-cell-only syndrome	10066833
Early onset familial Alzheimer's disease	10078036	Severe myoclonic epilepsy of infancy	10073677
Early onset primary dystonia	10076668	Sex chromosome abnormality	10061513
Ebstein's anomaly	10014075	Shigella sepsis	10074481
Ectopia cordis	10014144	Shock	10040560
Ectopic kidney	10063044	Shock symptom	10040581
Ectopic ovary	10074217	Shone complex	10066802
Ectopic posterior pituitary gland	10077557	Short-chain acyl-coenzyme A dehydrogenase deficiency	10072655
Ectopic thyroid	10069503	Shwachman-Diamond syndrome	10067940
Ectopic ureter	10014172	Sickle cell anaemia	10040641
Ehlers-Danlos syndrome	10014316	Sickle cell trait	10040650
Electrocardiogram P wave abnormal	10050384	Silver-Russell syndrome	10062282
Electrocardiogram PQ interval prolonged	10053656	Single umbilical artery	10049807
Electrocardiogram PQ interval shortened	10075328	Sinoatrial block	10040736
Electrocardiogram PR prolongation	10053657	Sinus arrest	10040738
Electrocardiogram PR shortened	10014374	Sinus arrhythmia	10040739
Electrocardiogram QRS complex prolonged	10014380	Sinus bradycardia	10040741
Electrocardiogram QT prolonged	10014387	Sinus node dysfunction	10075889
Electrocardiogram RR interval prolonged	10067652	Sinus tachycardia	10040752
Electrocardiogram U-wave abnormality	10055032	Sirenomelia	10072457
Electrocardiogram abnormal	10014363	Sjogren-Larsson syndrome	10048676
Electrocardiogram ambulatory abnormal	10014369	Skeletal dysplasia	10072610
Electrocardiogram change	10061116	Skin hypoplasia	10040869
Electrocardiogram delta waves abnormal	10014372	Skin malformation	10040888

Listing of preferred terms used for NNMQ rare events

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Electrocardiogram repolarisation abnormality	10052464	Skin necrosis	10040893
Elliptocytosis hereditary	10014490	Skull malformation	10062348
Ellis-van Creveld syndrome	10076418	Smith-Lemli-Opitz syndrome	10078573
Emanuel syndrome	10079203	Sotos' syndrome	10064387
Encapsulating peritoneal sclerosis	10075012	Special senses congenital anomaly	10041420
Encephalocele	10014617	Spherophakia	10041513
Encephalocutaneous angiomatosis	10057653	Spina bifida	10041524
Endocardial fibroelastosis	10014663	Spina bifida cystica	10071011
Enteric duplication	10076653	Spina bifida occulta	10041525
Entropion congenital	10014923	Spinal muscular atrophy	10041582
Eosinopenia	10014940	Spinal vessel congenital anomaly	10041603
Eosinophil count abnormal	10061125	Spine malformation	10041611
Eosinophil count decreased	10014943	Spinocerebellar ataxia	10057660
Eosinophil percentage decreased	10052221	Spleen malformation	10062350
Epidermal naevus	10014985	Splenic hamartoma	10076586
Epidermal naevus syndrome	10077952	Splenic varices	10067823
Epidermal necrosis	10059284	Splenic varices haemorrhage	10068662
Epidermolysis	10053177	Spondyloepiphyseal dysplasia	10062920
Epidermolysis bullosa	10014989	Stargardt's disease	10062766
Epilepsy congenital	10015039	Steatocystoma multiplex	10048905
Epispadias	10015088	Steatohepatitis	10076331
Erythema multiforme	10015218	Stevens-Johnson syndrome	10042033
Erythroblastosis foetalis	10015251	Stickler's syndrome	10063402
Erythrokeratodermia variabilis	10049048	Sticky platelet syndrome	10068788
Essential fructosuria	10015487	Strabismus congenital	10042161
Exfoliative rash	10064579	Sturge-Weber syndrome	10042265
Exomphalos	10015677	Subacute hepatic failure	10056956
Exophthalmos congenital	10050696	Subependymal nodular heterotopia	10071150
External auditory canal atresia	10054875	Sucrase-isomaltase deficiency	10066387
Extrarenal pelvis	10072727	Sudden cardiac death	10049418
Extrasystoles	10015856	Sudden death	10042434
Eye anterior chamber congenital anomaly	10061051	Supernumerary nipple	10042571
Eyelid oedema	10015993	Supernumerary vertebra	10077919
Eyelid ptosis congenital	10015996	Supraventricular extrasystoles	10042602
Fabry's disease	10016016	Supraventricular tachyarrhythmia	10065342
Face oedema	10016029	Supraventricular tachycardia	10042604
Faciodigitogenital dysplasia	10067141	Swelling face	10042682
Facioscapulohumeral muscular dystrophy	10064087	Swollen tongue	10042727
Factor I deficiency	10016075	Syncope	10042772
Factor II deficiency	10016076	Syndactyly	10042778
Factor II mutation	10065003	Synostosis	10042856
Factor III deficiency	10052473	Syringomyelia	10042928
Factor IX deficiency	10016077	T-lymphocyte count abnormal	10057284
Factor V Leiden carrier	10075652	T-lymphocyte count decreased	10051318
Factor V Leiden mutation	10058279	Tachyarrhythmia	10049447
Factor V deficiency	10048930	Tachycardia	10043071
Factor VII deficiency	10016079	Tachycardia foetal	10043074
Factor VIII deficiency	10016080	Tachycardia paroxysmal	10043079
Factor X deficiency	10052474	Talipes	10043101
Factor XI deficiency	10016082	Tangier disease	10051875
Factor XII deficiency	10051806	Tay-Sachs disease	10043147
Factor XIII deficiency	10016083	Telangiectasia congenital	10061575
Fallot's pentalogy	10059205	Teratogenicity	10043275
Fallot's tetralogy	10016193	Testicular dysplasia	10059271
Fallot's trilogy	10064011	Testotoxicosis	10063654
Familial amyloidosis	10016202	Tetrahydrobiopterin deficiency	10069116

Listing of preferred terms used for NNMQ rare events

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Familial amyotrophic lateral sclerosis	10077024	Thalassaemia	10043388
Familial cold autoinflammatory syndrome	10064570	Thalassaemia alpha	10043390
Familial haemophagocytic lymphohistiocytosis	10070904	Thalassaemia beta	10043391
Familial hemiplegic migraine	10067039	Thalassaemia sickle cell	10043395
Familial high density lipoprotein deficiency	10079119	Thalidomide embryopathy	10071249
Familial hypertriglyceridaemia	10059183	Thanatophoric dwarfism	10049808
Familial hypocalciuric hypercalcaemia	10068698	Thrombocytopenia	10043554
Familial infantile bilateral striatal necrosis	10077450	Thrombocytopenia-absent radius syndrome	10071719
Familial mediterranean fever	10016207	Thymus hypoplasia	10052645
Familial medullary thyroid cancer	10073153	Thyroglossal cyst	10051320
Familial periodic paralysis	10016208	Thyroglossal fistula	10062601
Familial polycythaemia	10016209	Thyroid hemiagenesis	10077609
Familial renal glycosuria	10073689	Thyroid malformation	10062125
Familial scaphocephaly syndrome	10072229	Tibial torsion	10064515
Familial tremor	10016212	Tilted disc syndrome	10079368
Fanconi syndrome	10016219	Timothy syndrome	10079205
Fatal familial insomnia	10072077	Tongue oedema	10043967
Fatty acid oxidation disorder	10077951	Tooth discolouration congenital	10044033
Febrile bone marrow aplasia	10053213	Tooth hypoplasia	10044041
Febrile neutropenia	10016288	Tooth malformation hereditary	10044047
Femoral anteversion	10064516	Tornwaldt cyst	10078492
Femoral retroversion	10064514	Torsade de pointes	10044066
Femur-fibula-ulna complex	10068448	Tourette's disorder	10044126
Fibrillary glomerulonephritis	10068279	Toxic epidermal necrolysis	10044223
Fibrodysplasia ossificans progressiva	10068715	Toxic skin eruption	10057970
Fibrous dysplasia of bone	10016664	Tracheal atresia	10054955
Fibrous dysplasia of jaw	10070535	Tracheal web	10077940
Fibula agenesis	10054882	Tracheo-oesophageal fistula	10044310
Fissure of tongue, congenital	10016715	Transitional vertebrae	10074306
Focal segmental glomerulosclerosis	10067757	Transposition of the great vessels	10044443
Foetal alcohol syndrome	10016845	Traumatic pancreatitis	10074894
Foetal anticonvulsant syndrome	10066485	Trichorhinophalangeal syndrome	10051956
Foetal arrhythmia	10016847	Trifascicular block	10044644
Foetal chromosome abnormality	10064041	Trifunctional protein deficiency	10077949
Foetal cystic hygroma	10052011	Trimethylaminuria	10068233
Foetal heart rate acceleration abnormality	10074642	Triple A syndrome	10073592
Foetal heart rate deceleration abnormality	10074636	Trisomy 11	10044685
Foetal heart rate disorder	10061158	Trisomy 12	10063092
Foetal malformation	10060919	Trisomy 13	10044686
Foetal megacystis	10073660	Trisomy 14	10071762
Foetal methotrexate syndrome	10071183	Trisomy 15	10062757
Foetal renal impairment	10078987	Trisomy 17	10053925
Foetal retinoid syndrome	10073720	Trisomy 18	10053884
Foetal tachyarrhythmia	10077575	Trisomy 21	10044688
Foetal warfarin syndrome	10051445	Trisomy 22	10044689
Foramen magnum stenosis	10064157	Trisomy 8	10053871
Fragile X carrier	10052657	Trisomy 9	10071547
Fragile X syndrome	10017324	Truncus arteriosus persistent	10044703
Freeman-Sheldon syndrome	10073655	Tuberous sclerosis	10045138
Frenulum breve	10072007	Tubulointerstitial nephritis	10048302
Friedreich's ataxia	10017374	Tubulointerstitial nephritis and uveitis syndrome	10069034

Listing of preferred terms used for NNMQ rare events

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Fryns syndrome	10075223	Tumour necrosis factor receptor-associated periodic syndrome	10067774
Full blood count abnormal	10017412	Turner's syndrome	10045181
Full blood count decreased	10017413	Twin reversed arterial perfusion sequence malformation	10073455
GNE myopathy	10077945	Type I hyperlipidaemia	10060749
Galactosaemia	10017604	Type I hypersensitivity	10045240
Gallbladder agenesis	10079018	Type II hyperlipidaemia	10045254
Gallbladder anomaly congenital	10061163	Type III hyperlipidaemia	10060751
Gallbladder varices	10072319	Type IIa hyperlipidaemia	10045261
Gastric variceal injection	10076237	Type IIb hyperlipidaemia	10045263
Gastric variceal ligation	10076238	Type IV hyperlipidaemia	10060753
Gastric varices	10051012	Type V hyperlipidaemia	10060755
Gastric varices haemorrhage	10057572	Tyrosinaemia	10063443
Gastroenteritis clostridial	10017898	Uhl's anomaly	10048951
Gastrointestinal arteriovenous malformation	10017932	Umbilical artery hypoplasia	10045445
Gastrointestinal disorder congenital	10061973	Umbilical malformation	10045469
Gastrointestinal malformation	10061596	Univentricular heart	10045545
Gastroschisis	10018046	Urachal abnormality	10066125
Gaucher's disease	10018048	Ureteric atresia	10078351
Gaucher's disease type I	10075697	Ureteric compression	10076715
Gaucher's disease type II	10075698	Ureteric dilatation	10046399
Gaucher's disease type III	10075699	Ureteric obstruction	10046406
Gelatinous transformation of the bone marrow	10078097	Ureteric stenosis	10046411
Gene mutation	10064571	Urethral atresia	10064895
Generalised resistance to thyroid hormone	10018096	Urethral valves	10046479
Genitalia external ambiguous	10018183	Urinary tract malformation	10046580
Gilbert's syndrome	10018267	Usher's syndrome	10063396
Gitelman's syndrome	10062906	Uterine aplasia	10067704
Gleich's syndrome	10066837	Uterine cervix hypoplasia	10063120
Glomerulonephritis	10018364	Uterine hypoplasia	10063146
Glomerulonephritis acute	10018366	Uvula aplasia	10053506
Glomerulonephritis chronic	10018367	VACTERL syndrome	10066022
Glomerulonephritis membranoproliferative	10018370	Vaginal atresia	10046879
Glomerulonephritis membranous	10018372	Vaginal hypoplasia	10053843
Glomerulonephritis minimal lesion	10018374	Vaginal septum	10064513
Glomerulonephritis proliferative	10018376	Varices oesophageal	10056091
Glomerulonephritis rapidly progressive	10018378	Varicose veins of abdominal wall	10072284
Glucose transporter type 1 deficiency syndrome	10078727	Vascular malformation	10074979
Glucose-6-phosphate dehydrogenase deficiency	10018444	Vein of Galen aneurysmal malformation	10077889
Glucose-galactose malabsorption	10066388	Velo-cardio-facial syndrome	10066430
Glutathione synthetase deficiency	10079364	Venous angioma of brain	10053485
Glycogen storage disease type I	10018464	Ventricular arrhythmia	10047281
Glycogen storage disease type II	10053185	Ventricular asystole	10047284
Glycogen storage disease type III	10053250	Ventricular dyssynchrony	10071186
Glycogen storage disease type IV	10053249	Ventricular extrasystoles	10047289
Glycogen storage disease type V	10018462	Ventricular fibrillation	10047290

Listing of preferred terms used for NNMQ rare events

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Glycogen storage disease type VI	10053240	Ventricular flutter	10047294
Glycogen storage disease type VII	10053241	Ventricular hypoplasia	10047296
Glycogen storage disease type VIII	10053242	Ventricular parasystole	10058184
Glycogen storage disorder	10061990	Ventricular pre-excitation	10049761
Gnathoschisis	10068845	Ventricular septal defect	10047298
Goitre congenital	10018499	Ventricular tachyarrhythmia	10065341
Gonadal dysgenesis	10018504	Ventricular tachycardia	10047302
Goodpasture's syndrome	10018620	Vertebral artery hypoplasia	10066907
Gorham's disease	10071283	Vertical talus	10066242
Graft versus host disease in liver	10064676	Very long-chain acyl-coenzyme A dehydrogenase deficiency	10072656
Granulocyte count decreased	10018681	Virilism foetal	10047487
Granulocytes abnormal	10018685	Vitello-intestinal duct remnant	10066969
Granulocytes maturation arrest	10050443	Von Hippel-Lindau disease	10047716
Granulocytopenia	10018687	Von Willebrand's disease	10047715
Granulocytopenia neonatal	10018688	Waardenburg syndrome	10069203
Granulomatosis with polyangiitis	10072579	Wagner's disease	10063383
Granulomatous liver disease	10018704	Wandering pacemaker	10047818
Greig's syndrome	10053878	Weill-Marchesani syndrome	10064963
Grey Turner's sign	10075426	Welander distal myopathy	10078052
Guillain-Barre syndrome	10018767	Werner's syndrome	10049429
HIV associated nephropathy	10070737	White blood cell analysis abnormal	10073323
Haemangioma congenital	10018818	White blood cell count abnormal	10047940
Haemangioma of retina	10018822	White blood cell count decreased	10047942
Haematotoxicity	10061188	White blood cell disorder	10061414
Haemochromatosis trait	10073217	White nipple sign	10078438
Haemodialysis	10018875	Wildervanck syndrome	10069402
Haemofiltration	10053090	Williams syndrome	10049644
Haemoglobin C disease	10018883	Winchester syndrome	10078901
Haemoglobin C trait	10055021	Wiskott-Aldrich syndrome	10047992
Haemoglobin D disease	10055019	Withdrawal arrhythmia	10047997
Haemoglobin D trait	10055020	Wolf-Hirschhorn syndrome	10050361
Haemoglobin E disease	10053215	Wolff-Parkinson-White syndrome	10048015
Haemoglobin E trait	10063740	Wolff-Parkinson-White syndrome congenital	10049291
Haemoglobin E-thalassaemia disease	10062917	Wolfram syndrome	10078338
Haemoglobinopathy	10060892	Wyburn Mason's syndrome	10048661
Haemophilia	10061992	X-linked chromosomal disorder	10056554
Haemophilia A with anti factor VIII	10056492	X-linked lymphoproliferative syndrome	10068348
Haemophilia A without inhibitors	10056493	XXX syndrome	10076910
Haemophilia B with anti factor IX	10056494	XXXY syndrome	10048228
Haemophilia B without inhibitors	10056495	XXYY syndrome	10048230
Haemophilia carrier	10051658	XYY syndrome	10056894
Haemorrhagic arteriovenous malformation	10064595	Xeroderma pigmentosum	10048220
Haemorrhagic necrotic pancreatitis	10076058	Y-linked chromosomal disorder	10056555
Hamartoma	10061193	Yellow skin	10048245
Hamartoma vascular	10019106	Young's syndrome	10063689

NNMQ: Novo Nordisk MedDRA querie
MedDRA version: 20.0

89. SMQ「投薬過誤」に含まれる基本語一覧

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Accidental device ingestion	10072950	Injury associated with device	10069803
Accidental device ingestion by a child	10072951	Intercepted accidental exposure to product by child	10079333
Accidental exposure to product	10073317	Intercepted drug administration error	10065639
Accidental exposure to product by child	10073318	Intercepted drug dispensing error	10065638
Accidental exposure to product packaging	10077659	Intercepted drug prescribing error	10072393
Accidental exposure to product packaging by child	10077660	Intercepted medication error	10064382
Accidental overdose	10000381	Intercepted product monitoring error	10079334
Accidental poisoning	10000383	Intercepted product preparation error	10079213
Accidental underdose	10074904	Intercepted product selection error	10076544
Accidental use of placebo	10073758	Intercepted product storage error	10079212
Booster dose missed	10073205	Intercepted wrong patient selected	10065645
Circumstance or information capable of leading to device use error	10074266	Interchange of vaccine products	10070574
Circumstance or information capable of leading to medication error	10064385	Labelled drug-disease interaction medication error	10064381
Communication issue	10079439	Labelled drug-drug interaction medication error	10064373
Complication of drug implant insertion	10078731	Labelled drug-food interaction medication error	10064374
Contraindicated device used	10077678	Lack of administration site rotation	10076087
Contraindicated drug prescribed	10078779	Lack of application site rotation	10076088
Contraindicated product administered	10078504	Lack of infusion site rotation	10076089
Contraindication to medical treatment	10010833	Lack of injection site rotation	10073752
Contraindication to vaccination	10010835	Lack of vaccination site rotation	10076090
Device adhesion issue	10069216	Medical device monitoring error	10077672
Device connection issue	10065066	Medication error	10027091
Device difficult to use	10069853	Medication monitoring error	10074433
Device infusion issue	10070617	Multiple use of single-use product	10072342
Device monitoring procedure not performed	10077720	Needle issue	10069217
Device use error	10072878	Occupational exposure to product	10073311
Device use issue	10077812	Occupational exposure to radiation	10030020
Device used for unapproved schedule	10079135	Overdose	10033295
Device-device incompatibility	10069845	Paravenous drug administration	10075353
Dietary supplement prescribing error	10075225	Poor quality device used	10078668
Difficulty inserting drug implant	10079522	Poor quality drug administered	10058121
Difficulty removing drug implant	10012802	Prescribed overdose	10051076
Documented hypersensitivity to administered product	10076470	Prescribed underdose	10073085
Dose calculation error	10076874	Product adhesion issue	10069889
Drug administered at inappropriate site	10013659	Product barcode issue	10069269

Listing of preferred terms used for SMQ medication errors
Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Drug administered in wrong device	10070470	Product commingling	10069297
Drug administered to patient of inappropriate age	10071062	Product compounding quality issue	10069329
Drug administration error	10064295	Product dosage form confusion	10071587
Drug dispensed to wrong patient	10065634	Product dosage form issue	10069232
Drug dispensing error	10064354	Product dropper issue	10069294
Drug dose omission	10064294	Product expiration date issue	10069271
Drug dose titration not performed	10074906	Product identification number issue	10069267
Drug monitoring procedure incorrectly performed	10075461	Product label confusion	10069273
Drug monitoring procedure not performed	10075462	Product label issue	10069289
Drug prescribing error	10064296	Product label on wrong product	10069268
Drug titration error	10074853	Product label strength missing	10079079
Expired device used	10073594	Product lot number issue	10069266
Expired product administered	10074902	Product name confusion	10069332
Exposure to contaminated device	10068515	Product packaging confusion	10074776
Exposure via contaminated device	10073301	Product packaging issue	10069405
Exposure via direct contact	10071411	Product preparation error	10076869
Exposure via eye contact	10073336	Product reconstitution quality issue	10079007
Exposure via ingestion	10073302	Product selection error	10076542
Exposure via inhalation	10073303	Product substitution error	10078984
Exposure via partner	10071412	Product use complaint	10079400
Exposure via skin contact	10071430	Product use in unapproved indication	10076476
Exposure via unknown route	10078762	Product use issue	10076309
Extra dose administered	10064366	Radiation overdose	10068518
Failure of child resistant mechanism for pharmaceutical product	10066374	Radiation underdose	10068519
Inadequate aseptic technique in use of product	10072608	Syringe issue	10069218
Inappropriate prescribing	10079271	Therapeutic drug monitoring analysis incorrectly performed	10073703
Inappropriate schedule of drug administration	10021597	Therapeutic drug monitoring analysis not performed	10073702
Incomplete course of vaccination	10072103	Transcription medication error	10076245
Incorrect disposal of product	10078390	Underdose	10057362
Incorrect dosage administered	10073768	Unintentional medical device removal	10072931
Incorrect dose administered	10064355	Unintentional use for unapproved indication	10076589
Incorrect dose administered by device	10068945	Vaccination error	10063972
Incorrect drug administration duration	10064307	Wrong device dispensed	10070469
Incorrect drug administration rate	10064306	Wrong device used	10070468
Incorrect drug dosage form administered	10064305	Wrong drug administered	10048055
Incorrect product formulation administered	10074946	Wrong patient received medication	10048056
Incorrect product storage	10069328	Wrong technique in device usage process	10077040
Incorrect route of drug administration	10064304	Wrong technique in product usage process	10076573

SMQ: Standardised MedDRA querie
SMQ code: 20000224
MedDRA version: 20.0

90. SMQ「薬剤性肝障害」に含まれる基本語一覧

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
5'nucleotidase increased	10000028	Hepatitis cholestatic	10019754
Acquired antithrombin III deficiency	10074561	Hepatitis chronic active	10019755
Acquired protein S deficiency	10068370	Hepatitis chronic persistent	10019759
Acute graft versus host disease in liver	10066263	Hepatitis fulminant	10019772
Acute hepatic failure	10000804	Hepatitis toxic	10019795
Acute on chronic liver failure	10077305	Hepatobiliary cancer	10073073
Acute yellow liver atrophy	10070815	Hepatobiliary cancer in situ	10073074
Alanine aminotransferase abnormal	10001547	Hepatobiliary disease	10062000
Alanine aminotransferase increased	10001551	Hepatobiliary neoplasm	10061203
Allergic hepatitis	10071198	Hepatobiliary scan abnormal	10066195
Ammonia abnormal	10001942	Hepatoblastoma	10062001
Ammonia increased	10001946	Hepatoblastoma recurrent	10019823
Anorectal varices	10068924	Hepatocellular carcinoma	10073071
Anorectal varices haemorrhage	10068925	Hepatocellular foamy cell syndrome	10053244
Anti factor X activity abnormal	10077670	Hepatocellular injury	10019837
Anti factor X activity decreased	10077674	Hepatomegaly	10019842
Anti factor X activity increased	10077671	Hepatopulmonary syndrome	10052274
Antithrombin III decreased	10049547	Hepatorenal failure	10019845
Ascites	10003445	Hepatorenal syndrome	10019846
Aspartate aminotransferase abnormal	10003477	Hepatosplenomegaly	10019847
Aspartate aminotransferase increased	10003481	Hepatotoxicity	10019851
Asterixis	10003547	Hyperammonaemia	10020575
Autoimmune hepatitis	10003827	Hyperbilirubinaemia	10020578
Bacterascites	10068547	Hypercholia	10051924
Benign hepatic neoplasm	10004269	Hyperfibrinolysis	10074737
Benign hepatobiliary neoplasm	10077922	Hypertransaminasaemia	10068237
Bile output abnormal	10051344	Hypoalbuminaemia	10020942
Bile output decreased	10051343	Hypocoagulable state	10020973
Biliary ascites	10074150	Hypofibrinogenaemia	10051125
Biliary cirrhosis	10004659	Hypoprothrombinaemia	10021085
Biliary cirrhosis primary	10004661	Hypothrombinaemia	10058517
Biliary fibrosis	10004664	Hypothromboplastinaemia	10058518
Bilirubin conjugated abnormal	10067718	Icterus index increased	10021209
Bilirubin conjugated increased	10004685	International normalised ratio abnormal	10022592
Bilirubin excretion disorder	10061009	International normalised ratio increased	10022595
Bilirubin urine present	10077356	Intestinal varices	10071502
Biopsy liver abnormal	10004792	Intestinal varices haemorrhage	10078058
Blood alkaline phosphatase abnormal	10059571	Intrahepatic portal hepatic venous fistula	10072629
Blood alkaline phosphatase increased	10059570	Ischaemic hepatitis	10023025
Blood bilirubin abnormal	10058477	Jaundice	10023126
Blood bilirubin increased	10005364	Jaundice cholestatic	10023129
Blood bilirubin unconjugated increased	10005370	Jaundice hepatocellular	10023136
Blood cholinesterase abnormal	10005429	Kayser-Fleischer ring	10023321
Blood cholinesterase decreased	10005430	Leucine aminopeptidase increased	10024275
Blood fibrinogen abnormal	10005518	Liver ablation	10074766
Blood fibrinogen decreased	10005520	Liver and small intestine transplant	10052280
Blood thrombin abnormal	10005818	Liver carcinoma ruptured	10050842
Blood thrombin decreased	10005820	Liver dialysis	10076640
Blood thromboplastin abnormal	10005824	Liver disorder	10024670
Blood thromboplastin decreased	10005826	Liver function test abnormal	10024690

Listing of preferred terms used for SMQ drug related hepatic disorders

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Bromosulphthalein test abnormal	10006408	Liver function test decreased	10077677
Child-Pugh-Turcotte score abnormal	10077020	Liver function test increased	10077692
Child-Pugh-Turcotte score increased	10068287	Liver induration	10052550
Cholaemia	10048611	Liver injury	10067125
Cholangiosarcoma	10077861	Liver iron concentration abnormal	10074352
Cholestasis	10008635	Liver iron concentration increased	10074354
Cholestatic liver injury	10067969	Liver operation	10062040
Cholestatic pruritus	10064190	Liver palpable	10075895
Chronic graft versus host disease in liver	10072160	Liver sarcoidosis	10068664
Chronic hepatic failure	10057573	Liver scan abnormal	10061947
Chronic hepatitis	10008909	Liver tenderness	10024712
Coagulation factor IX level abnormal	10061770	Liver transplant	10024714
Coagulation factor IX level decreased	10009746	Lupoid hepatic cirrhosis	10025129
Coagulation factor V level abnormal	10061771	Lupus hepatitis	10067737
Coagulation factor V level decreased	10009754	Minimal hepatic encephalopathy	10076204
Coagulation factor VII level abnormal	10061772	Mitochondrial aspartate aminotransferase increased	10064712
Coagulation factor VII level decreased	10009761	Mixed hepatocellular cholangiocarcinoma	10027761
Coagulation factor X level abnormal	10061774	Mixed liver injury	10066758
Coagulation factor X level decreased	10009775	Model for end stage liver disease score abnormal	10077291
Coagulation factor decreased	10009736	Model for end stage liver disease score increased	10077292
Coma hepatic	10010075	Molar ratio of total branched-chain amino acid to tyrosine	10066869
Computerised tomogram liver	10076215	Nodular regenerative hyperplasia	10051081
Computerised tomogram liver abnormal	10078360	Non-alcoholic fatty liver	10029530
Cryptogenic cirrhosis	10063075	Non-alcoholic steatohepatitis	10053219
Deficiency of bile secretion	10071634	Non-cirrhotic portal hypertension	10077259
Diabetic hepatopathy	10071265	Ocular icterus	10058117
Drug-induced liver injury	10072268	Oedema due to hepatic disease	10049631
Duodenal varices	10051010	Oesophageal varices haemorrhage	10030210
Focal nodular hyperplasia	10052285	Parenteral nutrition associated liver disease	10074151
Foetor hepaticus	10052554	Perihepatic discomfort	10054125
Galactose elimination capacity test abnormal	10059710	Peripancreatic varices	10073215
Galactose elimination capacity test decreased	10059712	Periportal oedema	10068821
Gallbladder varices	10072319	Peritoneal fluid protein abnormal	10069000
Gamma-glutamyltransferase abnormal	10017688	Peritoneal fluid protein decreased	10068999
Gamma-glutamyltransferase increased	10017693	Peritoneal fluid protein increased	10068998
Gastric variceal injection	10076237	Peritoneovenous shunt	10052716
Gastric variceal ligation	10076238	Pneumobilia	10066004
Gastric varices	10051012	Portal fibrosis	10074726
Gastric varices haemorrhage	10057572	Portal hypertension	10036200

Listing of preferred terms used for SMQ drug related hepatic disorders
Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Glutamate dehydrogenase increased	10049483	Portal hypertensive colopathy	10079446
Graft versus host disease in liver	10064676	Portal hypertensive enteropathy	10068923
Granulomatous liver disease	10018704	Portal hypertensive gastropathy	10050897
Guanase increased	10051333	Portal shunt	10036204
Haemangioma of liver	10018821	Portal shunt procedure	10077479
Haemorrhagic ascites	10059766	Portal tract inflammation	10075331
Haemorrhagic hepatic cyst	10067796	Portal vein cavernous transformation	10073979
Hepaplastin abnormal	10019621	Portal vein dilatation	10073209
Hepaplastin decreased	10019622	Portal vein flow decreased	10067337
Hepatectomy	10061997	Portal vein pressure increased	10064936
Hepatic adenoma	10019629	Portopulmonary hypertension	10067281
Hepatic angiosarcoma	10067388	Protein C decreased	10037005
Hepatic artery flow decreased	10068997	Protein S abnormal	10051736
Hepatic atrophy	10019637	Protein S decreased	10051120
Hepatic calcification	10065274	Prothrombin level abnormal	10037048
Hepatic cancer	10073069	Prothrombin level decreased	10037050
Hepatic cancer metastatic	10055110	Prothrombin time abnormal	10037057
Hepatic cancer recurrent	10073070	Prothrombin time prolonged	10037063
Hepatic cancer stage I	10059318	Prothrombin time ratio abnormal	10061918
Hepatic cancer stage II	10059319	Prothrombin time ratio increased	10037068
Hepatic cancer stage III	10059324	Radiation hepatitis	10051015
Hepatic cancer stage IV	10059325	Renal and liver transplant	10052279
Hepatic cirrhosis	10019641	Retinol binding protein decreased	10048473
Hepatic congestion	10019645	Retrograde portal vein flow	10067338
Hepatic cyst	10019646	Reye's syndrome	10039012
Hepatic cyst ruptured	10053973	Reynold's syndrome	10070953
Hepatic encephalopathy	10019660	Small-for-size liver syndrome	10069380
Hepatic encephalopathy prophylaxis	10066599	Spider naevus	10041519
Hepatic enzyme abnormal	10062685	Splenic varices	10067823
Hepatic enzyme decreased	10060794	Splenic varices haemorrhage	10068662
Hepatic enzyme increased	10060795	Splenorenal shunt	10041661
Hepatic failure	10019663	Splenorenal shunt procedure	10077281
Hepatic fibrosis	10019668	Spontaneous intrahepatic portosystemic venous shunt	10076239
Hepatic fibrosis marker abnormal	10074084	Steatohepatitis	10076331
Hepatic fibrosis marker increased	10074413	Stomal varices	10075186
Hepatic function abnormal	10019670	Subacute hepatic failure	10056956
Hepatic haemangioma rupture	10054885	Thrombin time abnormal	10051319
Hepatic hydrothorax	10067365	Thrombin time prolonged	10051390
Hepatic hypertrophy	10076254	Total bile acids increased	10064558
Hepatic infiltration eosinophilic	10064668	Transaminases abnormal	10062688
Hepatic lesion	10061998	Transaminases increased	10054889
Hepatic mass	10057110	Ultrasound liver abnormal	10045428
Hepatic necrosis	10019692	Urine bilirubin increased	10050792
Hepatic neoplasm	10019695	Urobilinogen urine decreased	10070480
Hepatic pain	10019705	Urobilinogen urine increased	10070479
Hepatic sequestration	10066244	Varices oesophageal	10056091
Hepatic steato-fibrosis	10077215	Varicose veins of abdominal wall	10072284
Hepatic steatosis	10019708	White nipple sign	10078438
Hepatic vascular resistance increased	10068358	X-ray hepatobiliary abnormal	10056536
Hepatitis	10019717	Yellow skin	10048245
Hepatitis acute	10019727		

SMQ: Standardised MedDRA querie
SMQ code: 20000006
MedDRA version: 20.0

91. SMQ「急性腎不全」に含まれる基本語一覧

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Acute kidney injury	10069339	Hyponatriuria	10077515
Acute phosphate nephropathy	10069688	Intradialytic parenteral nutrition	10074739
Acute prerenal failure	10001017	Kidney injury molecule-1	10069022
Albuminuria	10001580	Neonatal anuria	10049778
Anuria	10002847	Nephritis	10029117
Azotaemia	10003885	Nephropathy toxic	10029155
Blood creatinine abnormal	10005481	Oedema due to renal disease	10049630
Blood creatinine increased	10005483	Oliguria	10030302
Blood urea abnormal	10005846	Peritoneal dialysis	10034660
Blood urea increased	10005851	Prerenal failure	10072370
Blood urea nitrogen/creatinine ratio increased	10050760	Protein urine present	10053123
Continuous haemodiafiltration	10066338	Proteinuria	10037032
Creatinine renal clearance abnormal	10068447	Renal failure	10038435
Creatinine renal clearance decreased	10011372	Renal failure neonatal	10038447
Creatinine urine abnormal	10071021	Renal function test abnormal	10061480
Creatinine urine decreased	10055003	Renal impairment	10062237
Crystal nephropathy	10071503	Renal impairment neonatal	10049776
Dialysis	10061105	Renal transplant	10038533
Foetal renal impairment	10078987	Renal tubular disorder	10038537
Fractional excretion of sodium	10075142	Renal tubular dysfunction	10050335
Glomerular filtration rate abnormal	10018356	Renal tubular injury	10078933
Glomerular filtration rate decreased	10018358	Renal tubular necrosis	10038540
Haemodialysis	10018875	Tubulointerstitial nephritis	10048302
Haemofiltration	10053090	Urea renal clearance decreased	10046358
Hypercreatininaemia	10062747	Urine output decreased	10059895

SMQ: Standardised MedDRA querie
MedDRA version: 20.0

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92. NNMQ「病原体感染」に含まれる基本語一覧

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Air-borne transmission	10001534	Mycobacterial disease carrier	10075025
Bacterial disease carrier	10004017	Nosocomial infection	10029803
Community acquired infection	10067822	Primary transmission	10051856
Diphtheria carrier	10013024	Secondary transmission	10051854
Direct infection transmission	10013045	Sexual transmission of infection	10040488
Faecal-oral transmission of infection	10016096	Sexually transmitted disease carrier	10040491
HIV carrier	10020159	Suspected transmission of an infectious agent via product	10072754
HTLV-1 carrier	10069712	Transmission of an infectious agent via product	10072753
Human immunodeficiency virus transmission	10053500	Typhoid carrier	10045274
Iatrogenic infection	10064091	Vaccine virus shedding	10070583
Indirect infection transmission	10021714	Vector-borne transmission of infection	10047176
Infection transmission via personal contact	10021869	Vertical infection transmission	10047337
Infection via vaccinee	10021875	Viral hepatitis carrier	10047458
Infectious disease carrier	10062019		

NNMQ: Novo Nordisk MedDRA querie
MedDRA version: 20.0

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93. NNMQ「注射部位反応」に含まれる基本語一覧

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Administration site abscess	10068791	Infusion site joint erythema	10076077
Administration site abscess sterile	10075922	Infusion site joint infection	10076073
Administration site anaesthesia	10075923	Infusion site joint inflammation	10076074
Administration site atrophy	10075924	Infusion site joint movement impairment	10076075
Administration site bruise	10075094	Infusion site joint pain	10076076
Administration site calcification	10075925	Infusion site joint swelling	10076078
Administration site cellulitis	10075095	Infusion site joint warmth	10076079
Administration site coldness	10075926	Infusion site laceration	10076080
Administration site cyst	10075927	Infusion site lymphadenopathy	10065475
Administration site dermatitis	10075096	Infusion site macule	10076081
Administration site discharge	10075097	Infusion site mass	10065476
Administration site discolouration	10075098	Infusion site mobility decreased	10065477
Administration site discomfort	10075928	Infusion site necrosis	10065478
Administration site dryness	10075929	Infusion site nerve damage	10065479
Administration site dysaesthesia	10075930	Infusion site nodule	10065484
Administration site eczema	10075099	Infusion site oedema	10053998
Administration site erosion	10075931	Infusion site pain	10053483
Administration site erythema	10074796	Infusion site pallor	10076082
Administration site exfoliation	10075932	Infusion site papule	10076083
Administration site extravasation	10075933	Infusion site paraesthesia	10065485
Administration site fibrosis	10075934	Infusion site phlebitis	10053663
Administration site granuloma	10075935	Infusion site photosensitivity reaction	10065486
Administration site haematoma	10075100	Infusion site plaque	10076084
Administration site haemorrhage	10075101	Infusion site pruritus	10053664
Administration site hyperaesthesia	10075936	Infusion site pustule	10065487
Administration site hypersensitivity	10075102	Infusion site rash	10059830
Administration site hypertrichosis	10075314	Infusion site reaction	10054996
Administration site hypertrophy	10075937	Infusion site recall reaction	10076085
Administration site hypoaesthesia	10075938	Infusion site scab	10066211
Administration site indentation	10079278	Infusion site scar	10065488
Administration site induration	10075939	Infusion site streaking	10076086
Administration site infection	10066214	Infusion site swelling	10053505
Administration site inflammation	10074704	Infusion site thrombosis	10065489
Administration site injury	10075940	Infusion site ulcer	10054995
Administration site irritation	10075941	Infusion site urticaria	10065490
Administration site ischaemia	10075942	Infusion site vasculitis	10074851
Administration site joint discomfort	10075943	Infusion site vesicles	10065491
Administration site joint effusion	10075944	Infusion site warmth	10053484
Administration site joint erythema	10075949	Injected limb mobility decreased	10057664
Administration site joint infection	10075945	Injection site abscess	10022044
Administration site joint inflammation	10075946	Injection site abscess sterile	10022045
Administration site joint movement impairment	10075947	Injection site anaesthesia	10022046
Administration site joint pain	10075948	Injection site atrophy	10022048

Listing of preferred terms used for NNMQ injection site reactions

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Administration site joint warmth	10075950	Injection site bruising	10022052
Administration site laceration	10075951	Injection site calcification	10054812
Administration site lymphadenopathy	10075952	Injection site cellulitis	10050057
Administration site macule	10075953	Injection site coldness	10050082
Administration site mass	10075954	Injection site cyst	10022055
Administration site movement impairment	10075955	Injection site deformation	10079275
Administration site necrosis	10075956	Injection site dermatitis	10022056
Administration site nerve damage	10075957	Injection site discharge	10065600
Administration site nodule	10075765	Injection site discolouration	10051572
Administration site odour	10075103	Injection site discomfort	10054266
Administration site oedema	10075104	Injection site dryness	10067252
Administration site pain	10058049	Injection site dysaesthesia	10069124
Administration site pallor	10075958	Injection site eczema	10066221
Administration site papule	10075959	Injection site erosion	10022059
Administration site paraesthesia	10075105	Injection site erythema	10022061
Administration site phlebitis	10075960	Injection site exfoliation	10068689
Administration site photosensitivity reaction	10075961	Injection site extravasation	10022062
Administration site plaque	10075962	Injection site fibrosis	10022064
Administration site pruritus	10075106	Injection site granuloma	10022065
Administration site pustule	10075963	Injection site haematoma	10022066
Administration site rash	10071156	Injection site haemorrhage	10022067
Administration site reaction	10001315	Injection site hyperaesthesia	10073418
Administration site recall reaction	10075964	Injection site hypersensitivity	10022071
Administration site scab	10075965	Injection site hypertrichosis	10075313
Administration site scar	10075967	Injection site hypertrophy	10022072
Administration site streaking	10075966	Injection site hypoaesthesia	10074586
Administration site swelling	10075107	Injection site indentation	10079277
Administration site thrombosis	10075968	Injection site induration	10022075
Administration site ulcer	10075108	Injection site infection	10022076
Administration site urticaria	10075109	Injection site inflammation	10022078
Administration site vasculitis	10075969	Injection site injury	10066083
Administration site vesicles	10075970	Injection site irritation	10022079
Administration site warmth	10075971	Injection site ischaemia	10048648
Application site abscess	10057881	Injection site joint discomfort	10073459
Application site abscess sterile	10075999	Injection site joint effusion	10064494
Application site acne	10073457	Injection site joint erythema	10076327
Application site alopecia	10059046	Injection site joint infection	10074703
Application site anaesthesia	10003033	Injection site joint inflammation	10064111
Application site atrophy	10003035	Injection site joint movement impairment	10053979
Application site bruise	10050114	Injection site joint pain	10049261
Application site burn	10065059	Injection site joint swelling	10049260
Application site calcification	10076000	Injection site joint warmth	10049262
Application site cellulitis	10065301	Injection site laceration	10067253
Application site coldness	10076001	Injection site lymphadenopathy	10057665
Application site cyst	10076002	Injection site macule	10067255
Application site dermatitis	10003036	Injection site mass	10022081
Application site discharge	10052162	Injection site movement impairment	10056250
Application site discolouration	10059005	Injection site necrosis	10022082
Application site discomfort	10063072	Injection site nerve damage	10022083
Application site dryness	10048943	Injection site nodule	10057880
Application site dysaesthesia	10076003	Injection site oedema	10022085
Application site eczema	10050099	Injection site pain	10022086
Application site erosion	10065577	Injection site pallor	10066041
Application site erythema	10003041	Injection site papule	10066044

Listing of preferred terms used for NNMQ injection site reactions

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Application site exfoliation	10064578	Injection site paraesthesia	10022088
Application site extravasation	10076004	Injection site phlebitis	10022090
Application site fibrosis	10076005	Injection site photosensitivity reaction	10053396
Application site fissure	10065331	Injection site plaque	10073174
Application site folliculitis	10059136	Injection site pruritus	10022093
Application site granuloma	10076006	Injection site pustule	10054994
Application site haematoma	10068317	Injection site rash	10022094
Application site haemorrhage	10072694	Injection site reaction	10022095
Application site hyperaesthesia	10050100	Injection site recall reaction	10066797
Application site hypersensitivity	10063683	Injection site scab	10066210
Application site hypertrichosis	10075546	Injection site scar	10059009
Application site hypertrophy	10074535	Injection site streaking	10066778
Application site hypoaesthesia	10074585	Injection site swelling	10053425
Application site induration	10063839	Injection site telangiectasia	10079124
Application site infection	10049041	Injection site thrombosis	10022104
Application site inflammation	10049042	Injection site ulcer	10022105
Application site injury	10076007	Injection site urticaria	10022107
Application site irritation	10003046	Injection site vasculitis	10067995
Application site ischaemia	10076008	Injection site vesicles	10022111
Application site joint discomfort	10076009	Injection site warmth	10022112
Application site joint effusion	10076010	Instillation site abscess	10073602
Application site joint erythema	10076015	Instillation site anaesthesia	10073603
Application site joint infection	10076011	Instillation site atrophy	10073604
Application site joint inflammation	10076012	Instillation site bruise	10073630
Application site joint movement impairment	10076013	Instillation site burn	10073605
Application site joint pain	10076014	Instillation site coldness	10063769
Application site joint swelling	10076016	Instillation site complication	10071163
Application site joint warmth	10076017	Instillation site discharge	10073606
Application site laceration	10073779	Instillation site discolouration	10073607
Application site lymphadenopathy	10076018	Instillation site discomfort	10065652
Application site macule	10076019	Instillation site dryness	10063772
Application site mass	10058713	Instillation site erosion	10073608
Application site movement impairment	10076020	Instillation site erythema	10063762
Application site necrosis	10003048	Instillation site exfoliation	10073601
Application site nerve damage	10076021	Instillation site foreign body sensation	10063771
Application site nodule	10050101	Instillation site haematoma	10073609
Application site odour	10066149	Instillation site haemorrhage	10073610
Application site oedema	10003050	Instillation site hyperaesthesia	10073611
Application site pain	10003051	Instillation site hypersensitivity	10073612
Application site pallor	10050102	Instillation site hypoaesthesia	10074587
Application site papules	10049043	Instillation site induration	10073613
Application site paraesthesia	10050103	Instillation site infection	10073614
Application site perspiration	10054838	Instillation site inflammation	10073615
Application site phlebitis	10076022	Instillation site irritation	10055117
Application site photosensitivity reaction	10058730	Instillation site lacrimation	10065653
Application site plaque	10076023	Instillation site necrosis	10073616
Application site pruritus	10003053	Instillation site nodule	10073617
Application site purpura	10050182	Instillation site odour	10073618

Listing of preferred terms used for NNMQ injection site reactions

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Application site pustules	10049044	Instillation site oedema	10073619
Application site rash	10003054	Instillation site pain	10022459
Application site reaction	10003055	Instillation site papules	10073620
Application site recall reaction	10076024	Instillation site paraesthesia	10073558
Application site scab	10066209	Instillation site pruritus	10063763
Application site scar	10059008	Instillation site pustules	10073621
Application site streaking	10076025	Instillation site rash	10073622
Application site swelling	10053424	Instillation site reaction	10063765
Application site telangiectasia	10072640	Instillation site scab	10073623
Application site thrombosis	10076026	Instillation site swelling	10073624
Application site ulcer	10003059	Instillation site thrombosis	10073625
Application site urticaria	10050104	Instillation site ulcer	10073626
Application site vasculitis	10076027	Instillation site urticaria	10073627
Application site vesicles	10048941	Instillation site vesicles	10073628
Application site warmth	10003060	Instillation site warmth	10073629
Application site wound	10078380	Malabsorption from administration site	10076091
Embolia cutis medicamentosa	10058729	Malabsorption from application site	10076092
Infusion site abscess	10058464	Malabsorption from injection site	10025478
Infusion site abscess sterile	10076063	Oral administration complication	10062611
Infusion site anaesthesia	10065497	Puncture site abscess	10049863
Infusion site atrophy	10065454	Puncture site discharge	10068895
Infusion site bruising	10059203	Puncture site erythema	10074759
Infusion site calcification	10076064	Puncture site haemorrhage	10051101
Infusion site cellulitis	10065455	Puncture site hernia	10078035
Infusion site coldness	10065456	Puncture site hypoaesthesia	10074761
Infusion site cyst	10065457	Puncture site induration	10067681
Infusion site dermatitis	10065458	Puncture site infection	10063677
Infusion site discharge	10076065	Puncture site oedema	10074069
Infusion site discolouration	10065460	Puncture site pain	10065599
Infusion site discomfort	10069667	Puncture site reaction	10053996
Infusion site dryness	10076066	Puncture site swelling	10072161
Infusion site dysaesthesia	10076067	Systemic leakage	10065647
Infusion site eczema	10074850	Vessel puncture site anaesthesia	10066988
Infusion site erosion	10065461	Vessel puncture site bruise	10063881
Infusion site erythema	10048634	Vessel puncture site cellulitis	10077414
Infusion site exfoliation	10068687	Vessel puncture site discharge	10063960
Infusion site extravasation	10064774	Vessel puncture site erythema	10074760
Infusion site fibrosis	10065462	Vessel puncture site haematoma	10065902
Infusion site granuloma	10065505	Vessel puncture site haemorrhage	10054092
Infusion site haematoma	10065463	Vessel puncture site hypoaesthesia	10074588
Infusion site haemorrhage	10065464	Vessel puncture site induration	10073156
Infusion site hyperaesthesia	10076068	Vessel puncture site infection	10073157
Infusion site hypersensitivity	10065471	Vessel puncture site inflammation	10070647
Infusion site hypertrichosis	10076069	Vessel puncture site occlusion	10076838
Infusion site hypertrophy	10065472	Vessel puncture site pain	10066951
Infusion site hypoaesthesia	10065984	Vessel puncture site paraesthesia	10067519
Infusion site induration	10053482	Vessel puncture site phlebitis	10074993
Infusion site infection	10054997	Vessel puncture site pruritus	10067254
Infusion site inflammation	10056270	Vessel puncture site rash	10077117
Infusion site injury	10076070	Vessel puncture site reaction	10063880
Infusion site irritation	10065473	Vessel puncture site swelling	10070648
Infusion site ischaemia	10065474	Vessel puncture site thrombosis	10070649
Infusion site joint discomfort	10076071	Vessel puncture site vesicles	10077813

Listing of preferred terms used for NNMQ injection site reactions

Continued...

Preferred Term Text	Preferred Term ID	Preferred Term Text	Preferred Term ID
Infusion site joint effusion	10076072		

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MedDRA version: 20.0

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94. 3776 及び 3859 試験の両試験に参加した被験者の被験者番号一覧

Unique Subject Identifier (USUBJID)	Subject identifiers in the trials			
	Trial 3776	Trial 3859	Trial 3860	Trial 4033
NN7088_3776/				
NN7088_3776/				
NN7088_3776/				
NN7088_3776/				
NN7088_3776/				
NN7088_3776/				
NN7088_3776/				
NN7088_3776/				
NN7088_3776/				
NN7088_3776/				

In trial 3860 patients are asigned a different subject identifier for each surgery.

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95. NNMQ「アレルギー反応」（狭域検索）に含まれる基本語一覧

Preferred Term Text	Preferred Term ID
Allergic myocarditis	10001715
Alveolitis allergic	10001890
Anaphylactic reaction	10002198
Anaphylactic shock	10002199
Anaphylactoid reaction	10002216
Anaphylaxis treatment	10002222
Angioedema	10002424
Application site dermatitis	10003036
Application site rash	10003054
Atopy	10003645
Blepharitis allergic	10005149
Blood immunoglobulin E abnormal	10005589
Blood immunoglobulin E increased	10005591
Bromoderma	10006404
Bronchospasm	10006482
Circulatory collapse	10009192
Conjunctival oedema	10010726
Conjunctivitis allergic	10010744
Contrast media reaction	10010836
Corneal oedema	10011033
Cutaneous vasculitis	10011686
Dermatitis	10012431
Dermatitis acneiform	10012432
Dermatitis allergic	10012434
Dermatitis atopic	10012438

Dermatitis bullous	10012441
Dermatitis contact	10012442
Dermatitis exfoliative	10012455
Dermatitis exfoliative generalised	10012456
Dermatitis herpetiformis	10012468
Dermatitis infected	10012470
Drug eruption	10013687
Drug hypersensitivity	10013700
Eczema	10014184
Eczema infantile	10014198
Eczema nummular	10014201
Encephalopathy allergic	10014627
Epidermolysis bullosa	10014989
Epiglottic oedema	10015029
Erythema multiforme	10015218
Erythema nodosum	10015226
Eye allergy	10015907
Eye swelling	10015967
Eyelid oedema	10015993
Face oedema	10016029
Fixed eruption	10016741
Giant papillary conjunctivitis	10018258
Gingival swelling	10018291
Henoch-Schonlein purpura	10019617
Hereditary angioedema	10019860
Hypersensitivity	10020751

Hypersensitivity vasculitis	10020764
Idiopathic urticaria	10021247
Injection site dermatitis	10022056
Injection site hypersensitivity	10022071
Injection site rash	10022094
Injection site urticaria	10022107
Laryngeal oedema	10023845
Laryngospasm	10023891
Laryngotracheal oedema	10023893
Lip oedema	10024558
Lip swelling	10024570
Multiple allergies	10028164
Nephritis allergic	10029120
Nikolsky's sign	10029415
Oculomucocutaneous syndrome	10030081
Oedema mouth	10030110
Oropharyngeal spasm	10031111
Oropharyngeal swelling	10031118
Periorbital oedema	10034545
Pharyngeal oedema	10034829
Radioallergosorbent test positive	10037789
Rash	10037844
Rash erythematous	10037855
Rash follicular	10037857
Rash generalised	10037858
Rash macular	10037867

Rash maculo-papular	10037868
Rash morbilliform	10037870
Rash neonatal	10037871
Rash papulosquamous	10037879
Rash pruritic	10037884
Rash pustular	10037888
Rash scarlatiniform	10037890
Rash vesicular	10037898
Reaction to azo-dyes	10037973
Reaction to colouring	10037974
Red man syndrome	10038192
Rhinitis allergic	10039085
Scrotal oedema	10039755
Serum sickness	10040400
Serum sickness-like reaction	10040402
Shock	10040560
Shock symptom	10040581
Skin necrosis	10040893
Skin reaction	10040914
Skin test positive	10040934
Solar urticaria	10041307
Solvent sensitivity	10041316
Stevens-Johnson syndrome	10042033
Swelling face	10042682
Swollen tongue	10042727
Tongue oedema	10043967

Toxic epidermal necrolysis	10044223
Tracheal oedema	10044296
Type I hypersensitivity	10045240
Urticaria	10046735
Urticaria cholinergic	10046740
Urticaria contact	10046742
Urticaria papular	10046750
Urticaria physical	10046751
Urticaria pigmentosa	10046752
Urticaria vesiculosa	10046755
Vaginal ulceration	10046943
Vasculitic rash	10047111
Vulval ulceration	10047768
Acute generalised exanthematous pustulosis	10048799
Urticarial vasculitis	10048820
Allergic sinusitis	10049153
Gingival oedema	10049305
Rash maculovesicular	10050004
Application site eczema	10050099
Application site urticaria	10050104
Vulvovaginal ulceration	10050181
Allergic pharyngitis	10050639
Anti-neutrophil cytoplasmic antibody positive vasculitis	10050894
Scleritis allergic	10051126
Allergic cystitis	10051394
Kaposi's varicelliform eruption	10051891

Iodine allergy	10052098
Eye oedema	10052139
Circumoral oedema	10052250
Catheter site rash	10052271
Catheter site urticaria	10052272
Urticaria chronic	10052568
Allergic bronchitis	10052613
Epidermolysis	10053177
Type IV hypersensitivity reaction	10053613
Type III immune complex mediated reaction	10053614
Allergic cough	10053779
Type II hypersensitivity	10054000
Allergy to vaccine	10055048
Eczema weeping	10055182
Allergy test positive	10056352
Encephalitis allergic	10056387
Mucocutaneous rash	10056671
Palpable purpura	10056872
Palatal oedema	10056998
Allergic keratitis	10057380
Scleral oedema	10057431
Toxic skin eruption	10057970
Rash rubelliform	10057984
Dermatitis psoriasiform	10058675
Eczema vesicular	10058681
Hand dermatitis	10058898

Stoma site rash	10059071
Epidermal necrosis	10059284
Allergic colitis	10059447
Haemorrhagic urticaria	10059499
Infusion site rash	10059830
Allergic oedema	10060934
Arthritis allergic	10061430
Allergic otitis media	10061557
Heparin-induced thrombocytopenia	10062506
Dennie-Morgan fold	10062918
Anaphylactoid shock	10063119
Pruritus allergic	10063438
Allergic respiratory symptom	10063527
Allergic respiratory disease	10063532
Application site hypersensitivity	10063683
Implant site rash	10063786
Implant site urticaria	10063787
Implant site dermatitis	10063855
Implant site hypersensitivity	10063858
Antiallergic therapy	10064059
Vaginal exfoliation	10064483
Exfoliative rash	10064579
Reaction to drug excipients	10064787
Reaction to preservatives	10064788
Laryngitis allergic	10064866
Infusion site dermatitis	10065458

Infusion site hypersensitivity	10065471
Infusion site urticaria	10065490
Antiendomysial antibody positive	10065514
Eczema vaccinatum	10066042
Allergic transfusion reaction	10066173
Injection site eczema	10066221
Injection site recall reaction	10066797
Gleich's syndrome	10066837
Contrast media allergy	10066973
Anaphylactic transfusion reaction	10067113
Immediate post-injection reaction	10067142
Oculorespiratory syndrome	10067317
Contact stomatitis	10067510
Oropharyngeal blistering	10067950
Interstitial granulomatous dermatitis	10067972
Injection site vasculitis	10067995
Oral allergy syndrome	10068355
Palisaded neutrophilic granulomatous dermatitis	10068809
Vaccination site hypersensitivity	10068880
Kounis syndrome	10069167
Henoch-Schonlein purpura nephritis	10069440
Vaccination site dermatitis	10069477
Vaccination site rash	10069482
Vaccination site exfoliation	10069489
Vaccination site urticaria	10069622
Vaccination site vesicles	10069623

Limbal swelling	10070492
Distributive shock	10070559
Immune tolerance induction	10070581
Administration site rash	10071156
Allergic hepatitis	10071198
Chronic hyperplastic eosinophilic sinusitis	10071380
Chronic eosinophilic rhinosinusitis	10071399
Vulvovaginal rash	10071588
Device allergy	10072867
Incision site dermatitis	10073168
Idiopathic angioedema	10073257
Incision site rash	10073411
Drug reaction with eosinophilia and systemic symptoms	10073508
Instillation site hypersensitivity	10073612
Instillation site rash	10073622
Instillation site urticaria	10073627
Catheter site dermatitis	10073992
Catheter site eczema	10073995
Catheter site hypersensitivity	10073998
Catheter site vasculitis	10074014
Allergy to immunoglobulin therapy	10074079
Pathergy reaction	10074332
Drug provocation test	10074350
Palatal swelling	10074403
Stoma site hypersensitivity	10074509
Immune thrombocytopenic purpura	10074667

Infusion site eczema	10074850
Infusion site vasculitis	10074851
Allergic otitis externa	10075072
Aspirin-exacerbated respiratory disease	10075084
Administration site dermatitis	10075096
Administration site eczema	10075099
Administration site hypersensitivity	10075102
Administration site urticaria	10075109
Allergic eosinophilia	10075185
Mouth swelling	10075203
Allergic gastroenteritis	10075308
Allergy alert test positive	10075479
Medical device site dermatitis	10075572
Medical device site eczema	10075575
Medical device site hypersensitivity	10075579
Medical device site rash	10075585
Medical device site urticaria	10075588
Nodular rash	10075807
Administration site recall reaction	10075964
Administration site vasculitis	10075969
Application site recall reaction	10076024
Application site vasculitis	10076027
Infusion site recall reaction	10076085
Medical device site recall reaction	10076140
Vaccination site eczema	10076161
Vaccination site recall reaction	10076188

Vaccination site vasculitis	10076191
Intestinal angioedema	10076229
Documented hypersensitivity to administered product	10076470
Mast cell degranulation present	10076606
Dialysis membrane reaction	10076665
Drug cross-reactivity	10076743
Vessel puncture site rash	10077117
Allergy to surgical sutures	10077279
Immune-mediated adverse reaction	10077665
Vessel puncture site vesicles	10077813
Eosinophilic granulomatosis with polyangiitis	10078117
Symmetrical drug-related intertriginous and flexural exanthema	10078325
Oropharyngeal oedema	10078783
Allergic reaction to excipient	10078853

NNMQ: Novo Nordisk MedDRA querie
MedDRA version: 20.0

ツロクトコグ アルファ ペゴル（遺伝子組換え）

2.7.4.7 付録 2

ノボ ノルディスク ファーマ株式会社

Ingredient: **TUROCTOCOG ALFA PEGOL**

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
Study ID: NN7088-3908 (**14**)								
446827	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** 17.1 Iu/kg [60 Iu/kg-biw]	IV bolus	24-MAR-2015 to 19-APR-2015	18-APR-2015	s/p port placement - Prolonged Hospitalization due to bleeding secondary unresponsiveness to N8-GP [THERAPY NON-RESPONDER]	Recovered
			17.1 Iu/kg [60 Iu/kg-biw]	IV bolus	28-APR-2015 to 12-MAY-2015			

Case Seriousness?: Yes
Patient Subject #:
Study Center D:
Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)
Trial phase 3a

Investigational Drugs: N8-GP rFVIII, N8-GP 500U vial.

[redacted]

This Clinical Trial case from the [redacted] was reported by an Investigator as "s/p port placement - Prolonged Hospitalization due to bleeding secondary unresponsiveness to N8-GP", and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 24-MAR-2015 to 19-APR-2015 and again from 28-APR-2015 and until 12-MAY-2015 due to "Haemophilia A", "Factor VIII deficiency",

Medical history included severe haemophilia A, [redacted]

[redacted]

Prior to the event, on 17-APR-2015, the patient was admitted electively due to S/P port placement for monitoring, as per SOC (standard of care) for patients with haemophilia.

On 18-APR-2015, it was expected that the patient would be discharged home, however due to continued bleeding and progressive swelling followed by ecchymosis/bruising with some induration around the port the patient was kept at the hospital for continued monitoring. Site was concerned for bleeding into the surgical site.

[redacted]

00440919 10

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			[redacted]					
			On 12-MAY-2015 principal Investigator decides to cancel factor infusion and withdraw the patient from the study due to unresponsiveness to treatment. Last dose of trial product is given on 08-MAY-2015.					
			[redacted]					
			Action taken to N8-GP 500U vial was reported as Drug discontinued permanently. Trial drug was restarted on 28-APR-2015 at same dose but discontinued again permanently on 12-MAY-2015 due to unresponsiveness. There was no positive inhibitor level at the time of the EOT visit. Investigator's causality (N8-GP 500U vial) - s/p port placement - Prolonged Hospitalization due to bleeding secondary unresponsiveness to N8-GP : Probable Sponsor's causality (N8-GP 500U vial) - s/p port placement - Prolonged Hospitalization due to bleeding secondary unresponsiveness to N8-GP : Possible Narrative and relevant fields updated accordingly.					
558432	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK] 750 IU [750 IU-single]	IV bolus	20-JUN-2017 Ongoing 09-AUG-2017 to 09-AUG-2017	09-AUG-2017	head trauma [HEAD INJURY]	Recovered
			Case Seriousness?: Yes Patient Subject #: Study Center D: [redacted]					

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
		Case Narrative:	Trial ID: NN7088-3908 Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%) Trial phase 3a Trial Drugs: N8-GP rFVIII, N8-GP 500U vial. [redacted] This Clinical Trial case from [redacted] was reported by an Investigator as "head trauma" and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 20-JUN-2017 and ongoing due to "Factor VIII deficiency". Medical history included haemophilia A. On 09-AUG-2017 the patient experienced a head trauma. The boy had a mild head trauma, while he was walking. At the onset of the fall he was treated with 750 IU (60 IU/kg) of the trial drug. The patient was hospitalised just for preventive reasons. The boy had no problems during his hospitalization. Action taken to N8-GP 500U vial was reported as No Change. On 11-AUG-2017 the outcome for the event "head trauma" was Recovered and the patient was discharged. Investigator's causality (N8-GP 500U vial) - head trauma: Unlikely Sponsor's causality (N8-GP 500U vial) - head trauma: Unlikely				
450031	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [60 Iu/kg-UNK]	IV bolus	13-FEB-2015 Ongoing	26-FEB-2015	Pneumonia [PNEUMONIA]	Recovered
		Case Seriousness?:	Yes					
		Patient Subject #:	[redacted]					
		Study Center D:						
		Case Narrative:	Trial ID: NN7088-3908 Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%). Trial phase 3a Investigational Drugs: N8-GP rFVIII, N8-GP 500U vial.					

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			[redacted]					
453255	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** 7.15 Iu/kg [50 Iu/kg-qw]	IV bolus	13-FEB-2015 Ongoing	12-JUN-2015	Pneumonia [PNEUMONIA]	Recovered

Case Seriousness?: Yes
Patient Subject #:
Study Center D: [redacted]
Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)
Trial phase 3a

Investigational Drugs: N8-GP rFVIII, N8-GP 500U vial.

This Clinical Trial case from [redacted] was reported by an Investigator as "Pneumonia", and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 13-FEB-2015 and ongoing due to "Factor VIII deficiency",

Medical history included severe haemophilia a, [redacted]

[redacted]

On 26-FEB-2015 the patient presented with pneumonia and [redacted]

The patient received treatment and was discharged from hospital in a good general condition on 03-MAR-2015.

Action taken to N8-GP 500U vial was reported as No Change.

On 03-MAR-2015 the outcome for the event "Pneumonia" was Recovered.

Investigator's causality (N8-GP 500U vial) -
Pneumonia : Unlikely

Sponsor's causality (N8-GP 500U vial) -
Pneumonia : Unlikely

[redacted]

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			[redacted]					

This Clinical Trial case from [redacted] was reported by an Investigator as "Pneumonia", and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 13-FEB-2015 and ongoing due to "Factor VIII deficiency",

Medical history included haemophilia a, [redacted]

On 12-JUN-2015, the patient presented with fever up to 38.7 degrees Celcius and cough.

On 16-JUN-2015 the patient had a physical examination that revealed bilateral rales indicative of pneumonia. [redacted] The patient was hospitalised and started treatment on the same day.

On 21-JUN-2015 the patient recovered and was discharged.

Action taken to N8-GP 500U vial was reported as No Change.

Investigator's causality (N8-GP 500U vial) -
Pneumonia : Unlikely

Sponsor's causality (N8-GP 500U vial) -
Pneumonia : Unlikely

The case is linked to other Argus case 450031 (pneumonia).

484646	[redacted] Clinical Trial	[redacted] Male	**N8-GP rFVIII / Powder and solvent for solution for injection** UNK [biw]	IV bolus	13-FEB-2015 Ongoing	16-MAR-2016	Pneumonia caused by Haemophilus influenzae [PNEUMONIA HAEMOPH LUS]	Recovered

Case Seriousness?: Yes
Patient Subject #:
Study Center D: [redacted]
Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)
Trial phase 3a

Trial Drugs: N8-GP rFVIII, N8-GP 500U vial.

[redacted]

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			[redacted]					

This Clinical Trial case from [redacted] was reported by an Investigator as "Pneumonia caused by Haemophilus influenza" and concerned a [redacted] Male patient who was treated with N8-GP rFVIII (TUROCTOCOG ALFA PEGOL) from 13-FEB-2015 and ongoing due to "Factor VIII deficiency".

Medical history included haemophilia A, [redacted]

[redacted]

On 16-MAR-2016 the patient was hospitalised due to bronchitis with symptoms of dyspnea and cough.

The patient had a x-ray and a throat swap performed confirming the diagnosis of pneumonia caused by haemophilia influenza.

[redacted]

On 21-MAR-2016 the patient was discharged from the hospital.

Action taken to N8-GP rFVIII was reported as No Change.

On 21-MAR-2016 the outcome for the event "Pneumonia caused by Haemophilus influenza" was Recovered.

Investigator's causality (N8-GP rFVIII) -
Pneumonia caused by Haemophilus influenza : Unlikely

Sponsor's causality (N8-GP rFVIII) -
Pneumonia caused by Haemophilus influenza : Unlikely

531220	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK]	Intravenous	13-FEB-2015 Ongoing	07-DEC-2016	Pneumonia [PNEUMONIA]	Recovered

Case Seriousness?: Yes
Patient Subject #:
Study Center D: [redacted]
Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)

Trial phase 3a

Trial Drugs: N8-GP rFVIII, N8-GP 500U vial

[redacted]

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			This Clinical Trial case from [redacted] was reported by an Investigator as "pneumonia" and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 13-FEB-2015 and ongoing due to "Haemophilia A". Medical history included Haemophilia A, [redacted] On 07-DEC-2016 the patient presented with cough and nasal discharge. Gradually the cough worsened and the general practitioner (GP) made the diagnosis of pneumonia and advised hospital admission. On 09-DEC-2016 the patient presented with pneumonia and was admitted to hospital. The physical examination showed vesicular breathing with bilateral rales and rhonchi. The chest x-ray confirmed pneumonia. [redacted] Action taken to N8-GP 500U vial was reported as No Change. On 14-DEC-2016 the outcome for the event "pneumonia" was recovered. Investigator's causality (N8-GP 500U vial) - Pneumonia: Unlikely Sponsor's causality (N8-GP 500U vial) - Pneumonia: Unlikely					
526145	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK] UNK [UNK]	IV bolus IV bolus	09-SEP-2016 to 16-DEC-2016 16-DEC-2016 to 16-DEC-2016	18-NOV-2016	N8-GP inhibitors [FACTOR VIII INHIBITION]	Not recovered
			Case Seriousness?: Yes Patient Subject #: Study Center D: [redacted] Case Narrative: Trial ID: NN7088-3908 Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%) Trial phase 3a Trial Drugs: N8-GP rFVIII, N8-GP 500U vial [redacted]					

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			[redacted]					
			This Clinical Trial case from [redacted] was reported by an Investigator as "N8-GP inhibitors" and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 09-SEP-2016 to 16-DEC-2016 due to "Haemophilia A". Medical history included Haemophilia A. [redacted] On 18-NOV-2016 (V4 and reported as AE onset date) a re-testing was required, which showed [redacted] BU inhibitors (reference range 0-0 6) and confirmed the lack of recovery on 30 min. On 16-DEC-2016 last dose of the trial product was given. Same day Inhibitor antibodies result from central laboratory was [redacted] BU. [redacted] Action taken to N8-GP 500U vial was reported as Dose Increased. However, a stop date of trial product has been reported, since last dose given prior to withdrawal of consent was increased dose on 16-DEC-2016. The outcome for the event "N8-GP inhibitors" was Not recovered. Since last submission the case has been updated with following information: (NOT SUBMITTED WITH THIS INFORMATION) -Inhibitor antibodies [redacted] BU central lab on 16-DEC-2016 -Narrative updated accordingly Investigator's causality (N8-GP 500U vial) - N8-GP inhibitors: Possible Sponsor's causality (N8-GP 500U vial) - N8-GP inhibitors: Possible Company comment: Based on the nature of the event a causal relationship is possible.			
428527	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK] UNK [UNK]	IV bolus IV bolus	23-SEP-2014 to 02-DEC-2014 09-DEC-2014 to 27-JAN-2015	21-OCT-2014	Positive factorVIII inhibitor with high titre. [FACTOR VIII NH BITION]	Recovered

Case Seriousness?: Yes
Patient Subject #:
Study Center D: [redacted]

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome

Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)

Trial phase 3a

Investigational Drugs: N8-GP rFVIII, N8-GP 500U vial

[redacted]

This Clinical Trial case from [redacted] was reported by an Investigator as "Positive factorVIII inhibitor with high titre.", and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 23-SEP-2014 to 02-DEC-2014, and from 09-DEC-2014 to 27-JAN-2015 due to "Factor VIII deficiency", and other trial drug N8-GP rFVIII (TUROCTOCOG ALFA PEGOL) from 03-FEB-2015 and ongoing due to "Factor VIII deficiency".

Medical history included Haemophilia A and [redacted]

On 21-OCT-2014 the patient had a positive factor VIII inhibitor test measured by central lab. The inhibitor titre was [redacted] BU/ml (ref. range <0.6 BU/ml). [redacted]

[redacted]

[redacted]

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			[redacted]					
			Patient had no signs and symptoms of any bleeding episode. Action taken to N8-GP 500U vial was reported as Dose Increased. Action taken to N8-GP rFVIII was reported as No Change. On 10-JAN-2017 the patient recovered from the event "Positive factorVIII inhibitor with high titre." Investigator's causality (N8-GP 500U vial) - Positive factorVIII inhibitor with high titre.: Probable Sponsor's causality (N8-GP 500U vial) - Positive factorVIII inhibitor with high titre.: Possible Investigator's causality (N8-GP rFVIII) - Positive factorVIII inhibitor with high titre.: Probable Sponsor's causality (N8-GP rFVIII) - Positive factorVIII inhibitor with high titre.: Unlikely Since last submission the following information has been updated: - Final outcome and resolution date - Laboratory values - Investigator's alternative aetiology added Narrative updated accordingly Comment: company comment: Causality for N8-GP rFVIII (2000 U/vial) was assessed by sponsor as unlikely, as the product was administered more than 3 month after the onset date of the event.					
424994	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [30 Iu/kg-prn] 50 Iu/kg [25 Iu/kg-bid] 35 Iu/kg [35 Iu/kg-qd] 195 Iu/kg [65 Iu/kg-tid]	IV bolus IV bolus IV bolus IV bolus	30-SEP-2014 to 10-OCT-2014 07-OCT-2014 14 05 to 07-OCT-2014 17:30 08-OCT-2014 06 30 to 08-OCT-2014 06:30 08-OCT-2014 16 00 to 09-OCT-2014 14:30	05-OCT-2014	Epidural haematoma at the cervical thoracic spine from C6/C7 to T4 [SPINAL EPIDURAL HAEMATOMA]	Recovered

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			260 Iu/kg [65 Iu/kg-qid]	IV bolus	09-OCT-2014 18:40 to 10-OCT-2014 02:00			

Case Seriousness?: Yes
Patient Subject #: [redacted]
Study Center D:
Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)
Trial phase 3a

Investigational Drugs: N8-GP rFVIII, N8-GP 500U vial.

[redacted]

This Clinical Trial case from [redacted] was reported by an Investigator as "Epidural haematoma at the cervical thoracic spine from C6/C7 to T4", and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 30-SEP-2014 to 10-OCT-2014 due to "Factor VIII deficiency",

Medical history included haemophilia A, [redacted]

Treatment medications included - recombinant coagulation factor VIII (factor VIII, recombinant).

On 30-SEP-2014 the patient received a single dose of N8-GP (230 U) as a precaution [redacted]

On 05-OCT-2014 the patient presented with a spontaneous epidural bleed extending from C6/C7 to T4 with no focal neurological signs.

On 06-OCT-2014 the patient was hospitalised.

On 07-OCT-2014 [redacted] 1.6 ml N8-GP (25U/kg) administered at 14:05. [redacted] Additional 1 6 ml N8-GP (25U/kg) administered at 17:30.

On 08-OCT-2014 [redacted] 2.16ml N8-GP (35U/kg) administered at 06 30. [redacted] 4 3 ml N8-GP (65U/kg) charted 3 times daily and administered at 16:00 and 23:00.

On 09-OCT-2014: [redacted] 4 3ml N8-GP (65U/kg) administered at 06:00. [redacted] 4.3ml N8-GP (65U/kg) administered at 14 30. [redacted]

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			[redacted] 4.3ml N8-GP (65U/kg) administered at 18:40 and 22 00. On 10-OCT-2014: 4 3ml N8-GP (65U/kg) administered at 02:00. [redacted] Follow up FVIII inhibitor testing was performed again on 12-DEC-2014 which was negative. Action taken to N8-GP 500U vial was reported as Product discontinued. On 28-OCT-2014 the outcome for the event "Epidural haematoma at the cervical thoracic spine from C6/C7 to T4" was Recovered. Investigator's causality (N8-GP 500U vial) - Epidural haematoma at the cervical thoracic spine from C6/C7 to T4 : Unlikely Sponsor's causality (N8-GP 500U vial) - Epidural haematoma at the cervical thoracic spine from C6/C7 to T4 : Unlikely				
552754	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK] Case Seriousness?: Yes Patient Subject #: Study Center D: [redacted] Case Narrative: Trial ID: NN7088-3908 Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%) Trial phase 3a Trial Drugs: N8-GP rFVIII, N8-GP 500U vial [redacted]	IV bolus	23-JUN-2017 Ongoing	23-JUN-2017	Hospitalization Laceration wound Right Dorsum Tongue [TONGUE NJURY]	Recovered

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Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			This Clinical Trial case from [redacted] was reported by an Investigator as "Hospitalization Laceration wound Right Dorsum Tongue" and concerned a [redacted] Male patient who was treated with N8-GP rFVIII (TUROCTOCOG ALFA PEGOL) from 23-JUN-2017 and ongoing due to "Factor VIII deficiency". Medical history included haemophilia A. On 23-JUN-2017 the patient accidentally bit his tongue from a falling and 1 dose of IV N8-GP was infused but slow oozing medication. [redacted] On 02-JUL-2017 the patient was well and discharged Action taken to N8-GP rFVIII was reported as No Change. On 18-JUL-2017 the outcome for the event "Hospitalization Laceration wound Right Dorsum Tongue" was recovered. Investigator's causality (N8-GP rFVIII) - Hospitalization Laceration wound Right Dorsum Tongue: Unlikely Sponsor's causality (N8-GP rFVIII) - Hospitalization Laceration wound Right Dorsum Tongue: Unlikely This case is linked to ARGUS case 553809				
553809	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK] UNK [UNK]	IV bolus IV bolus	23-JUN-2017 Ongoing 05-JUL-2017 Ongoing	05-JUL-2017	Inhibitor to FVIII [FACTOR VIII INH BITION]	Not recovered
			Case Seriousness?: Yes Patient Subject #: Study Center D: [redacted] Case Narrative: Trial ID: NN7088-3908 Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%) Trial phase 3a Trial Drugs: N8-GP rFVIII, N8-GP 500U vial [redacted] This Clinical Trial case from [redacted] was reported by an Investigator as "Inhibitor to FVIII" and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 23-JUN-2017 and ongoing due to Haemophilia A, and N8-GP rFVIII (TUROCTOCOG ALFA PEGOL) from 16-JUN-2017 due to "Haemophilia A" and "Factor VIII deficiency".				

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome

Medical history included Haemophilia A.

[redacted]

Prior to the event:
On 23-JUN-2017 [redacted]

On 05-JUL-2017, the patient was admitted to hospital as there was bleeding again [redacted] inhibitor development and start on ITI with frequency of 75 IU/kg/dose twice daily [redacted]

[redacted]

On 11-JUL-2017, the patient was discharged from hospital.

Action taken to N8-GP 500U vial was reported as Dose Increased.
Action taken to N8-GP rFVIII was reported as Dose Increased.

The outcome for the event "Inhibitor to FVIII" was Not recovered.

Investigator's causality (N8-GP 500U vial) -
Inhibitor to FVIII: Probable

Sponsor's causality (N8-GP 500U vial) -
Inhibitor to FVIII: Possible

Investigator's causality (N8-GP rFVIII) -
Inhibitor to FVIII: Probable

Sponsor's causality (N8-GP rFVIII) -
Inhibitor to FVIII: Possible

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			Since last submission the case has been updated with following information: (NOT SUBMITTED) - Laboratory results updated Company comment: A known complication of haemophilia treatment with current FVIII products is FVIII inhibitor development and it is known that this condition can develop in previously untreated patients with haemophilia A following exposure to FVIII products. This case is linked to ARGUS case 552754					
461088	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK] Case Seriousness?: Yes Patient Subject #: Study Center D: [redacted] Case Narrative: Trial ID: NN7088-3908	IV bolus	18-DEC-2014 Ongoing	30-JUL-2015	F8 inhibitor test positive (1st and 2nd result of central lab) [FACTOR VIII INHIBITION]	Recovered

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)

Trial phase: 3a

Investigational Drugs: N8-GP rFVIII, N8-GP 500U vial.

[redacted]

This Clinical Trial case from [redacted] was reported by an Investigator as "F8 inhibitor test positive (1st and 2nd result of central lab)", and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 18-DEC-2014 and ongoing due to "Factor VIII deficiency".

Medical history included haemophilia A.

Pre-prophylaxis treatment with trial drug N8-GP was started on 18-DEC-2014, and from 21-MAY-2015 the patient began prophylaxis treatment with trial drug.

[redacted]

On 30-JUL-2015 the patient had first Anti factor VIII antibody test of [redacted] BU/ml (reference range < 0 6) following 15 exposure days. [redacted]

[redacted]

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			[redacted]					

The outcome for the event "F8 inhibitor test positive (1st and 2nd result of central lab)" was reported as recovered on16-FEB-2017.

Action taken to N8-GP 500U vial was reported as No Change.

Investigator's causality (N8-GP 500U vial) -
F8 inhibitor test positive (1st and 2nd result of central lab): Probable

Sponsor's causality (N8-GP 500U vial) -
F8 inhibitor test positive (1st and 2nd result of central lab): Possible

Since the last submission the case was updated with: (Not Submitted)
-Recovery date changed from 02-MAR-2017 to 16-FEB-2017
-FIII chromogen test added
-> added to inhibitor tests taken on 19-JAN-2017, 16-FEB-2017 and 02-MAR-2017 and thereby confirmed negative

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
461737	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK]	IV bolus	18-DEC-2014 Ongoing	24-AUG-2015	Head bruise [CONTUSION]	Recovered

Case Seriousness?: Yes
Patient Subject #:
Study Center D: [redacted]
Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)
Trial phase 3a

Investigational Drugs: N8-GP rFVIII, N8-GP 500U vial.

[redacted]

This Clinical Trial case from [redacted] was reported by an Investigator as "Head bruise", and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 18-DEC-2014 and ongoing due to "Factor VIII deficiency",

Medical history included haemophilia a.

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			[redacted]					
			On 24-AUG-2015 the patient experienced a head bruise leading to admission to hospital the same day. [redacted] Action taken to N8-GP 500U vial was reported as No Change. On 25-AUG-2015 the outcome for the event "Head bruise" was Recovered. Investigator's causality (N8-GP 500U vial) - Head bruise : Unlikely Sponsor's causality (N8-GP 500U vial) - Head bruise : Unlikely					
552065	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [60 Iu/kg-UNK] UNK [75 Iu/kg-UNK]	IV bolus IV bolus	14-NOV-2016 Ongoing	19-JUN-2017	FVIII inhibitor [FACTOR VIII INH BITION]	Not recovered
			Case Seriousness?: Yes Patient Subject #: Study Center D: Case Narrative: Trial ID: NN7088-3908 Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%) Trial phase 3a Trial Drugs: N8-GP rFVIII, N8-GP 500U vial [redacted] This Clinical Trial case from [redacted] was reported by an Investigator as "FVIII inhibitor" and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 14-NOV-2016 and ongoing due to "Factor VIII deficiency". Medical history included Haemophilia A, [redacted] On 19-JUN-2017 the patient experienced FVIII inhibitor. The patient did not seem to response to factor treatment following trauma. On the same day an anti factor VIII antibody from local laboratory was performed and showed [redacted] BU (<0 6). From central laboratory anti factor VIII antibody was [redacted] BU (reference range <0.6 BU).					

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			[redacted]					

No FVIII activity and clot stability test were performed in local laboratory, and no FVIII activity was taken in central laboratory because of weight limitation of the patient, only trough level.

Action taken to N8-GP 500U vial was reported as Dose Increased.
Novoseven to be considered during bleeds

The outcome for the event "FVIII inhibitor" was Not recovered.

Investigator's causality (N8-GP 500U vial) -
FVIII inhibitor: Possible

Sponsor's causality (N8-GP 500U vial) -
FVIII inhibitor: Possible

On 23-JUL-2017 this case was re-classified from non-serious to serious by Investigator

Since last submission the case has been updated with following information: (NOT SUBMITTED)
- Dosage regimen for treatment medication NovoSeven updated

Company comment:
Due to the nature of the event, it cannot be excluded that the event maybe possibly related to the trial drug.

Total number of case entries printed: 14
Total number of cases printed: 14

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Ingredient: **TUROCTOCOG ALFA PEGOL**

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
Study ID: NN7088-3908 (**3**)								
526145	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK]	IV bolus	09-SEP-2016 to 16-DEC-2016	18-NOV-2016	N8-GP inhibitors [FACTOR VIII INHIBITION]	Not recovered
			UNK [UNK]	IV bolus	16-DEC-2016 to 16-DEC-2016			

Case Seriousness?: Yes
Patient Subject #:
Study Center D: [redacted]
Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)

Trial phase 3a

Trial Drugs: N8-GP rFVIII, N8-GP 500U vial

[redacted]

This Clinical Trial case from [redacted] was reported by an Investigator as "N8-GP inhibitors" and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 09-SEP-2016 to 16-DEC-2016 due to "Haemophilia A".

Medical history included Haemophilia A.

[redacted]

On 18-NOV-2016 (V4 and reported as AE onset date) a re-testing was required, which showed [redacted] BU inhibitors (reference range 0-0.6) and confirmed the lack of recovery on 30 min.

On 16-DEC-2016 last dose of the trial product was given. Same day Inhibitor antibodies result from central laboratory was [redacted] BU.

[redacted]

Action taken to N8-GP 500U vial was reported as Dose Increased. However, a stop date of trial product has been reported, since last dose given prior to withdrawal of consent was increased dose on 16-DEC-2016.

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Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			The outcome for the event "N8-GP inhibitors" was Not recovered. Since last submission the case has been updated with following information: (NOT SUBMITTED WITH THIS INFORMATION) -Inhibitor antibodies [redacted] BU central lab on 16-DEC-2016 -Narrative updated accordingly Investigator's causality (N8-GP 500U vial) - N8-GP inhibitors: Possible Sponsor's causality (N8-GP 500U vial) - N8-GP inhibitors: Possible Company comment: Based on the nature of the event a causal relationship is possible.					
553809	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK] UNK [UNK]	IV bolus	23-JUN-2017 Ongoing IV bolus	05-JUL-2017	Inhibitor to FVIII [FACTOR VIII INH BITION]	Not recovered
					05-JUL-2017 Ongoing			
			Case Seriousness?: Yes Patient Subject #: Study Center D: [redacted] Case Narrative: Trial ID: NN7088-3908 Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%) Trial phase 3a Trial Drugs: N8-GP rFVIII, N8-GP 500U vial [redacted] This Clinical Trial case from [redacted] was reported by an Investigator as "Inhibitor to FVIII" and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 23-JUN-2017 and ongoing due to Haemophilia A, and N8-GP rFVIII (TUROCTOCOG ALFA PEGOL) from 16-JUN-2017 due to "Haemophilia A" and "Factor VIII deficiency". Medical history included Haemophilia A. [redacted] Prior to the event: On 23-JUN-2017 [redacted]					

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome

[redacted]

On 05-JUL-2017, the patient was admitted to hospital as there was bleeding again [redacted] BU inhibitor development and start on ITI with frequency of 75 IU/kg/dose twice daily. [redacted]

[redacted]

On 11-JUL-2017, the patient was discharged from hospital.

Action taken to N8-GP 500U vial was reported as Dose Increased.
Action taken to N8-GP rFVIII was reported as Dose Increased.

The outcome for the event "Inhibitor to FVIII" was Not recovered.

Investigator's causality (N8-GP 500U vial) -
Inhibitor to FVIII: Probable

Sponsor's causality (N8-GP 500U vial) -
Inhibitor to FVIII: Possible

Investigator's causality (N8-GP rFVIII) -
Inhibitor to FVIII: Probable

Sponsor's causality (N8-GP rFVIII) -
Inhibitor to FVIII: Possible

Since last submission the case has been updated with following information: (NOT SUBMITTED)
- Laboratory results updated

Company comment: A known complication of haemophilia treatment with current FVIII products is FVIII inhibitor development and it is known that this condition can develop in previously untreated patients with haemophilia A following exposure to FVIII products.

This case is linked to ARGUS case 552754

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
552065	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [60 Iu/kg-UNK] UNK [75 Iu/kg-UNK]	IV bolus IV bolus	14-NOV-2016 Ongoing	19-JUN-2017	FVIII inhibitor [FACTOR VIII INH BITION]	Not recovered

Case Seriousness?: Yes
Patient Subject #:
Study Center D: [redacted]
Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)

Trial phase 3a

Trial Drugs: N8-GP rFVIII, N8-GP 500U vial

[redacted]

This Clinical Trial case from [redacted] was reported by an Investigator as "FVIII inhibitor" and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 14-NOV-2016 and ongoing due to "Factor VIII deficiency".

Medical history included Haemophilia A, [redacted]

On 19-JUN-2017 the patient experienced FVIII inhibitor. The patient did not seem to response to factor treatment following trauma. On the same day an anti factor VIII antibody from local laboratory was performed and showed [redacted] BU (<0 6). From central laboratory anti factor VIII antibody was [redacted] BU (reference range <0.6 BU).

[redacted]

No FVIII activity and clot stability test were performed in local laboratory, and no FVIII activity was taken in central laboratory because of weight limitation of the patient, only trough level.

Action taken to N8-GP 500U vial was reported as Dose Increased.
Novoseven to be considered during bleeds

The outcome for the event "FVIII inhibitor" was Not recovered.

Investigator's causality (N8-GP 500U vial) -
FVIII inhibitor: Possible

Sponsor's causality (N8-GP 500U vial) -
FVIII inhibitor: Possible

On 23-JUL-2017 this case was re-classified from non-serious to serious by Investigator

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Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			Since last submission the case has been updated with following information: (NOT SUBMITTED) - Dosage regimen for treatment medication NovoSeven updated Company comment: Due to the nature of the event, it cannot be excluded that the event maybe possibly related to the trial drug.					

Total number of case entries printed: 3
Total number of cases printed: 3

Ingredient: TUROCTOCOG ALFA PEGOL

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
Study ID: NN7088-3908 (**6**)								
526145	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK]	IV bolus	09-SEP-2016 to 16-DEC-2016	18-NOV-2016	N8-GP inhibitors [FACTOR VIII INHIBITION]	Not recovered
			UNK [UNK]	IV bolus	16-DEC-2016 to 16-DEC-2016			

Case Seriousness?: Yes
Patient Subject #:
Study Center D: [redacted]
Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)

Trial phase 3a

Trial Drugs: N8-GP rFVIII, N8-GP 500U vial

[redacted]

This Clinical Trial case from [redacted] was reported by an Investigator as "N8-GP inhibitors" and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 09-SEP-2016 to 16-DEC-2016 due to "Haemophilia A".

Medical history included Haemophilia A.

[redacted]

On 18-NOV-2016 (V4 and reported as AE onset date) a re-testing was required, which showed [redacted] BU inhibitors (reference range 0-0.6) and confirmed the lack of recovery on 30 min.

On 16-DEC-2016 last dose of the trial product was given. Same day Inhibitor antibodies result from central laboratory was [redacted] BU.

[redacted]

Action taken to N8-GP 500U vial was reported as Dose Increased. However, a stop date of trial product has been reported, since last dose given prior to withdrawal of consent was increased dose on 16-DEC-2016.

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome

The outcome for the event "N8-GP inhibitors" was Not recovered.

Since last submission the case has been updated with following information: (NOT SUBMITTED WITH THIS INFORMATION)
-Inhibitor antibodies [redacted] BU central lab on 16-DEC-2016
-Narrative updated accordingly

Investigator's causality (N8-GP 500U vial) -
N8-GP inhibitors: Possible

Sponsor's causality (N8-GP 500U vial) -
N8-GP inhibitors: Possible

Company comment: Based on the nature of the event a causal relationship is possible.

428527	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK] UNK [UNK]	IV bolus IV bolus	23-SEP-2014 to 02-DEC-2014 09-DEC-2014 to 27-JAN-2015	21-OCT-2014	Positive factorVIII inhibitor with high titre. [FACTOR VIII NH BITION]	Recovered

Case Seriousness?: Yes
Patient Subject #:
Study Center D: [redacted]
Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)

Trial phase 3a

Investigational Drugs: N8-GP rFVIII, N8-GP 500U vial

[redacted]

This Clinical Trial case from [redacted] was reported by an Investigator as "Positive factorVIII inhibitor with high titre.", and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 23-SEP-2014 to 02-DEC-2014, and from 09-DEC-2014 to 27-JAN-2015 due to "Factor VIII deficiency", and other trial drug N8-GP rFVIII (TUROCTOCOG ALFA PEGOL) from 03-FEB-2015 and ongoing due to "Factor VIII deficiency".

Medical history included Haemophilia A and [redacted]

On 21-OCT-2014 the patient had a positive factor VIII inhibitor test measured by central lab. The inhibitor titre was [redacted] BU/ml (ref. range <0.6 BU/ml). [redacted]

[redacted]

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome



Patient had no signs and symptoms of any bleeding episode.

Action taken to N8-GP 500U vial was reported as Dose Increased.
Action taken to N8-GP rFVIII was reported as No Change.

On 10-JAN-2017 the patient recovered from the event "Positive factorVIII inhibitor with high titre."

Investigator's causality (N8-GP 500U vial) -
Positive factorVIII inhibitor with high titre.: Probable

Sponsor's causality (N8-GP 500U vial) -
Positive factorVIII inhibitor with high titre.: Possible

Investigator's causality (N8-GP rFVIII) -
Positive factorVIII inhibitor with high titre.: Probable

Sponsor's causality (N8-GP rFVIII) -
Positive factorVIII inhibitor with high titre.: Unlikely

Since last submission the following information has been updated:
- Final outcome and resolution date

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Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			- Laboratory values - Investigator's alternative aetiology added Narrative updated accordingly Comment: company comment: Causality for N8-GP rFVIII (2000 U/vial) was assessed by sponsor as unlikely, as the product was administered more than 3 month after the onset date of the event.					
425317	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [65 Iu/kg-prn]	IV bolus	30-SEP-2014 to 10-OCT-2014	08-OCT-2014	Rash on left leg unknown aetiology [RASH]	Recovered

Case Seriousness?: No
Patient Subject #:
Study Center D: [redacted]
Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)
Trial phase 3a

Investigational Drugs: N8-GP (turoctocog alfa pegol)

[redacted]

This Clinical Trial case from [redacted] was reported by an Investigator as "Rash on left leg, unknown aetiology", and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 30-SEP-2014 to 10-OCT-2014 due to "haemophilia A".

Medical history included Haemophilia A and [redacted]

On 08-OCT-2014, during the same hospitalisation the patient presented with rash on left leg. The rash was described as blanching, with circular macules noted on left leg. [redacted] The rash was monitored.

[redacted]

The patient did not receive treatment for the event.

As of 09-OCT-2014 the rash was improving.

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome

Action taken to N8-GP 500U vial was reported as No Change. On 10-OCT-2014 trial product was withdrawn due to other reasons than the event.

On 22-OCT-2014 the outcome for the event "Rash on left leg, unknown aetiology" was recovered.

Investigator's causality (N8-GP 500U vial) -
Rash on left leg, unknown aetiology : Possible

Sponsor's causality (N8-GP 500U vial) -
Rash on left leg, unknown aetiology : Possible

This case is linked to case 424994 (epidural haematoma at the cervical thoracic spine from C6/C7 to T4).

Company comment: Concomitant medication Paracetamol (paracetamol), Oxycodone (oxycodone), Propofol (propofol), Sevoflurane (sevoflurane) and Lmx4 (lidocaine) should be noted as confounding factors which may have attributed to the "rash on leg"

553809	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK]	IV bolus	23-JUN-2017 Ongoing	05-JUL-2017	Inhibitor to FVIII [FACTOR VIII INH BITION]	Not recovered
			UNK [UNK]	IV bolus	05-JUL-2017 Ongoing			

Case Seriousness?: Yes
Patient Subject #:
Study Center D: [redacted]
Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)

Trial phase 3a

Trial Drugs: N8-GP rFVIII, N8-GP 500U vial

[redacted]

This Clinical Trial case from [redacted] was reported by an Investigator as "Inhibitor to FVIII" and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 23-JUN-2017 and ongoing due to Haemophilia A, and N8-GP rFVIII (TUROCTOCOG ALFA PEGOL) from 16-JUN-2017 due to "Haemophilia A" and "Factor VIII deficiency".

Medical history included Haemophilia A.

[redacted]

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome

[redacted]

On 05-JUL-2017, the patient was admitted to hospital as there was bleeding again and [redacted] FVIII level repeated was <1% and develop inhibitor [redacted] BU inhibitor development and start on ITI with frequency of 75 IU/kg/dose twice daily. [redacted]

[redacted]

On 11-JUL-2017, the patient was discharged from hospital.

Action taken to N8-GP 500U vial was reported as Dose Increased.
Action taken to N8-GP rFVIII was reported as Dose Increased.

The outcome for the event "Inhibitor to FVIII" was Not recovered.

Investigator's causality (N8-GP 500U vial) -
Inhibitor to FVIII: Probable

Sponsor's causality (N8-GP 500U vial) -
Inhibitor to FVIII: Possible

Investigator's causality (N8-GP rFVIII) -
Inhibitor to FVIII: Probable

Sponsor's causality (N8-GP rFVIII) -
Inhibitor to FVIII: Possible

Since last submission the case has been updated with following information: (NOT SUBMITTED)
- Laboratory results updated

Company comment: A known complication of haemophilia treatment with current FVIII products is FVIII inhibitor development and it is known that this condition can develop in previously untreated patients with haemophilia A following exposure to FVIII products.

00440919 10

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			This case is linked to ARGUS case 552754					
461088	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [UNK]	IV bolus	18-DEC-2014 Ongoing	30-JUL-2015	F8 inhibitor test positive (1st and 2nd result of central lab) [FACTOR VIII INHIBITION]	Recovered

Case Seriousness?: Yes
Patient Subject #:
Study Center D: [redacted]
Case Narrative: Trial ID: NN7088-3908

Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%)

Trial phase: 3a

Investigational Drugs: N8-GP rFVIII, N8-GP 500U vial.

[redacted]

This Clinical Trial case from [redacted] was reported by an Investigator as "F8 inhibitor test positive (1st and 2nd result of central lab)", and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 18-DEC-2014 and ongoing due to "Factor VIII deficiency".

Medical history included haemophilia A.

Pre-prophylaxis treatment with trial drug N8-GP was started on 18-DEC-2014, and from 21-MAY-2015 the patient began prophylaxis treatment with trial drug.

[redacted]

On 30-JUL-2015 the patient had first Anti factor VIII antibody test of [redacted] BU/ml (reference range < 0 6) following 15 exposure days. [redacted]

[redacted]

The outcome for the event "F8 inhibitor test positive (1st and 2nd result of central lab)" was reported as recovered on16-FEB-2017.

00440919 1 0

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			Action taken to N8-GP 500U vial was reported as No Change. Investigator's causality (N8-GP 500U vial) - F8 inhibitor test positive (1st and 2nd result of central lab): Probable Sponsor's causality (N8-GP 500U vial) - F8 inhibitor test positive (1st and 2nd result of central lab): Possible Since the last submission the case was updated with: (Not Submitted) -Recovery date changed from 02-MAR-2017 to 16-FEB-2017 -FIII chromogen test added -> added to inhibitor tests taken on 19-JAN-2017, 16-FEB-2017 and 02-MAR-2017 and thereby confirmed negative					
552065	[redacted] Clinical Trial	[redacted] Male	**N8-GP 500U vial / Powder and solvent for solution for injection** UNK [60 Iu/kg-UNK] UNK [75 Iu/kg-UNK]	IV bolus IV bolus	14-NOV-2016 Ongoing	19-JUN-2017	FVIII inhibitor [FACTOR VIII INH BITION]	Not recovered
			Case Seriousness?: Yes Patient Subject #: [redacted] Study Center D: Case Narrative: Trial ID: NN7088-3908 Trial title: This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of previously untreated patients (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%) Trial phase 3a Trial Drugs: N8-GP rFVIII, N8-GP 500U vial [redacted] This Clinical Trial case from [redacted] was reported by an Investigator as "FVIII inhibitor" and concerned a [redacted] Male patient who was treated with N8-GP 500U vial (TUROCTOCOG ALFA PEGOL) from 14-NOV-2016 and ongoing due to "Factor VIII deficiency". Medical history included Haemophilia A, [redacted] On 19-JUN-2017 the patient experienced FVIII inhibitor. The patient did not seem to response to factor treatment following trauma. On the same day an anti factor VIII antibody from local laboratory was performed and showed [redacted] BU (<0 6). From central laboratory anti factor VIII antibody was [redacted] BU (reference range <0.6 BU). [redacted] No FVIII activity and clot stability test were performed in local laboratory, and no FVIII activity was taken in central laboratory because of weight limitation of the patient, only trough level.					

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term]	Patient Outcome
			Action taken to N8-GP 500U vial was reported as Dose Increased. Novoseven to be considered during bleeds The outcome for the event "FVIII inhibitor" was Not recovered. Investigator's causality (N8-GP 500U vial) - FVIII inhibitor: Possible Sponsor's causality (N8-GP 500U vial) - FVIII inhibitor: Possible On 23-JUL-2017 this case was re-classified from non-serious to serious by Investigator Since last submission the case has been updated with following information: (NOT SUBMITTED) - Dosage regimen for treatment medication NovoSeven updated Company comment: Due to the nature of the event, it cannot be excluded that the event maybe possibly related to the trial drug.					

Total number of case entries printed: 6
Total number of cases printed: 6

ツロクトコグ アルファ ペゴル（遺伝子組換え）

2.7.4.7 付録 3

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1 Rationale for adverse drug reactions included in the proposed N8-GP prescribing information

The dataset pool consisting of patients from trial NN7088-3776, NN7088-3859, NN7088-3885 and NN7088-4033 included 270 patients (Summary 2.7.4, Appendix 7.1, Table 37).

Areas of special interest were selected based on known pharmacological class effects. Additionally, rare events, all event types where at least one event is reported as possible related, all events defined as medical events of special interest (MESIs), all event types included in relevant competitor labels, and all events with a frequency above 5% were selected. Thorough medical evaluation of the identified events was performed to identify the adverse drug reactions (ADRs) where a causal relationship between N8-GP and the event was a reasonable possibility.

In accordance with guidelines,[1, 2] the following approach was used: ADRs were primarily enlisted as MedDRA preferred terms (PTs), frequencies were based on crude rates (i.e. frequency of all subjects reporting the event in question), and PTs were pooled if relevant to avoid diluting or obscuring the true effect. The ADRs are presented in Table 1.

Table 1 Adverse drug reactions included in the proposed N8-GP prescribing information

Adverse Drug Reaction	Rationale for inclusion in the prescribing information	Frequency	Data location
Inhibitor development	Known pharmacological class effect and reported in patients treated with N8-GP in the clinical development programme.	As of 15 August 2017, statistical analysis was applied for the endpoint incidence rate of FVIII inhibitors ≥0.6 BU. The estimated rate of inhibitory antibodies, together with a 1-sided 97.5% upper confidence limit, was based on an exact calculation for a binomial distribution. The number of patients at risk (denominator) was defined as patients who had a minimum of 50 exposure days to N8-GP or who had confirmed inhibitory antibodies against FVIII regardless of the number of exposure days. 1/235 (0.4%)	Summary 2.7.4, Appendix 7.1, Table 82
Allergic reactions	Known pharmacological class effect and reported in patients treated with N8-GP in the clinical development programme. Based on sponsor's medical evaluation the following PTs have been included: rashes, pruritus and erythema and hypersensitivity.	The frequency has been calculated including all patients reporting the event with the PTs listed below. Rash: 14/270 (5.2%) Erythema: 5/270 (1.9%) Pruritus: 4/270 (1.5%) Hypersensitivity: 2/270 (0.7%)	Summary 2.7.4, Appendix 7.1, Table 20
Injection site reactions	Known risk with administration of medication. Based on sponsor's medical evaluation the following NNMQ have been included: NNMQ Injection site reactions. Incidence rate include all injection site reactions (as defined above), regardless of the investigator's causality assessment.	The frequency has been calculated including all patients reporting an event included in NNMQ of injection site reactions 7/270 (2.6%)	Summary 2.7.4, Appendix 7.1, Table 36

PT: preferred term; SOC: system organ class; NNMQ: Novo Nordisk specific MedDRA query; MedDRA: medical dictionary for regulatory activities.

References

1. The European Commision. A Guideline on Summary of Product Characteristics (SmPC) (revision 2, dated September 2009).
2. U.S.Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for biologics Evaluation and Research (CBER). Guidance for Industry, Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products - Content and Format. Jan 2006.

ツロクトコグ アルファ ペゴル（遺伝子組換え）

2.7.5 参考文献

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2.7.5　参考文献

参考文献は、Module 2.5、Module 2.7.1、Module 2.7.2、Module 2.7.3 及び Module 2.7.4 の参考文献の項にそれぞれ示した。