フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

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

ADA	:	American Diabetes Association（米国糖尿病学会）
AE	:	adverse event（有害事象）
ALP	:	alkaline phosphatase（アルカリホスファターゼ）
ALT	:	alanine aminotransferase（アラニンアミノトランスフェラーゼ）
AST	:	aspartate aminotransferase（アスパラギン酸アミノトランスフェラーゼ）
ATC	:	anatomical therapeutic chemical（解剖治療化学）
BG	:	blood glucose〔血糖（値）〕
BMI	:	body mass index〔体容量指数：体重(kg)／身長$(m)^2$〕
BP	:	blood pressure（血圧）
CGM	:	continuous glucose monitor（持続血糖測定）
CI	:	confidence interval（信頼区間）
CLAE	:	clinical laboratory adverse event（臨床検査に関する有害事象）
CL_{CR}	:	creatinine clearance（クレアチニンクリアランス）
CRF	:	case report form（症例報告書）
CSII	:	continuous subcutaneous insulin infusion（持続皮下インスリン注入）
D	:	diastolic〔（心臓）拡張期の〕
DBL	:	database lock（データベースロック）
DUN	:	dispensing unit number（交付ユニット番号）
E	:	number of adverse events or hypoglycaemic episodes（有害事象又は低血糖の件数）
ECG	:	Electrocardiogram（心電図）
eGFR	:	estimated glomerular filtration rate（推算糸球体濾過量）
EOT	:	end of text
EU	:	European Union（欧州連合）
GW	:	gestational week（妊娠週数）
HbA1c	:	glycosylated haemoglobin（糖化ヘモグロビン A1c）
HDL	:	high-density lipoprotein（高比重リポタンパク）
ISPAD	:	international society for pediatric and adolescent diabetes（国際小児思春期糖尿病学会）
LDL	:	low-density lipoprotein（低比重リポタンパク）
MACE	:	major adverse cardiovascular event（重大な心血管系事象）
MedDRA	:	medical dictionary for regulatory activities（国際医薬用語集）
MESI	:	medical events of special interest（特に注目すべき医学的事象）
N	:	number of subjects（症例数）
NA	:	not applicable（該当なし）
NN	:	Novo Nordisk（ノボ ノルディスク）
PBRER	:	periodic benefit risk evaluation repor（定期的ベネフィット・リスク評価報告）
PG	:	plasma glucose（血漿中グルコース）
PSUR	:	periodic safety update report（定期的安全性最新報告）
PT	:	preferred term（基本語）
PYE	:	patient years of exposure（人・年）
R	:	rate （単位時間あたりの発現件数）
S	:	systolic〔（心臓）収縮期の〕
SD	:	standard deviation（標準偏差）

SAE	:	serious adverse event（重篤な有害事象）
SMBG	:	self-measured blood glucose（血糖自己測定）
SOC	:	system organ class（器官別大分類）
T1DM	:	type 1 diabetes mellitus（1 型糖尿病）
T2DM	:	type 2 diabetes mellitus（2 型糖尿病）
TEAE	:	treatment emergent adverse event（治験薬投与下で発現した有害事象）
%B/T	:	%B/T value is proportional to the antibody titre present in the sample; percent bound radioactivity (B) of the total amount of radioactivity (T)〔全体の放射能（T）に対する結合した放射能（B）の割合。%B/T 値は試料中の抗体の量（力価）に比例する〕

本臨床概要では、本剤（治験成分記号：NN1218）は faster aspart（fast-acting insulin aspart）」と記載し、本剤と同じインスリン アスパルトを有効成分とする、現在市販されている製剤をノボラピッド®注と記載する。

Faster aspart を用いて実施されたすべての臨床試験は、プロジェクト名（NN1218）の後に 4 桁の固有の番号をつけて NN1218-4131 のように表記する。本臨床概要では、4 桁の固有の番号を用いて「XXXX 試験」と表記する。

2.7.4.1 医薬品への曝露

2.7.4.1.1 総括的安全性評価計画及び安全性試験の叙述

2.7.4.1.1.1 背景

2.7.4.1.1.1.1 Faster aspart

Fast-acting insulin aspart（faster aspart）は、既承認の超速効型インスリンアナログのノボラピッド®注と同じ有効成分であるインスリン アスパルト（遺伝子組換え）を含有し、ノボラピッド®注と比較して血糖降下作用がより速く発現する Bolus インスリンとして開発した製剤である。ノボラピッド®注は日本では 2001 年に販売され、2009 年 10 月に再審査期間を終了している。現在、ノボラピッド®注は 1 型糖尿病患者及び 2 型糖尿病患者におけるインスリン療法で広く使用されている製剤である。

Faster aspart は、インスリン作用の発現がより速くなるようノボラピッド®注の処方を変更した製剤であり、これにより薬剤学的特性がノボラピッド®注と異なる。添加剤として追加されたニコチン酸アミドは、インスリン アスパルトの皮下投与後初期の吸収が速くなることに寄与しており、これによりノボラピッド®注と比較して初期の血糖降下作用が大きくなる。また、L-アルギニン塩酸塩は faster aspart 製剤の安定剤として追加されている。各添加剤の安全性プロファイルはよく知られている。両添加剤は日本薬局方に収載されており、各添加剤の一日最大使用量は、日本で承認されている一日最大使用量を超えていない[1]。

Faster aspart は、現在利用可能な治療法と比較して、食事時のより生理的なインスリン分泌パターンを模倣することを目指して開発された。Faster aspart は、インスリン アスパルトが血中により速く吸収されることで、ノボラピッド®注とは異なる薬物動態及び薬力学的作用プロファイルを示し、血糖降下作用の発現がより速くなり、食後血糖値の上昇を効果的に抑制し、食後血糖コントロールを改善する。Faster aspart は、インスリン作用の発現が速いことから、食直前又は食事開始後に投与可能という柔軟な投与方法を提供でき、臨床上のベネフィットも有する製剤である。Faster aspart の安全性プロファイルは、ノボラピッド®注と同様であることが示されている。

2.7.4.1.1.1.2 非臨床プログラムにおける安全性プロファイル

Faster aspart の有効成分であるインスリン アスパルトは、非臨床及び臨床の包括的な安全性情報が既に得られていることから、faster aspart の非臨床開発にあたっては必要な試験を選択して追加実施した。詳細については Module 2.4、非臨床試験の概括評価を参照。すなわち faster aspart の非臨床安全性評価は、ノボラピッド®注の承認取得以降に得られたインスリン アスパルトの安全性に関する文献調査の実施、容器及び施栓系からの溶出物の安全性評価、ならびにラット、ウサギ及びミニブタにおける局所刺激性の検討を行うことで、faster aspart による糖尿病患者の長期間にわたる治療を安全に実施できることを裏付けた。

2.7.4.1.1.1.3　安全性評価の概観

Faster aspart の臨床的安全性の評価は主として、日本人を含む 1 型糖尿病患者を組み入れた 2 つの検証的臨床試験（4131 及び 4101 試験）に基づき実施した。両試験のデザインの詳細は Module 2.7.3.1.3 に示す。両試験には、2 つの二重盲検の投与群〔faster aspart 及びノボラピッド®注を食前投与する群：それぞれ、faster aspart（食前投与）群とノボラピッド®注群とする〕と 1 つの非盲検の投与群〔faster aspart を食後投与する群：faster aspart（食後投与）群とする〕を含めた。食前投与は、食事開始の 0～2 分前に投与することと定義した。食後投与の定義は、4131 試験では「食事終了時（食事が 20 分で終了しない場合は食事開始後 20 分）に投与する」、4101 試験では「食事開始後 20 分に投与する」とした。

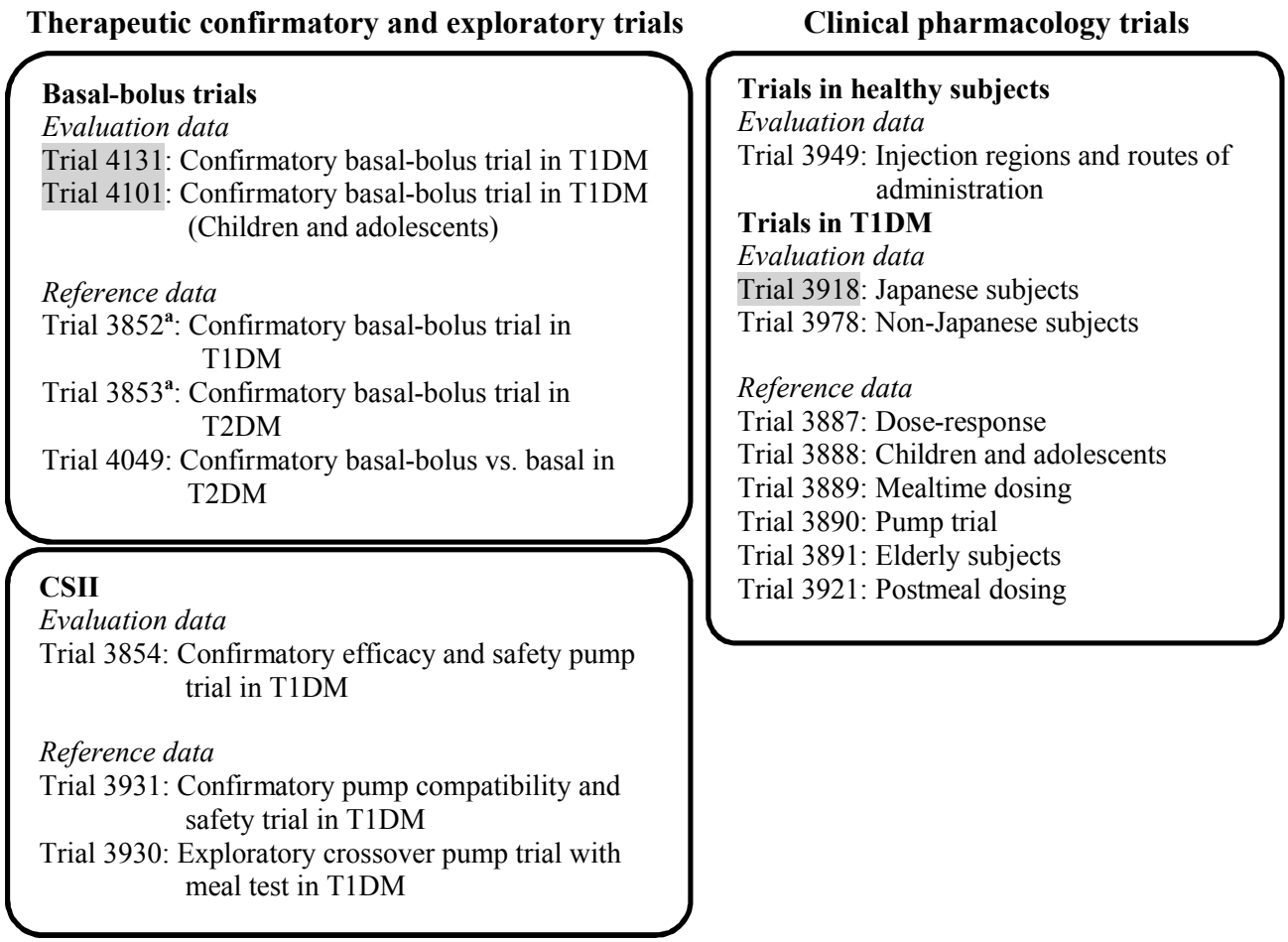
さらに、日本人 1 型糖尿病患者を対象に実施した臨床薬理試験（3918 試験）で得られた安全性情報について本臨床概要に提示した。

上記 3 試験以外に、faster aspart 臨床開発プログラムに含まれる日本人を組み入れていない臨床試験の結果も用いて、安全性情報を補足した。死亡、その他の重篤な有害事象及び特に注目すべき有害事象といった、安全性シグナルとなりうるが件数の少ない事象については、3852（52 週）、3853、4049 及び 3931 試験で構成される海外第 3 相試験の併合データ（以下、海外併合データ：2.7.4.1.1.2.5 項）の結果も提示した。死亡及びその他の重篤な有害事象については、図 2.7.4.1-1 に示す臨床薬理試験、ならびに進行中の試験で得られた情報も提示した。

また faster aspart の使用について、26 週を超える期間における安全性評価、2 型糖尿病患者を対象とした使用経験、ならびにインスリンポンプを用いて投与した持続皮下インスリン注入（CSII）療法における安全性及び適合性に関しては、日本人での検討は実施していない。そのため、グローバルの臨床開発プログラムより、完了した海外の 4 試験（3852 試験：1 型糖尿病患者を対象とした長期（52 週）有効性及び安全性、3853 試験：2 型糖尿病患者での使用経験、3854 及び 3931 試験：インスリンポンプ使用時の安全性及び適合性）の結果を、安全性の評価を補足するデータとして本臨床概要に試験ごとに提示した。

本臨床概要に提示する情報の cut-off date は、4101 試験のデータベースロック日である 2018 年 4 月 6 日としたが、進行中の試験（4113、4371 及び 4265 試験）における死亡、重篤な有害事象及び妊娠に関する盲検下の情報については、cut-off date を 2018 年 8 月 1 日とした。

Faster aspart の日本での承認申請のための臨床データパッケージに含める臨床試験の概要を、図 2.7.4.1-1 に示す。Faster aspart の臨床開発プログラム全体における完了した試験の概要は Module 5.2 に示す。これらの他には、4113、4371 及び 4265 試験が進行中である。本臨床概要に含めた、完了した各臨床試験の詳細は、Module 2.7.6 の試験概要、又は Module 5 の総括報告書に示す。



Note: Shaded text: trials including Japanese subjects

[a] Supportive efficacy and safety data

Abbreviations: T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus

図 2.7.4.1-1　Faster aspart の日本での承認申請のための臨床データパッケージに含める臨床試験の概要

2.7.4.1.1.2　安全性の評価方法

2.7.4.1.1.2.1　安全性の評価項目及びエンドポイント

Faster aspart の臨床的安全性の評価は主として、日本人を含む 1 型糖尿病患者を組み入れた 2 つの検証的臨床試験（4131 及び 4101 試験、いずれも Basal-Bolus 療法）に基づき実施した。両試験では、部分的二重盲検下で得られた 26 週間の安全性データを無作為割り付け群間で比較可能であり、主として faster aspart の安全性プロファイルをノボラピッド®注と比較した。さらに、両試験では日本人集団と全集団間の結果の一貫性も評価した。臨床薬理試験である 3918 試験は日本人を対象としており、安全性評価の一環として含めた。

本臨床概要では、以下に示す安全性の評価を行った：

- 曝露状況
- 有害事象
  - 比較的よく見られる有害事象
  - 死亡
  - その他の重篤な有害事象
  - その他の重要な有害事象
  - 器官別又は症候群別有害事象の解析（faster aspart の特に注目すべき安全性領域を含む）
  - 低血糖
- 臨床検査値
  - 抗インスリン アスパルト抗体
  - 血液学的検査及び血液生化学的検査
  - 脂質
  - 尿検査
- バイタルサイン、身体的所見及び安全性に関する他の観察項目
  - 血圧及び脈拍数
  - 身体所見
  - 体重
  - 心電図
  - 眼底写真／眼底検査
  - テクニカルな苦情
- 特別な患者集団及び状況下における安全性
  - 日本人 1 型糖尿病患者を対象とした臨床薬理試験における安全性
  - 日本人集団と全集団の結果の一貫性の検討
  - 内因性及び外因性民族的要因（4131 試験）
  - 小児及び青年期の患者における年齢グループ別の検討（4101 試験）
  - 薬物相互作用
  - 妊娠及び授乳時の使用
  - 過量投与
  - 薬物乱用
  - 離脱症状及び反跳現象
  - 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
  - インスリンポンプ使用時の安全性及び適合性（3854 及び 3931 試験）
  - 成人 1 型糖尿病患者を対象とした長期安全性（3852 試験）

– 成人 2 型糖尿病患者を対象とした安全性（3853 試験）

- 市販後データ

2.7.4.1.1.2.2 安全性の結果の提示

4131 及び 4101 試験については、試験ごとに結果を示した。

安全性における日本人集団と全集団の結果の一貫性を検討するため、4131 及び 4101 試験の日本人集団における以下の結果を提示した。

- 有害事象、有害事象と治験薬との因果関係、重篤な有害事象及び治験薬投与の中止に至った有害事象：2.7.4.5.3.2.3～2.7.4.5.3.2.5 項
- 低血糖：2.7.4.5.3.2.6 項

死亡、重篤な有害事象及び特に注目すべき有害事象は、海外併合データにおいても評価する（詳細は 2.7.4.1.1.2.5 項）。加えて、死亡及びその他の重篤な有害事象は、すべての臨床薬理試験及び進行中の 3 試験についても提示する。さらに、すべての試験において、該当事例がある場合、妊娠についても提示する。

インスリンポンプ使用時の faster aspart に関する安全性評価のため、有効性及び安全性を検討した 3854 試験ならびに適合性を検討した 3931 試験（いずれも検証的試験）の結果を提示する（2.7.4.5.12 項）。

1 型糖尿病患者を対象とした長期安全性の評価のため、3852 試験（52 週）の結果を提示する（2.7.4.5.13 項）。

2 型糖尿病患者を対象とした安全性を補足するため、3853 試験の結果を提示する（2.7.4.5.14 項）。

すべての安全性の結果に関する詳述は、Module 2.7.6 及び Module 5 に試験ごとに示す。

2.7.4.1.1.2.3 安全性のデータベース

完了した臨床試験の安全性に関する情報は、ノボ ノルディスク社の臨床データベース〔cut-off date（2018 年 4 月 6 日）までにデータベースロックが完了している試験〕に基づく。また、進行中の試験における妊娠及び重篤な有害事象（死亡を含む）に関する情報は、ノボ ノルディスク社の安全性データベース（cut-off date：2018 年 8 月 1 日）に基づく。

本臨床概要に示す結果の詳細は、各試験の総括報告書、本臨床概要の付録及び Safety Appendix 1～5（M 5.3.5.1）にも示す。

2.7.4.1.1.2.4　解析対象集団

安全性の評価のため、以下の 2 つの解析対象集団を用いた。

- 安全性解析対象集団（safety analysis set）：被験薬又は対照薬の投与が少なくとも 1 回行われたすべての被験者を含めた。安全性解析対象集団の被験者は「治療されたとおりの（as treated）」評価に寄与した。
- 最大の解析対象集団（full analysis set）：無作為割り付けされたすべての被験者を含めた。例外的な場合に無作為割り付けされた被験者を最大の解析対象集団から除外することがあり、その場合は、除外する理由を正当に示し文書として記録することとした。最大の解析対象集団の被験者は「無作為割り付けされたとおりの（as randomised）」評価に寄与した。

本臨床概要のすべての解析は、特記しない限り安全性解析対象集団に基づいて実施した。

治験薬投与下で発現した有害事象（TEAE）の定義については 2.7.4.2.2.1.1 項を参照、治験薬投与下で発現した低血糖の定義については 2.7.4.2.4.1 項を参照のこと。

2.7.4.1.1.2.5　統計解析及び結果の提示

一般的に、安全性の結果の提示には記述統計量を用いた。

治験薬投与下で発現した有害事象は、MedDRA の器官別大分類（SOC）及び基本語（PT）を用いて要約した（詳細は 2.7.4.2.2.1 項を参照）。治験薬投与下で発現したすべての有害事象、あるいは faster aspart（食前投与及び食後投与）又はノボラピッド®注（食前投与）の投与を受けた被験者の 5%以上又は 1%以上に発現した治験薬投与下の有害事象について、要約表を作成した。

低血糖の分類及び統計解析は 2.7.4.2.4.1.2 及び 2.7.4.2.4.1.3 項、脂質の解析は 2.7.4.3.4.1 項参照。

日本人集団と全集団間の一貫性の検討

4131 及び 4101 試験は、「国際共同治験に関する基本的考え方（平成 19 年 9 月 28 日付、薬食審査発第 0928010 号厚生労働省医薬食品局審査管理課長通知）」に従い、国際共同試験として実施した[2]。4131 及び 4101 試験の結果に基づき、有効性及び安全性の結果について日本人集団と全集団間の一貫性を検討した。両試験の安全性に関する日本人集団と全集団間の一貫性の検討は、2.7.4.5.3 項に示した（被験者の内訳、有効性及びインスリン投与量における一貫性の検討は Module 2.7.3 を参照）。

4131 及び 4101 試験における安全性に関する両集団間の一貫性は、主に記述統計量に基づいて検討した。ただし、4131 試験の低血糖に関する評価は、日本人集団及び全集団それぞれにおける、faster aspart（食前投与）とノボラピッド®注、又は faster aspart（食後投与）とノボラピッド®注の投与群間の比の推定値に基づいて実施した。なお、日本人集団の統計解析は日本から参加した被験者のみを対象としており、事前に規定した解析モデルにおける因子として地域は含めない。

4101 試験では、無作為割り付けされた 3 歳未満の日本人被験者は非常に少なかった。したがって、日本人集団における統計解析は行わないこととした。

日本人集団に関するすべての図表は M 5.3.5.1 に含めた。

内因性／外因性民族的要因の評価

4131 試験では、表 2.7.4.1-1 に示す部分集団における faster aspart の安全性を評価した。

表 2.7.4.1-1　　内因性／外因性民族的要因及び部分集団

Subgroups and levels
• **Age** at baseline (years): ≥18 − <65; ≥65 • **Sex**: female; male • **BMI** at baseline (kg/m^2): <25; ≥25 − <30; ≥30 • **HbA$_{1c}$** at baseline (%): <8.0, ≥8.0 • **Duration of diabetes** at baseline (years): <15 ; ≥15 • **Renal impairment** at baseline based on estimated creatinine clearance (mL/min): normal: ≥90; mild: ≥60 − <90 ; moderate: ≥30 − <60 ; severe : <30 • **Hepatic impairment** at baseline based on baseline transaminases (ALT and AST) (hepatic function); either one or both exceeded the upper limit of normal range or not : No; Yes • **Method of insulin dose adjustment**: bolus dosing algorithm; flexible dosing with carbohydrate counting

Abbreviations: ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: Body mass index.

4101 試験では、安全性の結果の一部を、年齢グループ（1 歳以上 6 歳未満、6 歳以上 12 歳未満、12 歳以上 18 歳未満）別に示した。

海外併合データ

患者への総曝露期間（人・年）を増やすため、4 つの検証的臨床試験〔3852（52 週）、3853、4049 及び 3931 試験〕による海外併合データに基づく追加の評価を実施した。海外併合データの評価として、併合した faster aspart 群（食前投与、食後投与及びインスリンポンプを用いた持続皮下注入を併合）及び併合した対照薬群（ノボラピッド®注投与群及び Basal インスリン投与群を 1 つに併合）で投与群間の比較を行うことで、各併合群で治療の方法に関わらず起こり得る有害事象を検出する可能性を高めた。試験間の曝露の差を考慮し、事象を発現した被験者の割合や事象の単位時間あたりの発現件数は、Cochran-Mantel-Haenszel 法を用いて調整した。ある試験において事象の発現がなかった場合でも、当該試験の被験者は、事象を発現した被験者の割合や事象の単位時間あたりの発現件数を算出する際に用いる曝露の情報には寄与する。

2.7.4.1.1.3　各臨床試験の叙述

すべての結果に関する詳細は Module 5 の各試験の総括報告書に記す。

2.7.4.1.1.4　文献情報の要約

定期的かつ継続的なレビューを実施している 4 つの主要な文献データベース（Biosis、Current Contents、Embase 及び Medline）を用いた検索で、ノボラピッド®注及び faster aspart のベネフィットーリスクプロファイルに関する科学文献を特定した。文献検索基準は付録 2.7.4.7.6 に提示する。検索基準は、臨床又は非臨床の安全性又は有効性の所見を含む、すべての公表文献を収集できるように設定した。その際、重要な新規の安全性所見、ならびにインスリン製剤では既知の特に注目すべき領域における新規の情報について評価した。最新のレビューは faster aspart 及びノボラピッド®注の定期的安全性最新報告／定期的ベネフィット・リスク評価報告（PSUR/PBRER）を踏まえて行い、2016 年 10 月 1 日～2017 年 9 月 30 日までの期間をカバーした。レビューした文献から新しい安全性に関連した所見は認められず、faster aspart のベネフィットーリスクプロファイルには影響しなかった。

2.7.4.1.2　全般的な曝露状況

2.7.4.1.2.1　曝露の概観

4131 試験では、成人 1 型糖尿病患者 1025 例がいずれかの治験薬の投与を受けた。総曝露期間（人・年）は、faster aspart（食前投与）群で 171.3 人・年、faster aspart（食後投与）群及びノボラピッド®注群で各 170.2 人・年であった。

4101 試験では、小児及び青年期の 1 型糖尿病患者 777 例がいずれかの治験薬の投与を受けた。総曝露期間は faster aspart（食前投与）群 128.4 人・年、faster aspart（食後投与）群及びノボラピッド®注群がともに 127.7 人・年であった。

被験者の大部分は 26 週以上の治験薬投与を受けた。4131 及び 4101 試験では、合計で 205 例の日本人被験者が faster aspart の投与を、106 例の日本人がノボラピッド®注の投与を受けた（付録 2.7.4.7.1、表 2.7.4.7.1-3 及び 2.7.4.7.1-4）。

試験に組み入れられた被験者の年齢及び性別は、目標とする faster aspart の治療対象集団を代表するものと考えられた。全体として、インスリン投与量に基づく曝露状況は、各臨床試験の投与群間で同様であった。

全体として、試験の中止又は治験薬投与の中止に至った被験者はほとんどおらず、すべての臨床試験で試験完了率は高かった。試験の中止に至った被験者及び治験薬投与の中止に至った被験者の割合は、faster aspart 群とノボラピッド®注群で同様であった。

2.7.4.1.2.2　曝露状況

2.7.4.1.2.2.1　評価方法

4131 及び 4101 試験において、faster aspart 又はノボラピッド®注の投与期間中の曝露状況は、治験薬のあらゆる投与量又は投与方法による実際の曝露期間（run-in 期間を除く）に基づく。

2.7.4.1.2.2.2　検証的試験

4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

342 例が faster aspart（食前投与）、341 例が faster aspart（食後投与）、342 例がノボラピッド®注の投与を受けた。

投与期間における総曝露期間（人・年）は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群で、それぞれ 171.3、170.2 及び 170.2 人・年であった〔Trial 4131（M 5.3.5.1）EOT Table 14.2.1〕。

Run-in 期間（すべての被験者にノボラピッド®注を投与）の曝露は、その後 faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群に無作為割り付けされた被験者で、それぞれ 54.6、54.4 及び 54.4 人・年であった〔Trial 4131（M 5.3.5.1）EOT Table 14.2.3〕。

全集団の 3 つの投与群すべてにおいて、被験者の大部分は 6 ヵ月以上にわたり治験薬の投与を受けた（付録 2.7.4.7.1、表 2.7.4.7.1-1）。日本人集団の 3 つの投与群における曝露期間の分布も、同様であった（付録 2.7.4.7.1、表 2.7.4.7.1-3）。

性別、人種、民族及び年齢ごとの曝露状況を、Trial 4131（M 5.3.5.1）EOT Table 14.2.6～14.2.13 に示す。これら人口統計学的特性別の部分集団間で、曝露の程度に顕著な違いはみられなかった。

4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

261 例が faster aspart（食前投与）、258 例が faster aspart（食後投与）、258 例がノボラピッド®注の投与を受けた。

投与期間における総曝露期間（人・年）は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群で、それぞれ 128.4、127.7 及び 127.7 人・年であった〔Trial 4101（M 5.3.5.1）EOT Table 14.2.1〕。

Run-in 期間（すべての被験者にノボラピッド®注を投与）の曝露は、faster aspart（食前投与）群及び faster aspart（食後投与）群で各 60.3 人・年、ならびにノボラピッド®注群で 59.9 人・年であった〔Trial 4101（M 5.3.5.1）EOT Table 14.2.3〕。

全集団の 3 つの投与群すべてにおいて、被験者の大部分は 6 ヵ月以上にわたり治験薬の投与を受けた（付録 2.7.4.7.1、表 2.7.4.7.1-2）。日本人集団の 3 つの投与群における曝露期間の分布も、同様であった（付録 2.7.4.7.1、表 2.7.4.7.1-4）。

性別、人種、民族及び年齢ごとの曝露状況を、Trial 4101（M 5.3.5.1）EOT Table 14.2.6～14.2.13 に示す。人口統計学的特性別の部分集団間で、曝露の程度に顕著な違いはみられなかった。

2.7.4.1.2.3　投与量

投与量に関する情報は Module 2.7.3 を参照のこと。

2.7.4.1.2.4　被験者の内訳

2.7.4.1.2.4.1　評価方法

2.7.4.1.2.4 項では、試験及び／又は投与期間を完了した被験者の割合、ならびに試験の中止又は治験薬投与の中止に至った理由を含め、臨床試験に組み入れられた被験者の概観を示す。被験者の内訳として、無作為割り付けされた被験者数、治験薬の投与を受けた被験者数を、また中止・脱落した被験者数は治験責任医師が報告した分類（「有害事象」「治験実施計画書違反」「有効性の欠如」「追跡不能」「妊娠」「被験者からの申し出」及び「その他」の理由による）に則って、それぞれ提示する。

2.7.4.1.2.4.2　検証的試験

4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

表 2.7.4.1-2 で要約したとおり、1025 例の被験者を 3 つの投与群に 1:1:1 の割合で割り付けた〔faster aspart（食前投与）群 342 例、faster aspart（食後投与）群 341 例及びノボラピッド®注群 342 例〕。無作為割り付けされた 1025 例のすべての被験者が治験薬の投与を受けた。

無作為割り付けされた被験者のうち 1007 例（98.2%）が試験を完了した〔faster aspart（食前投与）群の 98.8%、faster aspart（食後投与）群の 97.9%及びノボラピッド®注群の 98.0%〕。各投与群で投与期間を完了した被験者の割合は、いずれも同様に高かった。

26 例（2.5%）が無作為割り付けされた治験薬の投与を早期に中止した。治験薬の投与を早期に中止した主な理由は、被験者からの申し出（14 例）であった〔faster aspart（食前投与）群 5 例、faster aspart（食後投与）群 3 例及びノボラピッド®注群 6 例〕。低血糖、又は治験実施計画書違反のために治験薬の投与を早期に中止した被験者はいなかった。

18 例（1.8%）が無作為割り付け以降に試験を中止・脱落した。試験を中止・脱落した主な理由は、被験者からの申し出（14 例）であった〔faster aspart（食前投与）群 4 例、faster aspart（食後投与）群 6 例及びノボラピッド®注群 4 例〕（表 2.7.4.1-2）。詳細は Trial 4131（M 5.3.5.1）の総括報告書を参照。

表 2.7.4.1-2　　被験者の内訳－要約－すべての被験者（4131 試験）

	Faster aspart (meal) N (%)	Faster aspart (post) N (%)	NovoRapid (meal) N (%)	Total N (%)
Screened				1362
Screening failures				254
Run-in failures				83
Randomised	342 (100.0)	341 (100.0)	342 (100.0)	1025 (100.0)
Exposed*	342 (100.0)	341 (100.0)	342 (100.0)	1025 (100.0)
Prematurely discontinued randomised treatment due to	7 (2.0)	9 (2.6)	10 (2.9)	26 (2.5)
Adverse event	0	0	1 (0.3)	1 (0.1)
Pregnancy	1 (0.3)	1 (0.3)	2 (0.6)	4 (0.4)
Decision of subject	5 (1.5)	3 (0.9)	6 (1.8)	14 (1.4)
Other	1 (0.3)	5 (1.5)	1 (0.3)	7 (0.7)
Withdrawn from trial	4 (1.2)	7 (2.1)	7 (2.0)	18 (1.8)
Adverse event	0	0	1 (0.3)	1 (0.1)
Lost to follow-up	0	1 (0.3)	1 (0.3)	2 (0.2)
Withdrawal by subject	4 (1.2)	6 (1.8)	4 (1.2)	14 (1.4)
Other	0	0	1 (0.3)	1 (0.1)
Completed treatment period	335 (98.0)	332 (97.4)	332 (97.1)	999 (97.5)
Completed trial period	338 (98.8)	334 (97.9)	335 (98.0)	1007 (98.2)

%: Percentage of randomised subjects, *: Includes subjects 'as treated', N: Number of subjects
Treatment period: The period from visit 10 (Week 0) to visit 36 (Week 26) without premature discontinuation of randomised treatment.
Trial period: The period from visit 10 (Week 0) to visit 38 (Week 30).

4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

表 2.7.4.1-3 で要約したとおり、777 例の被験者を 3 つの投与群に 1:1:1 の割合で割り付けた〔faster aspart（食前投与）群 260 例、faster aspart（食後投与）群 259 例及びノボラピッド®注群 258 例〕。無作為割り付けされた 777 例のすべての被験者が治験薬の投与を受けた。

無作為割り付けされた被験者のうち 760 例（97.8%）が試験を完了した〔faster aspart（食前投与）群の 98.5%、faster aspart（食後投与）群の 96.9%及びノボラピッド®注群の 98.1%〕。各投与群で投与期間を完了した被験者の割合は、いずれも同様に高かった。

21 例（2.7%）が無作為割り付けされた治験薬の投与を早期に中止した。治験薬の投与を早期に中止した理由は、被験者からの申し出（6 例）、被験者の親又は法定代理人からの申し出（5 例）、その他（10 例）であった。有害事象、低血糖、治験実施計画書違反、又は妊娠のために治験薬の投与を早期に中止した被験者はいなかった。

17 例（2.2%）が無作為割り付け以降に試験を中止・脱落した。試験を中止・脱落した主な理由は、被験者の親又は法定代理人からの申し出（9 例）であった〔faster aspart（食前投与）群 4 例、faster aspart（食後投与）群 4 例及びノボラピッド®注群 1 例〕（表 2.7.4.1-3）。詳細は総括報告書〔Trial 4101（M 5.3.5.1）〕参照。

表 2.7.4.1-3　　被験者の内訳－要約－すべての被験者（4101 試験）

	Faster aspart (meal) N (%)	Faster aspart (post) N (%)	NovoRapid (meal) N (%)	Total N (%)
Screened				933
Screening failures				99
Run-in failures				57
Randomised	260 (100.0)	259 (100.0)	258 (100.0)	777 (100.0)
Exposed[a]	261[b]	258[b]	258	777
Prematurely discontinued randomised treatment	6 (2.3)	9 (3.5)	6 (2.3)	21 (2.7)
Decision of subject	0	3 (1.2)	3 (1.2)	6 (0.8)
Decision of parent/guardian	3 (1.2)	2 (0.8)	0	5 (0.6)
Other	3 (1.2)	4 (1.5)	3 (1.2)	10 (1.3)
Withdrawn from trial	4 (1.5)	8 (3.1)	5 (1.9)	17 (2.2)
Withdrawal by subject	0	1 (0.4)	4 (1.6)	5 (0.6)
Withdrawal by parent/guardian	4 (1.5)	4 (1.5)	1 (0.4)	9 (1.2)
Other	0	3 (1.2)	0	3 (0.4)
Completed treatment period	254 (97.7)	250 (96.5)	252 (97.7)	756 (97.3)
Completed trial period	256 (98.5)	251 (96.9)	253 (98.1)	760 (97.8)

%: Percentage of randomised subjects, N: Number of subjects
Treatment period: The period from visit 14 (Week 0) to visit 40 (Week 26) without premature discontinuation of randomised treatment.
Trial period: The period from visit 14 (Week 0) to visit 42 (Week 30).
[a] Includes subjects 'as treated'
[b] One subject was randomised to the postmeal faster aspart group but was exposed to mealtime faster aspart throughout the treatment period. The subject was included in the mealtime faster aspart group for the safety analysis set and per protocol analysis set but not the full analysis set. This is not considered to have an overall impact on data interpretation

2.7.4.1.3　　治験対象集団の人口統計学的特性及びその他の特性

2.7.4.1.3.1　　人口統計学的特性の概観

4131 及び 4101 試験の被験者において、ベースラインの人口統計学的特性及び糖尿病特性に、投与群間での偏りは認められなかった。

全体として、併発疾患、既往歴及び試験開始前の糖尿病治療薬の使用状況は、いずれの投与群においても同様であった。

被験者は 1 型糖尿病患者を代表しており、試験を実施した国及び地域の人口統計学的特性を反映していた。

試験対象集団の人口統計学的特性の詳細は以下に示す。

2.7.4.1.3.2　ベースラインの人口統計学的特性及び糖尿病特性

2.7.4.1.3.2.1　評価方法

検証的試験である 4131 及び 4101 の両試験の選択／除外基準は、ベースラインの人口統計学的特性、併発疾患ならびに糖尿病の種類、罹病期間及び重症度といった観点から、目標とする対象集団が被験者として組み入れられるように選択された。

試験対象集団に関する詳細は、Module 2.7.3.1.3.2 参照。

人口統計学的特性の分布は、Module 2.7.3.3.1.2 において、詳細に検討し投与群ごとに提示する。

2.7.4.1.3.2.2　検証的試験

4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

本試験には、1 型糖尿病の男女が組み入れられた。人口統計学的特性及びベースライン特性は、いずれの投与群においても同様であった。

被験者の 53.6%が男性であり、大部分が白人（60.8%）又はアジア人（37.5%）であり、また非ヒスパニック系／非ラテン系（96.8%）であった。被験者は、欧州（33.7%）、北アメリカ（29.4%）、日本（23.9%）及びアジア（日本を除く）（13.1%）で組み入れられた。平均年齢は 41.09 歳であり、被験者の大部分（94.0%）が 18～64 歳、残り 6.0%が高齢者（65 歳以上）であった。

ベースラインにおいて、被験者の BMI の平均値は 25.07 kg/m^2（範囲：14.4～37.9 kg/m^2）、HbA1c の平均値は 7.42%（範囲：5.2～15.1%）、平均糖尿病罹病期間は 16.69 年（範囲：1.2～66 年）であった。

ベースラインの人口統計学的特性及び糖尿病特性の詳細は、総括報告書〔Trial 4131（M 5.3.5.1）〕参照。

4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

本試験には、小児及び青年期（2 歳以上 18 歳未満）の 1 型糖尿病の男女が組み入れられた。人口統計学的特性及びベースライン特性は、いずれの投与群においても同様であった。

被験者の 53.9%が男性であり、大部分が白人（81.3%）又はアジア人（16.2%）であり、また非ヒスパニック系／非ラテン系（94.2%）であった。大部分の被験者は、アメリカ（25.1%）、ロシア（13.4%）及び日本（8.5%）で組み入れられた。ベースライン（来院 14）の被験者の平均年齢は 11.68 歳（範囲：2～17 歳）であった。

ベースラインにおいて、被験者の BMI の平均値は 19.66 kg/m^2（範囲：11.8～33.5 kg/m^2）、HbA1c の平均値は 7.56%（範囲：4.9～10.6%）、平均糖尿病罹病期間は 4.38 年（範囲：0.5～16.3 年）であった。

ベースラインの人口統計学的特性及び糖尿病特性の詳細は、総括報告書〔Trial 4101 （M 5.3.5.1）〕参照。

2.7.4.1.3.3　ベースラインの併発疾患及び併用薬剤

2.7.4.1.3.3.1　評価方法

併発疾患とは、試験開始時（スクリーニング来院時）に罹患している又はスクリーニング手順により発見されたすべての疾患（糖尿病は除く）と定義した。既往歴とは、被験者が過去に経験した医学的事象であり、本試験に関連すると治験責任医師により判断されたものを含めた。既往歴及び併発疾患の詳細はスクリーニング時に記録され、MedDRA 分類を用いてコード化された。糖尿病合併症（ニューロパチー、網膜症、腎症及び大血管障害を含む）もスクリーニング時に記録され MedDRA を用いてコード化され、検証的臨床試験での報告は専用の form に入力することとした。各試験に用いた MedDRA のバージョンの詳細は 2.7.4.2.2.1.2 項を参照。

ベースラインの腎機能は、Cockcroft & Gault 計算式[3]により推定されるクレアチニンクリアランス（CL_{CR}）に基づいて評価した。腎機能は、正常（CL_{CR} が 90 mL/min 以上）もしくは軽度（CL_{CR} が 60 mL/min 以上 90 mL/min 未満 ）、中等度（CL_{CR} が 30 mL/min 以上 60 mL/min 未満）又は重度（CL_{CR} が 30 mL/min 未満）に分類した。なお 4131 試験では、推算糸球体濾過量（eGFR）が 60 mL/min/1.73 m^2 以下の腎機能障害を除外基準に含めた。4101 試験では、腎機能障害に関連する除外基準は設定しなかった。

4131 試験では、アラニンアミノトランスフェラーゼ（ALT）が基準値上限の 2.5 倍以上に該当する肝機能障害を除外基準に含めた。4101 試験では、肝機能障害に関連する除外基準は設定しなかった。

併用薬剤には、試験期間中（スクリーニング期間及び run-in 期間を含む）に使用された治験薬以外のすべての薬剤が該当する。併用薬剤の変更は、被験者日誌に記録することとした。

2.7.4.1.3.3.2　検証的試験

4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

全体として、4131 試験で報告された併用薬剤及び併発疾患は、1 型糖尿病患者において予測される内容を反映していた。

いずれの投与群においても高頻度で認められた併発疾患は、高血圧（23.5%）、脂質異常症（15.9%）及び高脂血症（14.3%）であった。これらの疾患及びその他の疾患の罹患率は、3 つの投与群とも同程度であった。

ベースラインで高頻度に使用されていた併用薬剤は、解剖治療化学（ATC）分類における「循環器系」（被験者の 36.4%）、「消化管と代謝作用」（被験者の 19.3%）及び「全身性ホルモン製剤、性ホルモンとインスリンを除く」（被験者の 16.8%）の薬剤であった。全体として、ベースラインで併用薬剤の使用を報告した被験者の割合は、3 つの投与群とも同程度であった。

ベースラインの併発疾患及び併用薬剤の詳細は、Trial 4131（M 5.3.5.1）EOT Table 14.1.13 及び 14.1.14 ならびに Appendix 16.2.4、Listing 16.2.4.6 及び 16.2.4.7 参照。

4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

全体として、4101 試験で報告された併用薬剤及び併発疾患は、小児及び青年期の 1 型糖尿病患者において予測される内容を反映していた。

いずれの投与群においても高頻度で認められた併発疾患は、器官別大分類で「皮膚および皮下組織障害」〔被験者の 10.3%で報告。主に、後天性リポジストロフィー（2.1%）及び脂肪肥大症（1.9%）関連〕及び「内分泌障害」〔被験者の 8.5%で報告。主に、自己免疫性甲状腺炎（4.1%）及び甲状腺機能低下症（3.6%）関連〕であった。併発疾患の罹患率は、3 つの投与群とも同程度であった〔Trial 4101（M 5.3.5.1）EOT Table 14.1.23 及び Appendix 16.2.4、Listing 16.2.4.7〕。

ベースラインで高頻度に使用されていた併用薬剤は、「消化管と代謝作用」（被験者の 8.0%）、「全身性ホルモン製剤、性ホルモンとインスリンを除く」（被験者の 7.6%）及び「呼吸器系」（被験者の 6.4%）に分類される薬剤であった。ベースラインで併用薬剤の使用を報告した被験者の割合は、3 つの投与群とも同程度であった〔Trial 4101（M 5.3.5.1） Table 14.1.24 及び Appendix 16.2.4、Listing 16.2.4.6〕。

2.7.4.2 有害事象

2.7.4.2.1 有害事象の概観

全体として、faster aspart は安全で、その忍容性は良好であり、小児、青年期及び成人の 1 型糖尿病患者への使用において予想されない安全性上の問題は特定されなかった。

これまでに得られた結果から、ノボラピッド®注と比較して、faster aspart の投与による重篤な有害事象や死亡リスクの増加は示唆されなかった。試験の中止、治験薬投与の中止あるいは Bolus インスリン又は Basal インスリンの投与量の減量に至った有害事象に関して、投与群間で臨床的に意味のある差は認められなかった。また 4131 及び 4101 試験ならびに海外併合データから、特に注目すべき安全性領域の有害事象に関して、faster aspart 群と対照薬群間で臨床的に意味のある差は認められなかった。

低血糖の評価は試験ごとに実施した。Faster aspart（食前投与）群とノボラピッド®注群間、ならびに faster aspart（食後投与）群とノボラピッド®注群間で、重大な低血糖ならびに重大な又は血糖値確定低血糖の単位時間あたりの発現件数に統計的な有意差はみられなかった。4131 及び 4101 試験において、食後の重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、faster aspart の各群とノボラピッド®注群で同程度であった。

全体として、日中及び夜間の重大な又は血糖値確定低血糖の単位時間あたりの発現件数は faster aspart 群とノボラピッド®注群間で同程度であり、大部分は日中に発現した。ただし 4101 試験では、夜間の重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、faster aspart（食後投与）群がノボラピッド®注群と比較して統計的に有意に高かった。内因性及び外因性民族的要因別（4131 試験）あるいは年齢グループ別（4101 試験）の部分集団間で、重大な又は血糖値確定低血糖の単位時間あたりの発現件数に、臨床的に意味のある差は認められなかった。

2.7.4.2.2 有害事象の解析

2.7.4.2.2.1 評価方法

2.7.4.2.2.1.1 定義

有害事象

有害事象（AE）とは、医薬品（治験薬を含む）が投与された患者又は被験者に生じたあらゆる好ましくない医療上の出来事であり、投与との因果関係があるとは限らない。

すなわち、有害事象とは、医薬品（治験薬を含む）の使用と時間的に関連のある、あらゆる好ましくない、意図しない徴候（臨床検査値の異常を含む）、症状又は疾病のことであり、当該医薬品（治験薬を含む）との因果関係の有無は問わない。

以下については、有害事象として報告することとした：

- 併発疾患の臨床的に有意な悪化

- 臨床検査に関する有害事象（CLAE）：臨床的に有意な臨床検査値の異常（疾患及び／又は臓器毒性を示し、積極的な対応が必要な重度の異常値）。積極的な対応とは、医薬品の投与量／投与頻度の変更や異常値の追跡調査といった、積極的な治療又はさらなる検査等が該当する。

ただし、以下については、有害事象としては報告**しない**こととした：

- スクリーニングにより発見された、以前から存在していた病状（以前から存在していた病状は、既往歴又は併発疾患として記録する）。
- 前もって予定された処置。ただし、処置を予定された病状が、被験者が同意書に署名した後、最初の「治験に関連する手順」開始以降に悪化した場合を除く。
- 重篤でない低血糖（重篤な有害事象の基準を満たさない低血糖。下記参照）は有害事象であるが、「AE form」の代わりに、「hypoglycaemic episode form」に報告することとした。
- 4101 試験：重篤でない高血糖（重篤な有害事象の基準を満たさない高血糖。下記参照）は有害事象であるが、「AE form」の代わりに、「hyperglycaemic episode form」に報告した
- 3854 試験：重篤でない原因が特定できない高血糖は、「AE form」の代わりに、「unexplained hyperglycaemic form」に報告した。

治験薬投与下で発現した有害事象

治験薬投与下で発現した有害事象（TEAE）は、無作為割り付けされた治療の投与開始日から最終投与日の 7 日後までに発現した事象と定義する。すなわち、run-in 期間中に発現した有害事象は、治験薬投与下で発現した有害事象に該当しない。

本臨床概要に記載する有害事象は、特記しない限りすべて治験薬投与下で発現した有害事象とした。

重篤な有害事象

投与状況を問わず、以下のいずれかに該当する事象を重篤な有害事象（SAE）と定義した：

- 死に至るもの
- 生命を脅かすもの [a)]
- 入院 [b)]又は入院期間の延長が必要であるもの
- 永続的又は顕著な障害・機能不全に陥るもの [c)]
- 先天異常を来すもの
- 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 [a)]」又は「入院 [b)]又は入院期間の延長が必要であるもの」に至らなくとも、被験者を危機にさらしたり、上記のような結果に至らぬように内科的又は外科的処置を必要とした場合には、適切な医学的判断に基づいて、重篤な有害事象と判断する。

a) 「生命を脅かす」とは、その事象が起こった際に患者が死の危険にさらされていたという意味であり、その事象がもっと重症なものであったなら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」とは、被験者が以下に該当する場合に用いる：

– 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場合
– 治療のため又は観察のために 24 時間以上病院に滞在した場合
– 常に医学的判断に基づき、疑わしい場合には、病院受診は入院と判断する。管理上の入院、治験のための入院又は社会的理由のための入院は、有害事象には該当しないことから、有害事象又は重篤な有害事象としての報告は不要である。さらに、治験前に計画していた外科的処置のための入院も有害事象又は重篤な有害事象には該当しない。

c) 「障害・機能不全に陥るもの」とは、被験者が日常生活を行うための機能に重大な障害を来すことであり、例えば、被験者の身体機能、身体構造、身体活動及び／又は生活の質（QOL）において、永続的又は恒久的で顕著な、変化、障害、損傷又は失調を生じることである。

d) 「その他の医学的に重要な状態」とは、救急処置室等又は自宅において集中治療を必要とするアレルギー性気管支痙攣、入院には至らないものの血液障害又は痙攣を来した場合、薬物依存症又は薬物乱用等が挙げられる。

以下の事象は常に重篤な有害事象として報告しなければならなかった。重篤の定義に該当するものがなければ、その他の医学的に重要な状態として報告した。

- 肝障害のリスク〔ALT 又はアスパラギン酸アミノトランスフェラーゼ（AST）値が基準値上限の 3 倍超及び総ビリルビン値が基準値上限の 2 倍超で、治験薬以外の要因が存在しない（Hy’s law）〕
- 治験薬による病原体感染の疑いがある場合

重篤でない有害事象

重篤な有害事象の定義に該当しない有害事象を重篤でない有害事象として定義した。

特に注目すべき安全性領域

特定の種類の有害事象は、糖尿病及びインスリン治療と関連があり特に注目すべきとみなされており、faster aspart の安全性を評価する際に特別な注意が必要である。インスリンの注目すべき安全性領域及び糖尿病に臨床的関連のある領域に基づき、これらの領域を選定した。本臨床概要で faster aspart の特に注目すべき有害事象として評価する領域は、以下のとおりである。

- 心血管系事象
- 投薬過誤
- 免疫原性に関連する有害事象（アレルギー反応）

- 注射／注入部位反応及びリポジストロフィー
- 末梢性浮腫
- 眼障害（糖尿病網膜症及び屈折障害）
- 末梢性ニューロパチー
- 高血糖（4101 試験のみ）
- 原因が特定できない高血糖（3854 試験のみ。2.7.4.5.12.2.11 項参照）
- 稀な事象
- 治験薬による病原体感染の疑いがある場合
- 低血糖
- 抗体産生（2.7.4.3.2 項）

特に注目すべき安全性領域の評価方法及び評価の結果は、別の項に示す。

テクニカルな苦情

テクニカルな苦情とは、治験薬等（治験薬又は医療機器）の不具合を主張する、書面による、電子的な又は口頭による連絡と定義した。テクニカルな苦情は有害事象を伴うことがあるが、有害事象自体に関わるものではない。

テクニカルな苦情の例：

- 治験薬の物理的又は化学的な外観（変色、粒子、異物混入等）
- 包装資材（漏出、亀裂、カートリッジのゴム栓の問題、表示文章のミス等）
- 医療機器に関連する問題（投与機構、用量設定、注入ボタン、ペンと針の連結の不具合等）

2.7.4.2.2.1.2　有害事象の報告

治験責任医師はすべての有害事象を「AE form」に記録した。治験責任医師は、可能な限り診断名を記録した。診断名が記載できない場合は、すべての徴候及び症状を個々の有害事象として個別の「AE form」に記録した。

重篤な有害事象を報告する際には、「AE form」に加え「safety information form」を作成しなければならなかった。複数の症状又は診断名が、同じ臨床像の一部として起きた場合、重篤な有害事象を報告する際には 1 つの「safety information form」を作成すればよいこととした。

Faster aspart 臨床開発プログラムでは、妊婦、妊娠を希望する女性は、除外基準に抵触することとした。試験中に妊娠した又は妊娠を希望した女性被験者は、直ちに治験薬の投与を中止し、また 4131 及び 4101 試験では当該事例が run-in 期間に発覚した場合のみ、試験の中止基準に抵触することとした。治験責任医師は試験中の被験者の妊娠を治験依頼者に報告し、妊娠の転帰が得られるまで追跡調査を

することとした。さらに、新生児が月齢 1 ヵ月になるまで追跡調査を実施することとした。治験責任医師は、妊娠に関連する有害事象、新生児や胎児に発現した有害事象と同様に、妊娠、妊娠の転帰及び新生児の健康状態に関する情報を報告することとした。

重症度の評価における定義

有害事象の重症度を評価する際には、以下の定義を用いた：

- 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評価における定義

有害事象と治験薬との因果関係を評価する際には、以下の用語を用いた：

- 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）：因果関係が考えられ、それを否定することはできない
- なし（unlikely）：治験薬以外の要因との関連が最も考えられる

転帰の分類と定義

有害事象の最終的な転帰を評価する際には、以下の定義を用いた：

- 回復（recovered/resolved）：完全に回復した場合、あるいは、内科的又は外科的処置により、被験者が同意書に署名した後の最初の「『治験に関連する手順』実施時に認められた状態」に復した場合。
- 軽快（recovering/resolving）：被験者の状態が改善されつつあり、被験者が事象から回復することが予測される状態をいう。「軽快」である有害事象は治験を終了した被験者又は他の有害事象により死亡した被験者のみに使用する。
- 回復したが後遺症あり（recovered/resolved with sequelae）：被験者の状態は回復したが、疾病、障害、治療又は治験の手順のために永続的な影響がある場合。後遺症が「重篤」の定義に合致する場合、重篤な有害事象として分類される。
- 未回復（not recovered/not resolved）：被験者の状態が改善せずかつ症状も変化がない、もしくは転帰が不明である場合に使用する。
- 死亡（fatal）：報告された有害事象に関連した状態の結果として、死亡に至った場合にのみ該当する。死亡前に報告されたその他の有害事象の転帰は、「回復」、「軽快」、「回復したが後遺症あり」又は「未回復」のいずれかで評価する。転帰が「死亡」の有害事象は、重篤な有害事象として報告する。
- 不明（unknown）：被験者の追跡調査ができない場合にのみ使用される。

有害事象のコーディング

すべての有害事象を MedDRA を用いてコーディングした。4131 及び 4101 試験ならびに本臨床概要用に特別に出力した結果について、MedDRA バージョンは 20.0 版を用いた。海外併合データについて、MedDRA バージョンは 17.0 版を用いた。その他の臨床試験に用いた MedDRA バージョンの詳細は、Module 5 の各試験の総括報告書を参照のこと。

テクニカルな苦情

治験の提供品の最初の使用から最後の使用までに生じたすべての苦情を収集し、ノボ ノルディスク社の Customer Complaint Centre に報告することとした。治験責任医師は、テクニカルな苦情が有害事象、重篤な有害事象及び／又は投薬過誤のいずれかに関連しているかどうかを評価した。

2.7.4.2.2.1.3　有害事象の提示

比較的よく見られる有害事象（2.7.4.2.2.2 項）及び重篤な有害事象（2.7.4.2.2.4 項）について、有害事象を報告した被験者の割合、有害事象の単位時間あたりの発現件数、及び／又は必要な場合は事象の発現件数、重症度、事象の種類、治験薬との因果関係ならびに転帰に重点を置き、説明及び評価を行う。有害事象は試験別に提示する。海外併合データについては、死亡、重篤な有害事象及び特に注目すべき有害事象を提示する。海外併合データにおける各項目の定義及び評価方法は、付録 2.7.4.7.7 に詳細を示す。

加えて、死亡及び重篤な有害事象は、すべての臨床薬理試験及び進行中の試験で報告された事象も提示する。報告されたすべての死亡は 2.7.4.2.2.3 項に、及びその他の重篤な有害事象については 2.7.4.2.2.4 項に示す。治験薬投与の中止に至った有害事象、試験の中止に至った有害事象、ならびに投与量の減量に至った有害事象については、その他の重要な有害事象に含める（2.7.4.2.2.5 項）。

死亡、その他の重篤な有害事象、治験薬投与の中止に至った有害事象及び試験の中止に至った有害事象に関する叙述は、Module 5 に示す。

特に注目すべき安全性領域について、4131 及び 4101 試験の結果は器官別又は症候群別に 2.7.4.2.3 項に、海外併合データに関しては 2.7.4.2.3.11 項に提示する。

「AE form」を用いて報告された低血糖は、実際に報告された低血糖の発現件数の一部であり、比較的よく見られる有害事象及び重篤な有害事象の評価に含めた。すべての低血糖を含む包括的な評価は、2.7.4.2.4 項に示した。

2.7.4.2.2.2　比較的よく見られる有害事象

2.7.4.2.2.2.1　検証的試験

4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

全体として、26 週の投与期間を通じ、有害事象プロファイルに投与群間で臨床的に意味のある違いは認められなかった。有害事象を報告した被験者の割合はいずれの投与群においても同様であった。有害事象の単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 378.9、385.4 及び 368.5 件/100 人・年であった（表 2.7.4.2-1）。高頻度（いずれかの群の 5%以上の被験者）で報告された有害事象を表 2.7.4.2-2 に要約した。最も高頻度で報告された有害事象（基本語）は、ウイルス性上気道感染であった。

有害事象の重症度

全投与群を通じ、有害事象の大部分は軽度又は中等度であった（表 2.7.4.2-1）。ノボラピッド®注群における中等度の有害事象がわずかに少なかった点を除き、軽度及び中等度の有害事象の単位時間あたりの発現件数は、いずれの投与群においても同程度であった。全体として、最も高頻度で報告された軽度及び中等度の有害事象は、器官別大分類の「感染症および寄生虫症」に分類されるものであった（Module 2.7.6.10.2、表 2.7.6.10.2-6 及び 2.7.6.10.2-7）。軽度又は中等度の有害事象の種類について、投与群間で臨床的に意味のある違いは認められなかった。

重度の有害事象の単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 9.9、12.3 及び 10.0 件/100 人・年であった（表 2.7.4.2-1）。重度の有害事象はほとんどが 1 例ないし少数例からの報告であり、器官別大分類を通じた分布に目立った偏りはなく、投与群間で顕著な差は認められなかった。重度の有害事象全体の単位時間あたりの発現件数について、投与群間で臨床的に意味のある違いはないと考えられた。重度の有害事象として最も高頻度で報告されたのは、低血糖及び低血糖性意識消失であった（Module 2.7.6.10.2、表 2.7.6.10.2-5）（低血糖の詳細は 2.7.4.2.4.2.1 項）。重度の有害事象の大部分（55 件中 43 件）は、重篤であった〔Trial 4131（M 5.3.5.1）Memo Appendix 16.2.7、Listing 16.2.7.4〕。

重症度別ならびに器官別大分類及び基本語別の有害事象の表は、Module 2.7.6.10.2、表 2.7.6.10.2-5～2.7.6.10.2-7 を参照。

有害事象と治験薬との因果関係

有害事象の大部分は、治験責任医師により治験薬（faster aspart 又はノボラピッド®注）との因果関係は「なし」と判定された（表 2.7.4.2-1）。

治験薬との因果関係が「可能性あり」又は「あり」の有害事象は、Module 2.7.6.10.2、表 2.7.6.10.2-4 に要約した。治験薬との因果関係が「可能性あり」又は「あり」とされた有害事象の発現頻度及び種類に、投与群間で顕著な差は認められなかった。

治験責任医師により治験薬との因果関係が「可能性あり」又は「あり」と判定された有害事象のうち、いずれの投与群においても最も高頻度で報告されたのは、血中ブドウ糖減少、低血糖、誤薬投与であった。

治験責任医師により治験薬との因果関係が「可能性あり」又は「あり」と判定された重度の有害事象の単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 5.8、6.5 及び 4.1 件/100 人・年であった。事象の大部分は低血糖〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 6、6 及び 5 件〕及び低血糖性意識消失〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 2、3 及び 1 件〕であった〔Trial 4131（M5.3.5.1）Section 12.3.2.3 ならびに Memo Appendix 16.2.7, Listing 16.2.7.3 及び 16.2.7.4〕。

有害事象の転帰

3 つの投与群間を通じ、有害事象の大部分について、試験終了時の転帰は、回復又は軽快であった（表 2.7.4.2-1）。

重度の有害事象を報告した被験者の大部分が、試験終了時には回復していた。重度の有害事象から回復しなかった被験者は 6 例いたが、いずれも治験責任医師により治験薬との因果関係は「なし」と判定された。Faster aspart（食後投与）群の 1 例では、2 件の重度の有害事象（増殖性網膜症及び硝子体出血）が未回復であった。その他の試験終了時に回復しなかった重度の有害事象は、椎間板突出（ノボラピッド®注群）、ビタミン D 欠乏〔faster aspart（食後投与）群〕、変形性脊椎症〔faster aspart（食前投与）群〕、硝子体出血〔faster aspart（食後投与）群〕、憩室炎（ノボラピッド®注群）で、いずれも別々の被験者からの報告であった。詳細は Trial 4131（M.5.3.5.1）Memo Appendix 16.2.7、Listing 16.2.7.4 参照。

表 2.7.4.2-1　有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	342			341			342		
Total exposure (yrs)	171.3			170.2			170.2		
Total events	240 (70.2)	649	378.9	237 (69.5)	656	385.4	248 (72.5)	627	368.5
Serious									
Yes	20 (5.8)	27	15.8	17 (5.0)	23	13.5	17 (5.0)	19	11.2
No	237 (69.3)	622	363.2	232 (68.0)	633	371.9	243 (71.1)	608	357.3
Severity									
Severe	13 (3.8)	17	9.9	13 (3.8)	21	12.3	15 (4.4)	17	10.0
Moderate	70 (20.5)	111	64.8	61 (17.9)	103	60.5	59 (17.3)	81	47.6
Mild	224 (65.5)	521	304.2	213 (62.5)	532	312.6	223 (65.2)	529	310.9
Related to randomised trial product									
Probable	40 (11.7)	50	29.2	31 (9.1)	44	25.9	24 (7.0)	29	17.0
Possible	32 (9.4)	35	20.4	24 (7.0)	30	17.6	24 (7.0)	28	16.5
Unlikely	215 (62.9)	519	303.0	206 (60.4)	532	312.6	218 (63.7)	520	305.6
Missing	38 (11.1)	45	26.3	41 (12.0)	50	29.4	43 (12.6)	50	29.4
Related to basal compone									
Probable	38 (11.1)	47	27.4	32 (9.4)	42	24.7	26 (7.6)	34	20.0
Possible	43 (12.6)	54	31.5	32 (9.4)	42	24.7	35 (10.2)	37	21.7
Unlikely	202 (59.1)	501	292.5	201 (58.9)	512	300.8	214 (62.6)	510	299.7
Missing	26 (7.6)	47	27.4	21 (6.2)	60	35.3	25 (7.3)	46	27.0
Related to a technical complaint									
Yes	0			1 (0.3)	1	0.6	0		
No	235 (68.7)	604	352.6	222 (65.1)	605	355.4	231 (67.5)	577	339.1
Missing	38 (11.1)	45	26.3	41 (12.0)	50	29.4	43 (12.6)	50	29.4
Outcome									
Recovered/resolved	230 (67.3)	571	333.4	224 (65.7)	550	323.1	240 (70.2)	547	321.5
Recovering/resolving	15 (4.4)	19	11.1	17 (5.0)	22	12.9	14 (4.1)	15	8.8
Recovered/resolved with sequelae	1 (0.3)	1	0.6	0			1 (0.3)	1	0.6
Not recovered/not resolved	42 (12.3)	58	33.9	54 (15.8)	84	49.4	45 (13.2)	63	37.0
Fatal	0			0			0		
Unknown	0			0			1 (0.3)	1	0.6

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigators assessment. MedDRA version 20.0. Technical complaint is related to randomised trial product.

表 2.7.4.2-2　器官別大分類及び基本語別の有害事象－治験薬投与下で発現－5%以上の被験者で報告－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal)				Faster aspart (post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	342				341				342			
Total exposure (yrs)	171.3				170.2				170.2			
感染症および寄生虫症												
ウイルス性上気道感染	73	(21.3)	101	59.0	70	(20.5)	100	58.8	80	(23.4)	118	69.3
上気道感染	30	(8.8)	38	22.2	26	(7.6)	34	20.0	27	(7.9)	34	20.0
インフルエンザ	21	(6.1)	22	12.8	14	(4.1)	14	8.2	10	(2.9)	10	5.9
臨床検査												
血中ブドウ糖減少	58	(17.0)	81	47.3	67	(19.6)	83	48.8	68	(19.9)	82	48.2
代謝および栄養障害												
低血糖	21	(6.1)	22	12.8	6	(1.8)	9	5.3	12	(3.5)	13	7.6

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. MedDRA version 20.0.

4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

全体として、26 週の投与期間を通じ、有害事象プロファイルに投与群間で臨床的に意味のある違いは認められなかった。有害事象を報告した被験者の割合は、いずれの投与群においても同程度であった。有害事象の単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 448.6、531.1 及び 464.5 件/100 人・年であった（表 2.7.4.2-3）。高頻度（いずれかの群の 5%以上の被験者）で報告された有害事象を表 2.7.4.2-4 に要約した。最も高頻度で報告された有害事象（基本語）は、ウイルス性上気道感染であった。

有害事象の重症度

全投与群を通じ、有害事象の大部分は軽度又は中等度であった（表 2.7.4.2-3）。軽度及び中等度の有害事象の単位時間あたりの発現件数は、いずれの投与群においても同程度であった。最も高頻度で報告された軽度及び中等度の有害事象は、主に器官別大分類の「感染症および寄生虫症」に分類されるものであった（Module 2.7.6.11.2、表 2.7.6.11.2-6 及び 2.7.6.11.2-7）。軽度又は中等度の有害事象の種類について、投与群間で臨床的に意味のある違いは認められなかった。

重度の有害事象の単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 3.1、7.1 及び 3.1 件/100 人・年であった。重度の有害事象は、2 例 2 件の糖尿病性ケトアシドーシスを除き、いずれの投与群でも 1 例ずつの報告であり、器官別大分類の分布に偏りはなく、投与群間で顕著な差は認められなかった（Module 2.7.6.11.2、表 2.7.6.11.2-5）。重

度の有害事象の大部分（17 件中 14 件）は、重篤であった〔Trial 4101（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.4〕。

重症度別ならびに器官別大分類及び基本語別の有害事象の表は、Module 2.7.6.11.2、表 2.7.6.11.2-5～2.7.6.11.2-7 を参照。

有害事象と治験薬との因果関係

有害事象の大部分は、治験責任医師により治験薬（faster aspart 又はノボラピッド®注）との因果関係は「なし」と判定された（表 2.7.4.2-3）。

治験薬との因果関係が「可能性あり」又は「あり」の有害事象は、Module 2.7.6.11.2、表 2.7.6.11.2-4 に要約した。治験薬との因果関係が「可能性あり」又は「あり」とされた有害事象の頻度及び種類に、投与群間で顕著な差は認められなかった。

治験責任医師により治験薬との因果関係が「可能性あり」又は「あり」と判定された有害事象のうち、いずれの投与群においても最も高頻度で報告されたのは、低血糖、脂肪肥大症及び偶発的過量投与であった。

重度の有害事象 17 件中 4 件について、無作為割り付けされた治験薬との因果関係が「可能性あり」又は「あり」と判定された〔faster aspart（食前投与）群の 1 例 2 件（偶発的過量投与及び 低血糖）ならびに faster aspart（食後投与）群の 1 例 2 件（偶発的過量投与及び低血糖性意識消失）〕〔Trial 4101（M5.3.5.1）Appendix 16.2.7、Listing 16.2.7.4〕。

有害事象の転帰

3 つの投与群間を通じ、有害事象の大部分について、試験終了時の転帰は、回復又は軽快であった（表 2.7.4.2-3）。

重度の有害事象のほとんど（17 件中 15 件）が、試験終了時には回復していた。残り 2 件の転帰は、回復したが後遺症ありだった〔faster aspart（食後投与）群の情動障害および素行障害を伴う適応障害、及びノボラピッド®注群の胃炎〕〔Trial 4101（M.5.3.5.1） Appendix 16.2.7、Listing 16.2.7.4〕。

表 2.7.4.2-3　有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	261				258				258			
Total exposure (yrs)	128.4				127.7				127.7			
Total events	193	(73.9)	576	448.6	199	(77.1)	678	531.1	203	(78.7)	593	464.5
Serious												
Yes	5	(1.9)	7	5.5	13	(5.0)	15	11.8	9	(3.5)	13	10.2
No	192	(73.6)	569	443.2	199	(77.1)	663	519.4	202	(78.3)	580	454.3
Missing	0				0				0			
Severity												
Severe	3	(1.1)	4	3.1	7	(2.7)	9	7.1	3	(1.2)	4	3.1
Moderate	52	(19.9)	80	62.3	58	(22.5)	100	78.3	51	(19.8)	77	60.3
Mild	178	(68.2)	492	383.2	185	(71.7)	569	445.7	186	(72.1)	512	401.0
Missing	0				0				0			
Related to randomised trial product												
Probable	10	(3.8)	12	9.3	13	(5.0)	16	12.5	11	(4.3)	12	9.4
Possible	3	(1.1)	3	2.3	6	(2.3)	7	5.5	9	(3.5)	12	9.4
Unlikely	192	(73.6)	547	426.0	196	(76.0)	647	506.8	200	(77.5)	559	437.9
Missing	14	(5.4)	14	10.9	8	(3.1)	8	6.3	10	(3.9)	10	7.8
Related to basal component												
Probable	4	(1.5)	6	4.7	15	(5.8)	19	14.9	15	(5.8)	15	11.7
Possible	10	(3.8)	12	9.3	9	(3.5)	9	7.1	11	(4.3)	13	10.2
Unlikely	193	(73.9)	558	434.6	199	(77.1)	650	509.2	201	(77.9)	564	441.8
Missing	0				0				1	(0.4)	1	0.8
Related to a technical complaint												
Yes	2	(0.8)	2	1.6	0				1	(0.4)	1	0.8
No	193	(73.9)	560	436.2	197	(76.4)	670	524.9	202	(78.3)	582	455.9
Missing	14	(5.4)	14	10.9	8	(3.1)	8	6.3	10	(3.9)	10	7.8
Outcome												
Recovered/resolve	187	(71.6)	538	419.0	196	(76.0)	647	506.8	202	(78.3)	573	448.8
Recovering/resolving	12	(4.6)	14	10.9	8	(3.1)	8	6.3	9	(3.5)	10	7.8
Recovered/resolved with sequelae	0				1	(0.4)	1	0.8	3	(1.2)	3	2.3
Not recovered/not resolved	20	(7.7)	24	18.7	20	(7.8)	22	17.2	6	(2.3)	7	5.5
Fatal	0				0				0			
Unknown	0				0				0			
Missing	0				0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator assessment. MedDRA version 20.0.Technical complaint is related to randomised trial product.

表 2.7.4.2-4　器官別大分類及び基本語別の有害事象－治験薬投与下で発現－5%以上の被験者で報告－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)		
	N	(%) E	R	N	(%) E	R	N	(%) E	R
Number of subjects	261			258			258		
Total exposure (yrs)	128.4			127.7			127.7		
感染症および寄生虫症									
ウイルス性上気道感染	60	(23.0) 73	56.9	53	(20.5) 79	61.9	48	(18.6) 75	58.7
上気道感染	22	(8.4) 31	24.1	32	(12.4) 41	32.1	26	(10.1) 32	25.1
インフルエンザ	20	(7.7) 28	21.8	15	(5.8) 20	15.7	14	(5.4) 21	16.4
胃腸炎	13	(5.0) 15	11.7	16	(6.2) 17	13.3	22	(8.5) 27	21.1
鼻炎	10	(3.8) 16	12.5	16	(6.2) 24	18.8	11	(4.3) 16	12.5
ウイルス感染	7	(2.7) 8	6.2	9	(3.5) 11	8.6	14	(5.4) 20	15.7
神経系障害									
頭痛	16	(6.1) 21	16.4	26	(10.1) 38	29.8	22	(8.5) 35	27.4
呼吸器、胸郭および縦隔障害									
咳嗽	10	(3.8) 11	8.6	11	(4.3) 14	11.0	16	(6.2) 21	16.4
口腔咽頭痛	10	(3.8) 12	9.3	9	(3.5) 13	10.2	13	(5.0) 16	12.5
一般・全身障害および投与部位の状態									
発熱	22	(8.4) 26	20.3	16	(6.2) 16	12.5	18	(7.0) 20	15.7
胃腸障害									
嘔吐	9	(3.4) 9	7.0	21	(8.1) 24	18.8	7	(2.7) 7	5.5

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.2.2.2　結論

全体として、faster aspart の忍容性は良好で安全であり、小児、青年期及び成人の 1 型糖尿病患者への使用において予想されない安全性上の問題は特定されなかった。さらに、26 週の投与期間を通じ、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群間で、有害事象プロファイルに臨床的に意味のある違いは認められなかった。

2.7.4.2.2.3　死亡

2.7.4.2.2.3.1　検証的試験

4131 試験では、死亡の報告はなかった。

4101 試験では、治験薬投与下でない死亡が 1 例報告された。ノボラピッド®注群に無作為割り付けされた [redacted] 歳の [redacted]（無作為割り付け時点では [redacted] 歳）が、30 日間の事後調査期間中に海で溺死した。死亡時に、被験者は市販薬による治療を受けていたが、最後に投与した Basal インスリン及び Bolus インスリンの投与量に関する情報は得られていない。治験責任医師及びノボ ノルディスク社により治験薬との因果関係は「なし」と判定された。詳細は Trial 4101（M 5.3.5.1）Section 14.3.3 参照。

2.7.4.2.2.3.2　海外併合データ

海外併合データに含めた試験（2.7.4.1.1.2.5 項）において、無作為割り付け後に 5 例の死亡が報告された〔3852 試験で 2 例、3853 試験で 3 例（うち 1 例が 30 日間の事後調査期間）〕。さらに、run-in 期間中に報告された死亡が 2 例あった（3852 試験で 1 例、4049 試験で 1 例）。死亡の例数は、faster aspart とノボラピッド®注で同様であった（表 2.7.4.2-5）。

海外併合データのうち、3931 試験では、死亡に至った有害事象の報告はなかった（Module 5 の各試験の総括報告書参照）。

表 2.7.4.2-5　死亡に至った有害事象－海外併合データ

Treatment	Subject ID	Trial	Age (years)/ Sex (M/F)/	Trial day	Preferred term	Serious/Relation/ Severity/Treatment emergent
Deaths occurring after randomisation:						
Faster aspart[a]	704006	3852	39/M	96	不整脈	Y/Unlikely/Severe/Y
Faster aspart	502003	3853	63/M	204	肺塞栓症	Y/Possible/Severe/Y
NovoRapid®	801001	3852	57/M	220	心筋梗塞	Y/Unlikely/Severe/Y
NovoRapid®	302007	3853	52/M	20	心筋梗塞	Y/Unlikely/Severe/Y
NovoRapid®	605002[b]	3853	66/M	205	心停止	Y/Unlikely/Severe/N
Deaths occurring before randomisation:						
NA (run-in)	206008	4049	60/M	NA	急性心筋梗塞	Y/Unlikely/Severe/N
NA (run-in)	713018	3852	55/M	NA	自傷行動	Y/Unlikely/Severe/N

Y: Yes, N: No, F: Female, M: Male, NA: not applicable. Relationship is based on investigator assessment.
[a] Postmeal faster aspart
[b] This event of cardiac arrest occurred during the 30-day follow-up period of trial 3853.

死亡に至った有害事象の叙述及び一覧は、試験ごとに Module 5 に示す。

2.7.4.2.2.3.3　進行中の試験

2018 年 8 月 1 日の cut-off date（2.7.4.1.1.1.3 項）時点では、faster aspart の 3 つの臨床試験が進行中であった〔病態の進行した 2 型糖尿病患者を対象とする検証的試験の 4113 試験、ならびに臨床薬理試験 2 試験（小児を含む 1 型糖尿病患者を対象とする 4371 試験、病態の進行した成人 2 型糖尿病患者を対象とする 4265 試験）〕。

4113 試験では、cut-off date までに 1200 例以上の被験者が組み入れられ、4 例の死亡が報告されている。内訳は、治験薬（run-in 期間のインスリン デグルデク含む）の投与開始前に 1 例（死亡）、run-in 期間中（faster aspart 又はノボラピッド®注への曝露前）に 2 例（心筋梗塞及び冠動脈疾患）、無作為割り付け後に盲検下で 1 例（出血性卒中）であった。治験薬への曝露後に発現した当該事象について、治験責任医師により治験薬との因果関係は「なし」と判定された。

4371 及び 4265 試験では死亡の報告はなかった。

2.7.4.2.2.3.4　結論

結論として、得られた結果からは、ノボラピッド®注と比較して、faster aspart の投与による死亡リスクの増加は示唆されなかった。

2.7.4.2.2.4　その他の重篤な有害事象

2.7.4.2.2.4.1　検証的試験

4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

全体として、重篤な有害事象のほとんどは、いずれの投与群でも 1 例ずつないし少数例からの報告であり、器官別大分類を通じた分布に目立った偏りはなく、投与群間で顕著な差は認められなかった（Module 2.7.6.10.2、表 2.7.6.10.2-2）。

重篤な有害事象を報告した被験者の割合は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 5.8、5.0 及び 5.0%であった。重篤な有害事象の単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 15.8、13.5 及び 11.2 件/100 人・年であった（表 2.7.4.2-6）。

5%以上の被験者で発現した重篤な有害事象は、いずれの投与群においてもなかった〔Trial 4131（M 5.3.5.1）EOT Table 14.3.1.9〕。最も高頻度で報告された重篤な有害事象（いずれかの群の 1%以上の被験者で発現）は低血糖であった（表 2.7.4.2-7）。重篤な有害事象 69 件中 43 件が重度であった〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 14、16 及び 13 件〕。投与群に特有の発現パターンは認められなかった（表 2.7.4.2-6）。

試験の中止に至った重篤な有害事象については 2.7.4.2.2.5.1 項に記載した。

4131 試験における重篤な有害事象の叙述及び一覧は、Module 5 に示す。

重篤な有害事象と治験薬との因果関係

重篤な有害事象 69 件中 31 件が、治験薬との因果関係が「可能性あり」又は「あり」とされた。治験責任医師により治験薬との因果関係が「可能性あり」又は「あり」と判定された重篤な有害事象の単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 7.0、6.5 及び 4.7 件/100 人・年であった（表 2.7.4.2-8）。治験薬との因果関係が「可能性あり」又は「あり」とされた重篤な有害事象のうち、最も高頻度で報告されたのは低血糖であり、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 4.7、3.5 及び 2.9 件/100 人・年であった。

重篤な有害事象の転帰

重篤な有害事象の大部分が、試験終了時には回復していた。試験終了時に 1 例（ノボラピッド®注群）が軽快、3 例が未回復であった（表 2.7.4.2-6）。被験者が回復しなかった事象は、うつ病〔faster aspart（食前投与）群〕、椎間板突出及び血中ブドウ糖変動（いずれもノボラピッド®注群）であった。いずれの事象も治験責任医師により治験薬との因果関係は「なし」と判定された〔Trial 4131（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.2〕。

表 2.7.4.2-6　重篤な有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	342				341				342			
Total exposure (yrs)	171.3				170.2				170.2			
Total events	20	(5.8)	27	15.8	17	(5.0)	23	13.5	17	(5.0)	19	11.2
Severity												
Severe	11	(3.2)	14	8.2	10	(2.9)	16	9.4	12	(3.5)	13	7.6
Moderate	6	(1.8)	8	4.7	4	(1.2)	4	2.4	5	(1.5)	5	2.9
Mild	5	(1.5)	5	2.9	3	(0.9)	3	1.8	1	(0.3)	1	0.6
Related to randomised trial product												
Probable	6	(1.8)	6	3.5	3	(0.9)	4	2.4	5	(1.5)	5	2.9
Possible	6	(1.8)	6	3.5	4	(1.2)	7	4.1	3	(0.9)	3	1.8
Unlikely	9	(2.6)	14	8.2	9	(2.6)	11	6.5	11	(3.2)	11	6.5
Missing	1	(0.3)	1	0.6	1	(0.3)	1	0.6	0			
Related to basal component												
Probable	5	(1.5)	5	2.9	3	(0.9)	4	2.4	4	(1.2)	4	2.4
Possible	7	(2.0)	7	4.1	3	(0.9)	6	3.5	5	(1.5)	5	2.9
Unlikely	10	(2.9)	15	8.8	11	(3.2)	13	7.6	10	(2.9)	10	5.9
Related to a technical complaint												
Yes	0				0				0			
No	20	(5.8)	26	15.2	16	(4.7)	22	12.9	17	(5.0)	19	11.2
Missing	1	(0.3)	1	0.6	1	(0.3)	1	0.6	0			
Outcome												
Recovered/resolved	20	(5.8)	26	15.2	17	(5.0)	23	13.5	14	(4.1)	16	9.4
Recovering/resolving	0				0				1	(0.3)	1	0.6
Recovered/resolved with sequelae	0				0				0			
Not recovered/not resolved	1	(0.3)	1	0.6	0				2	(0.6)	2	1.2
Fatal	0				0				0			
Unknown	0				0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
MedDRA version 20.0.
Technical complaint is related to randomised trial product.

表 2.7.4.2-7　器官別大分類及び基本語別の重篤な有害事象－治験薬投与下で発現－1%以上の被験者で報告－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects	342	341	342
Total exposure (yrs)	171.3	170.2	170.2
代謝および栄養障害			
低血糖	8 (2.3) 8 4.7	3 (0.9) 6 3.5	6 (1.8) 6 3.5

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

表 2.7.4.2-8　Faster aspart 又はノボラピッド®注との因果関係が「可能性あり」又は「あり」と判定された器官別大分類及び基本語別の重篤な有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects	342	341	342
Total exposure (yrs)	171.3	170.2	170.2
Total events	12 (3.5) 12 7.0	7 (2.1) 11 6.5	7 (2.0) 8 4.7
代謝および栄養障害	8 (2.3) 8 4.7	4 (1.2) 7 4.1	5 (1.5) 5 2.9
低血糖	8 (2.3) 8 4.7	3 (0.9) 6 3.5	5 (1.5) 5 2.9
無自覚性低血糖	0	1 (0.3) 1 0.6	0
神経系障害	4 (1.2) 4 2.3	4 (1.2) 4 2.4	1 (0.3) 1 0.6
低血糖性意識消失	2 (0.6) 2 1.2	3 (0.9) 3 1.8	1 (0.3) 1 0.6
低血糖性痙攣	2 (0.6) 2 1.2	1 (0.3) 1 0.6	0
傷害、中毒および処置合併症	0	0	2 (0.6) 2 1.2
誤薬投与	0	0	2 (0.6) 2 1.2

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
MedDRA version 20.0.

4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

27 例（3.5%）から 35 件の重篤な有害事象が報告された。重篤な有害事象を報告した被験者の割合は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 1.9、5.0 及

び 3.5%であった。重篤な有害事象の単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 5.5、11.8 及び 10.2 件/100 人・年であった（表 2.7.4.2-9）。

ノボラピッド®注群の 3 例（1.2%）で胃腸炎が報告されたことを除き、1%以上の被験者で報告された重篤な有害事象はいずれの投与群においてもなかった（表 2.7.4.2-10）。全体で、重篤な有害事象 35 件中 14 件が重度であった〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 3、8 及び 3 件〕。投与群に特有の発現パターンは認められなかった（表 2.7.4.2-9）。

4101 試験における重篤な有害事象の叙述及び一覧は、Module 5 に示す。

重篤な有害事象と治験薬との因果関係

全体で、重篤な有害事象 35 件中 7 件が治験薬との因果関係が「あり」とされた〔faster aspart（食前投与）群で 2 件（偶発的過量投与及び低血糖）、faster aspart（食後投与）群で 4 件（偶発的過量投与 2 件及び低血糖性意識消失 2 件）ならびにノボラピッド®注群で 1 件（低血糖）〕（表 2.7.4.2-11）。

重篤な有害事象の転帰

重篤な有害事象の大部分（35 件中 31 件）の転帰は回復であった（表 2.7.4.2-9）。2 件の重篤な有害事象の転帰が、回復したが後遺症あり〔faster aspart（食後投与）群の情動障害および素行障害を伴う適応障害、及びノボラピッド®注群の胃炎〕であり、残りの 2 件の転帰は未回復〔faster aspart（食前投与）群の特発性部分てんかん及び faster aspart（食後投与）群のネフローゼ症候群〕であった〔Trial 4101（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.2〕。

表 2.7.4.2-9　重篤な有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal)				Faster aspart (post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	261				258				258			
Total exposure (yrs)	128.4				127.7				127.7			
Total events	5	(1.9)	7	5.5	13	(5.0)	15	11.8	9	(3.5)	13	10.2
Severity												
Severe	2	(0.8)	3	2.3	7	(2.7)	8	6.3	2	(0.8)	3	2.3
Moderate	2	(0.8)	3	2.3	4	(1.6)	5	3.9	7	(2.7)	8	6.3
Mild	1	(0.4)	1	0.8	2	(0.8)	2	1.6	2	(0.8)	2	1.6
Related to randomised trial product												
Probable	1	(0.4)	2	1.6	2	(0.8)	4	3.1	1	(0.4)	1	0.8
Possible	0				0				0			
Unlikely	4	(1.5)	5	3.9	11	(4.3)	11	8.6	8	(3.1)	12	9.4
Related to basal component												
Probable	1	(0.4)	2	1.6	1	(0.4)	1	0.8	1	(0.4)	1	0.8
Possible	0				0				0			
Unlikely	4	(1.5)	5	3.9	12	(4.7)	14	11.0	8	(3.1)	12	9.4
Related to a technical complaint												
Yes	0				0				0			
No	5	(1.9)	7	5.5	13	(5.0)	15	11.8	9	(3.5)	13	10.2
Outcome												
Recovered/resolved	4	(1.5)	6	4.7	11	(4.3)	13	10.2	9	(3.5)	12	9.4
Recovering/resolving	0				0				0			
Recovered/resolved with sequelae	0				1	(0.4)	1	0.8	1	(0.4)	1	0.8
Not recovered/not resolved	1	(0.4)	1	0.8	1	(0.4)	1	0.8	0			
Fatal	0				0				0			
Unknown	0				0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigators assessment. MedDRA version 20.0.Technical complaint is related to randomised trial product.

表 2.7.4.2-10　器官別大分類及び基本語別の重篤な有害事象－治験薬投与下で発現－1%以上の被験者で報告－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	261				258				258			
Total exposure (yrs)	128.4				127.7				127.7			
感染症および寄生虫症												
胃腸炎	0				0				3	(1.2)	3	2.3

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

表 2.7.4.2-11　Faster aspart 又はノボラピッド®注との因果関係が「可能性あり」又は「あり」と判定された器官別大分類及び基本語別の重篤な有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	261				258				258			
Total exposure (yrs)	128.4				127.7				127.7			
Total events	1	(0.4)	2	1.6	2	(0.8)	4	3.1	1	(0.4)	1	0.8
傷害、中毒および処置合併症	1	(0.4)	1	0.8	2	(0.8)	2	1.6	0			
偶発的過量投与	1	(0.4)	1	0.8	2	(0.8)	2	1.6	0			
代謝および栄養障害	1	(0.4)	1	0.8	0				1	(0.4)	1	0.8
低血糖	1	(0.4)	1	0.8	0				1	(0.4)	1	0.8
神経系障害	0				2	(0.8)	2	1.6	0			
低血糖性意識消失	0				2	(0.8)	2	1.6	0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
MedDRA version 20.0.

2.7.4.2.2.4.2　海外併合データ

海外併合データ全体では、重篤な有害事象の単位時間あたりの発現件数は faster aspart 群で 15.3 件/100 人・年、対照薬群で 13.3 件/100 人・年であった（付録 2.7.4.7.2.3、表 2.7.4.7.2.3-1）。最も高頻度で報告された重篤な有害事象（1%以上の被験者）は低血糖であった。その他に、1%以上の被験者で報告された重篤な有害事象はなかった（付録 2.7.4.7.2.3、表 2.7.4.7.2.3-2）。治験責任医師により治験薬と

の因果関係が「可能性あり」又は「あり」と判定された重篤な有害事象の単位時間あたりの発現件数は、faster aspart 群で 4.8 件/100 人・年及び対照薬群で 3.0 件/100 人・年であった（付録 2.7.4.7.2.3、表 2.7.4.7.2.3-3）。重篤な有害事象の大部分（faster aspart 群で 114 件中 105 件及び対照薬群で 77 件中 68 件）が、試験終了時の転帰は回復又は軽快であった（付録 2.7.4.7.2.3、表 2.7.4.7.2.3-1）。

重篤な有害事象の叙述及び一覧は、試験ごとに Module 5 に示す。

2.7.4.2.2.4.3　進行中の試験

2018 年 8 月 1 日時点で、4113 試験において 114 例 166 件、4265 試験において 2 例 5 件の重篤な有害事象が報告された。4371 試験では重篤な有害事象の報告はなかった。

2.7.4.2.2.4.4　結論

結論として、これまで得られた結果から、ノボラピッド®注と比較して、faster aspart の投与による重篤な有害事象のリスクの増加は示唆されなかった。

2.7.4.2.2.5　その他の重要な有害事象

2.7.4.2.2.5.1　検証的試験

4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

ノボラピッド®注群の 1 例が、重篤な有害事象（椎間板突出）のため治験薬の投与を早期に中止した（Module 2.7.6.10.2、表 2.7.6.10.2-8）。この事象について、治験責任医師により治験薬との因果関係は「なし」と判定された。当該事象により、同被験者は試験の中止に至った（Module 2.7.6.10.2、表 2.7.6.10.2-9）。同被験者の他に、有害事象のため治験薬の投与を早期に中止した被験者はいなかった。

Bolus インスリン又は Basal インスリンの投与量の減量に至った有害事象を報告した被験者の割合は、いずれの投与群においても同程度であった。投与量の減量に至った有害事象の単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 13.4、11.2 及び 10.0 件/100 人・年であった〔Trial 4131（M 5.3.5.1）Memo Table 14.3.1.24〕。

器官別大分類及び基本語別の、投与量の減量に至った有害事象の要約は、総括報告書に提示する〔Trial 4131（M 5.3.5.1）Memo Table 14.3.1.25〕。最も高頻度で報告された投与量の減量に至った有害事象（基本語）は、血中ブドウ糖減少及び低血糖であった。投与量の減量に至った有害事象 59 件のうち、39 件で Bolus インスリンを減量し、39 件で Basal インスリンを減量した〔Trial 4131（M 5.3.5.1）Memo Table 14.3.2.3 及び EOT Table 14.3.2.4〕。投与量の減量に至った有害事象のうち 20 件が重篤な有害事象であった〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 7 例（2.0%）7 件、4 例（1.2%）6 件及び 7 例（2.0%）7 件であった〔Trial 4131（M 5.3.5.1）Memo Table 14.3.1.24〕。

4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

有害事象のため治験薬の投与を早期に中止、又は試験を中止した被験者はいなかった（表 2.7.4.1-3）。

Bolus インスリン又は Basal インスリンの投与量の減量に至った有害事象を報告した被験者の割合は、いずれの投与群においても同程度であった〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群で、それぞれ 4.2、 6.2 及び 7.4%〕。投与量の減量に至った有害事象の単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 9.3、18.8 及び 20.4 件/100 人・年であった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.38〕。

投与量の減量に至ったすべての有害事象の要約は、総括報告書に提示する〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.39〕。いずれかの投与群で 1%以上の被験者から報告された投与量の減量に至った有害事象（基本語）は、胃腸炎、嘔吐、低血糖及び血中ブドウ糖減少であったが、3 つの投与群とも、これら事象の報告は稀であった。全体として投与量の減量に至った有害事象は 62 件であり、うち 45 件で Bolus インスリンを減量し、35 件で Basal インスリンを減量した〔Trial 4101（M 5.3.5.1）EOT Listing 14.3.2.3 及び 14.3.2.4〕。投与量の減量に至った有害事象 62 件のうち 9 件が重篤な有害事象であった〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群で、それぞれ 0 件、4 例（1.6%）5 件及び 4 例（1.6%）4 件〕〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.38〕。

2.7.4.2.2.5.2　結論

4131 又は 4101 試験において、試験の中止、治験薬投与の中止あるいは Bolus インスリン又は Basal インスリンの投与量の減量に至った有害事象に関して、投与群間で臨床的に意味のある違いは認められなかった。

2.7.4.2.3　　器官別又は症候群別有害事象の解析

Faster aspart の安全性の評価に際し、特定の種類の有害事象を、糖尿病やインスリン治療に関連する特に注目すべき安全性領域の事象として、特別に検討を行った。

器官別又は症候群別有害事象は、4131 及び 4101 試験については試験ごとに評価し、補足情報として海外併合データの結果（2.7.4.2.3.11 項）も提示する。また 3854 試験（CSII 療法）に基づく評価は 2.7.4.5.12.2.11 項に提示する。

2.7.4.2.3.1　　心血管系事象

喫煙、肥満、糖尿病、高コレステロール血症及び高血圧は、世界的に心疾患及び脳卒中の主要なリスクと考えられている[4]。糖尿病と合併することの多い心血管系疾患には、虚血性心疾患、脳卒中、末梢動脈疾患及びうっ血性心不全が含まれる[5,6]。糖尿病患者における心筋梗塞の発症率は、非糖尿病患者

と比較して、男性では 2～4 倍、女性では 4～5 倍高い。このことから、心血管系事象は特に注目すべき安全性領域とした。

2.7.4.2.3.1.1　評価方法

4131 及び 4101 試験において、付録 2.7.4.7.8 に示す一覧の基本語を用いた基本語検索に基づき、心血管系事象を特定した。心血管系事象のイベント判定は実施しなかった。

2.7.4.2.3.1.2　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

4131 試験では、計 5 件の心血管系事象が報告され（表 2.7.4.2-12）、内訳は、faster aspart（食前投与）群及び faster aspart（食後投与）群でそれぞれ 4 例 4 件及び 1 例 1 件であった。5 件中 2 件が重篤な有害事象として報告されたが、どちらの被験者も当該事象から回復した。5 件中 4 件（重篤な有害事象を含む）が faster aspart との因果関係は「なし」と判定された。これらの事象について、以下に要約する。

- 1 件の硬膜外血腫：重度の重篤な有害事象として報告された。治験責任医師により faster aspart（食前投与）との因果関係は「なし」と判定された。転帰は回復であった。
- 1 件の頚動脈硬化症：軽度の重篤でない有害事象として報告された。治験責任医師により faster aspart（食前投与）との因果関係は「可能性あり」と判定された。転帰は未回復であった。
- 1 件の心筋虚血：中等度の重篤でない有害事象として報告された。治験責任医師により faster aspart（食前投与）との因果関係は「なし」と判定された。転帰は未回復であった。
- 1 件の冠動脈疾患：軽度の重篤でない有害事象として報告された。治験責任医師により faster aspart（食前投与）との因果関係は「なし」と判定された。転帰は未回復であった。
- 1 件の脳血管発作：中等度の重篤な有害事象として報告された。治験責任医師により faster aspart（食後投与）との因果関係は「なし」と判断された。転帰は回復であった。

これらの事象の詳細については、付録 2.7.4.7.2.1、表 2.7.4.7.2.1-2 及び Trial 4131（M 5.3.5.1）Memo Appendix 16.2.7、Listing 16.2.7.1 を参照。

表 2.7.4.2-12　器官別大分類及び基本語別の心血管系有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	342				341				342			
Total exposure (yrs)	171.3				170.2				170.2			
Total events	4	(1.2)	4	2.3	1	(0.3)	1	0.6	0			
心臓障害	2	(0.6)	2	1.2	0				0			
冠動脈疾患	1	(0.3)	1	0.6	0				0			
心筋虚血	1	(0.3)	1	0.6	0				0			
神経系障害	1	(0.3)	1	0.6	1	(0.3)	1	0.6	0			
頚動脈硬化症	1	(0.3)	1	0.6	0				0			
脳血管発作	0				1	(0.3)	1	0.6	0			
傷害、中毒および処置合併症	1	(0.3)	1	0.6	0				0			
硬膜外血腫	1	(0.3)	1	0.6	0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. MedDRA version 20.0.

2.7.4.2.3.1.3　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

4101 試験では心血管系事象は報告されなかった（付録 2.7.4.7.2.1、表 2.7.4.7.2.1.3）。

2.7.4.2.3.1.4　結論

全体として、心血管系事象の発現件数は少なく、明確な結論は得られなかった。しかしながら、心血管系事象に関する結果からは、ノボラピッド®注と比較して、faster aspart 投与による心血管リスクの増加は示唆されず、このことは海外併合データに基づく結果と一致している（2.7.4.2.3.11 項）。

2.7.4.2.3.2　投薬過誤

投薬過誤は低血糖や高血糖を引き起こす可能性があるため、faster aspart 臨床開発プログラムにおいて特に注目すべき安全性領域とした[7]。

2.7.4.2.3.2.1　評価方法

概観を示すため、基本語検索により投薬過誤を特定した。また、特定の投薬過誤については、すべての試験の治験実施計画書で、特に注目すべき医学的事象（MESI）と定義した。以下の定義の 1 つ以上に該当する投薬過誤が MESI である。各定義の詳細は、個々の試験間でわずかに異なっていた。これ

らの投薬過誤については、事象に関する追加情報を収集することとした。MESI の定義は以下のとおり：

- 誤った薬剤の投与
  4131 試験では、run-in 期間及び faster aspart（食後投与）群（非盲検下）の被験者が誤った交付ユニット番号（DUN）を使用した場合、結果的に誤った薬剤が投与されなければ、投薬過誤としないこととした。
  4101 試験では、誤った DUN を使用した場合、結果として誤った薬剤が投与されなければ、投薬過誤としないこととした。
- 皮下投与の代わりに筋肉投与といったような、誤った経路による投与
- 自身を傷つけることを意図した過量投与（自殺企図等）
- 偶発的な低用量又は高用量の投与
  4131 及び 4101 試験では、重大な健康への影響をもたらす可能性があると治験責任医師が判断する用量（重大な有害事象の基準を満たすか否かは問わない）とした。

4131 及び 4101 試験において、付録 2.7.4.7.8、Trial 4131（M 5.3.5.1）Appendix 16.2.7、 Listing 16.2.7.13 及び Trial 4101（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.14 に示す一覧の基本語を用いた基本語検索に基づき、投薬過誤に関連する有害事象を特定した。

2.7.4.2.3.2.2　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

投薬過誤は、Faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 8 例 9 件、13 例 16 件及び 6 例 6 件報告された（表 2.7.4.2-13）。これらのうち 2 件を除くすべての事象が、誤薬投与として報告された。残りの 2 件は誤用量投与に分類され、1 件が偶発的過量投与、1 件が偶発的過少量投与であった〔いずれも faster aspart（食後投与）群〕。いずれの事象も転帰は回復であった。誤薬投与として報告された事象のうち、11 件の投薬過誤で低血糖が報告された〔faster aspart（食後投与）群で 4 例 6 件、ノボラピッド®注群で 5 例 5 件〕〔Trial 4131（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.6〕。

ノボラピッド®注群の 2 例において、誤薬投与が重篤な投薬過誤として報告された（1 例は Basal インスリンの代わりに Bolus インスリンを投与した疑い、1 例は Basal インスリンの代わりに Bolus インスリンを投与）。試験の中止や治験薬投与の中止に至った事象はなかった：

- 被験者は夕食時に Bolus インスリンを 9 単位投与し、就寝前に Basal インスリンを 28 単位投与した。しかし、照明が不十分であったため、就寝前に投与したのが正しいインスリン（インスリン デグルデク）かどうか不明確であった。翌朝の起床時に、被験者は低血糖（49 mg/dL）を発現し、被験者自身により処置ができなかった。被験者は救急搬送され、グルコースが静脈内投与された。本被験者は回復した。

- 被験者は、注意散漫により、朝の Basal インスリンを投与する代わりに Bolus インスリンを 26 単位投与した。被験者は、低血糖を数回発現したが回復し、処置は行われなかった。

投薬過誤に関する叙述は、Trial 4131（M 5.3.5.1）Section.14.3.3 参照。

表 2.7.4.2-13　投薬過誤－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)		
	N	(%)	E R	N	(%)	E R	N	(%)	E R
Number of subjects	342			341			342		
Total exposure (yrs)	171.3			170.2			170.2		
Total events	8	(2.3)	9 5.3	13	(3.8)	16 9.4	6	(1.8)	6 3.5
Outcome									
Recovered/resolved	8	(2.3)	9 5.3	13	(3.8)	16 9.4	6	(1.8)	6 3.5
誤薬投与									
Related to randomised trial product									
Probable	6	(1.8)	6 3.5	7	(2.1)	9 5.3	4	(1.2)	4 2.4
Unlikely	3	(0.9)	3 1.8	5	(1.5)	5 2.9	2	(0.6)	2 1.2
Related to basal component									
Probable	4	(1.2)	4 2.3	5	(1.5)	5 2.9	2	(0.6)	2 1.2
Unlikely	4	(1.2)	5 2.9	8	(2.3)	9 5.3	4	(1.2)	4 2.4
偶発的過量投与									
Related to randomised trial product									
Probable	0			1	(0.3)	1 0.6	0		
Related to basal component									
Unlikely	0			1	(0.3)	1 0.6	0		
偶発的過少量投与									
Related to randomised trial product									
Unlikely	0			1	(0.3)	1 0.6	0		
Related to basal component									
Unlikely	0			1	(0.3)	1 0.6	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigators assessment. Events included are selected based on preferred terms. MedDRA version 20.0.

2.7.4.2.3.2.3　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

6 例 6 件の投薬過誤が報告され、内訳は Faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 3 例 3 件、2 例 2 件及び 1 例 1 件であった。すべての事象の転帰は回復

であった。投薬過誤の概観を表 2.7.4.2-14 に、詳細は Trial 4101（M 5.3.5.1）EOT Table 14.3.1.51 に提示する。

5 件の投薬過誤が偶発的過量投与として報告され〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 2、2 及び 1 件〕、1 件の投薬過誤が誤用量投与として報告された〔faster aspart（食前投与）群〕（表 2.7.4.2-14）。偶発的過量投与の 4 件で低血糖が報告された〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 1、2 及び 1 件〕〔Trial 4101（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.6〕。

3 件の偶発的過量投与が重篤な投薬過誤として報告された。試験の中止や治験薬投与の中止に至った事象はなかった：

- Faster aspart（食前投与）群：投薬過誤の主な理由は、新しいスライディングスケールに関する混乱によるものと考えられた。偶発的過量投与に起因する低血糖が身体活動に関連して発現した。発熱やその他の疾患の徴候はなく、血糖値は 38 mg/dL であった。被験者は入院したが、回復した。
- Faster aspart（食後投与）群：養護教諭が、インスリン／カーボ比（1 単位：20g）を間違えたか、もしくはインスリン投与量の計算を間違えた。低血糖性意識消失が報告されたが、身体活動に関連して発現したものか、発熱やその他の疾患の徴候があったかは不明である。血糖値は 37 mg/dL であった。被験者は、救急搬送され、グルコースが静脈内投与されて、回復した。
- Faster aspart（食後投与）群：被験者は余分に摂取した食事に対して、誤って高用量のインスリンを投与した。低血糖性意識消失が報告され、血糖値は 44 mg/dL であった。被験者は、救急搬送され、グルコースが静脈内投与されて、回復した。

投薬過誤に関する叙述は、Trial 4101（M 5.3.5.1）Section 14.3.3 参照。

表 2.7.4.2-14　投薬過誤－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	261				258				258			
Total exposure (yrs)	128.4				127.7				127.7			
Total events	3	(1.1)	3	2.3	2	(0.8)	2	1.6	1	(0.4)	1	0.8
Outcome												
Recovered/resolved	3	(1.1)	3	2.3	2	(0.8)	2	1.6	1	(0.4)	1	0.8
偶発的過量投与												
Related to randomised trial product												
Probable	2	(0.8)	2	1.6	2	(0.8)	2	1.6	1	(0.4)	1	0.8
Related to basal component												
Probable	1	(0.4)	1	0.8	0				0			
Unlikely	1	(0.4)	1	0.8	2	(0.8)	2	1.6	1	(0.4)	1	0.8
誤用量投与												
Related to randomised trial product												
Probable	1	(0.4)	1	0.8	0				0			
Related to basal component												
Unlikely	1	(0.4)	1	0.8	0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigators assessment.

2.7.4.2.3.2.4　結論

全体として、投薬過誤の発現頻度はすべての投与群において低かった。4131 及び 4101 試験の結果からは、ノボラピッド®注と比較して、faster aspart による投薬過誤リスクの増加は示唆されず、このことは海外併合データに基づく結果と一致している（2.7.4.2.3.11 項）。なお臨床試験では、Basal インスリン（インスリン デグルデク）含む治験薬を、同じペン型注入器に市販製剤用とは異なる臨床試験専用のラベルを貼付した状態で交付していた。

2.7.4.2.3.3　免疫原性に関連する有害事象（アレルギー反応）

Faster aspart は、他のインスリン製剤と同様タンパク製剤であるため、免疫原性に関連する有害事象（アレルギー反応）の潜在的リスクがある[8]。アレルギー反応には、局所性反応及び全身性反応のいずれもありうる。アナフィラキシー反応を含む過敏症反応は、死に至ることもある。このため、アレルギー反応を、faster aspart における特に注目すべき安全性領域とした。

2.7.4.2.3.3.1　評価方法

4131 及び 4101 試験において、付録 2.7.4.7.8、Trial 4131（M 5.3.5.1）Appendix 16.2.7、 Listing 16.2.7.13 及び Trial 4101（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.14 に示す一覧の基本語を用いた基本語検索に基づき、アレルギー反応に関連する有害事象を特定した。

これら事象の叙述は、各試験の総括報告書（M 5.3.5.1）Section 14.3.3 を参照のこと。

2.7.4.2.3.3.2　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

全体として、アレルギー反応の種類やアレルギー反応を発現した被験者の割合に、投与群間で臨床的に意味のある違いは認められなかった。

アレルギー反応は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 9 例 13 件、14 例 16 件及び 11 例 11 件報告された。単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 7.6、9.4 及び 6.5 件/100 人・年であった。最も高頻度（いずれかの群の 1%以上の被験者）で報告された有害事象（基本語）は皮膚炎であった（表 2.7.4.2-15）。アレルギー反応に関連する有害事象はいずれも非重篤で、軽度又は中等度であった〔Trial 4131（M 5.3.5.1）Section 12.5.7〕。

基本語検索で特定された 7 件の有害事象は、治験責任医師により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。

- 蕁麻疹 3 件（各投与群それぞれ 1 例）。これら 3 例のうちノボラピッド®注群の 1 例が、被験者からの申し出により試験を中止した〔Trial 4131（M 5.3.5.1）Appendix 16.2.1、Listing 16.2.1.5〕。
- 発疹 1 件（ノボラピッド®注群）
- 注射部位発疹 1 件〔faster aspart（食後投与）群〕
- 紅斑性皮疹 1 件〔faster aspart（食前投与）群〕
- 注射部位過敏反応 1 件〔faster aspart（食後投与）群〕

軽度の蕁麻疹が未回復であった 1 例の被験者〔faster aspart（食前投与）群〕を除き、いずれの被験者も治験薬との因果関係が「あり」又は「可能性あり」と判定されたアレルギー反応に関連する有害事象から回復した〔Trial 4131（M 5.3.5.1）Memo Appendix 16.2.7、Listing 16.2.7.3〕。

表 2.7.4.2-15　器官別大分類及び基本語別のアレルギー反応－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	342				341				342			
Total exposure (yrs)	171.3				170.2				170.2			
Total events	9	(2.6)	13	7.6	14	(4.1)	16	9.4	11	(3.2)	11	6.5
皮膚および皮下組織障害												
皮膚炎	1	(0.3)	3	1.8	4	(1.2)	4	2.4	0			
蕁麻疹	2	(0.6)	2	1.2	3	(0.9)	3	1.8	2	(0.6)	2	1.2
接触皮膚炎	1	(0.3)	1	0.6	0				2	(0.6)	2	1.2
湿疹	2	(0.6)	2	1.2	0				1	(0.3)	1	0.6
アトピー性皮膚炎	1	(0.3)	1	0.6	0				1	(0.3)	1	0.6
発疹	0				0				2	(0.6)	2	1.2
紅斑性皮疹	1	(0.3)	1	0.6	0				0			
そう痒性皮疹	1	(0.3)	1	0.6	0				0			
皮膚反応	0				1	(0.3)	1	0.6	0			
免疫系障害												
過敏症	0				1	(0.3)	3	1.8	1	(0.3)	1	0.6
複合アレルギー	0				0				1	(0.3)	1	0.6
呼吸器、胸郭および縦隔障害												
アレルギー性鼻炎	2	(0.6)	2	1.2	1	(0.3)	1	0.6	1	(0.3)	1	0.6
眼障害												
アレルギー性結膜炎	0				1	(0.3)	1	0.6	0			
眼瞼浮腫	0				1	(0.3)	1	0.6	0			
一般・全身障害および投与部位の状態												
注射部位過敏反応	0				1	(0.3)	1	0.6	0			
注射部位発疹	0				1	(0.3)	1	0.6	0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Events included are selected based on preferred terms.
MedDRA version 20.0.

2.7.4.2.3.3.3　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

全体として、アレルギー反応の種類やアレルギー反応を発現した被験者の割合に、投与群間で臨床的に意味のある違いは認められなかった。

アレルギー反応は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 13 例 17 件、8 例 8 件及び 9 例 13 件報告された。単位時間あたりの発現件数は、faster aspart

（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 13.2、6.3 及び 10.2 件/100 人・年であった。最も高頻度（いずれかの群の 1%以上の被験者）で報告された有害事象（基本語）はアレルギー性鼻炎及び発疹であった（表 2.7.4.2-16）。アレルギー反応に関連する有害事象はいずれも非重篤で、軽度又は中等度であった〔Trial 4101（M 5.3.5.1）Section 12.3.7〕。

ノボラピッド®注群において報告された 1 件の中等度の有害事象（蕁麻疹）が、治験責任医師により治験薬との因果関係が「可能性あり」と判定された〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.50 及び Appendix 16.2.7、Listing 16.2.7.3〕。転帰は回復であった。

表 2.7.4.2-16　器官別大分類及び基本語別のアレルギー反応－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	261			258			258		
Total exposure (yrs)	128.4			127.7			127.7		
Total events	13 (5.0)	17	13.2	8 (3.1)	8	6.3	9 (3.5)	13	10.2
皮膚および皮下組織障害									
発疹	4 (1.5)	4	3.1	1 (0.4)	1	0.8	2 (0.8)	2	1.6
皮膚炎	1 (0.4)	1	0.8	1 (0.4)	1	0.8	1 (0.4)	2	1.6
湿疹	2 (0.8)	2	1.6	1 (0.4)	1	0.8	1 (0.4)	1	0.8
蕁麻疹	1 (0.4)	2	1.6	1 (0.4)	1	0.8	1 (0.4)	1	0.8
アレルギー性皮膚炎	1 (0.4)	1	0.8	1 (0.4)	1	0.8	0		
斑状皮疹	0			1 (0.4)	1	0.8	0		
顔面腫脹	0			0			1 (0.4)	1	0.8
呼吸器、胸郭および縦隔障害									
アレルギー性鼻炎	2 (0.8)	5	3.9	0			4 (1.6)	4	3.1
アレルギー性咳嗽	0			0			1 (0.4)	1	0.8
眼障害									
アレルギー性結膜炎	1 (0.4)	1	0.8	0			1 (0.4)	1	0.8
胃腸障害									
口唇腫脹	0			1 (0.4)	1	0.8	0		
免疫系障害									
過敏症	1 (0.4)	1	0.8	0			0		
感染症および寄生虫症									
感染性皮膚炎	0			1 (0.4)	1	0.8	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years, Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. MedDRA version 20.0.

2.7.4.2.3.3.4　結論

結論として、4131 及び 4101 試験における免疫原性に関連する有害事象は、投与群間で臨床的に意味のある違いは認められなかった。これらの試験において、アレルギー反応の検索用に特定された有害事象（基本語）の単位時間あたりの発現件数は、いずれの投与群においても同程度であった。得られた結果から、ノボラピッド®注と比較して、faster aspart によるアレルギー反応のリスクの増加は示唆されず、このことは海外併合データに基づく結果と一致している（表 2.7.4.2-11 項）。

2.7.4.2.3.4　　注射部位反応及びリポジストロフィー

注射部位反応（注射部位の発疹、発赤、炎症、内出血及びそう痒感）は、薬剤の皮下投与における潜在的リスクである。さらに、注射部位反応は、ノボラピッド®注、faster aspart（既承認の国において）及び他のインスリン製剤の添付文書に、高頻度で報告される副作用として記載されている。一般的に、インスリンの皮下投与による注射部位反応は、一過性かつ軽度であることが多い。しかしながら、持続的な注射部位反応によりインスリン治療の変更が必要となる場合もある。注射部位反応は、稀にアレルギー反応の症状として現れることがあり、極端な場合には、アナフィラキシー反応を含む I 型過敏症反応を引き起こす場合もある。このため、注射部位反応を、faster aspart における特に注目すべき安全性領域とした。

リポジストロフィー（脂肪肥大症及び脂肪組織萎縮症を含む）はインスリン注射部位に発現することがある。リポジストロフィーはインスリンの副作用としてよく知られており、添付文書にも記載されている。リポジストロフィー発現部位からのインスリン吸収は不安定になり、理想的な血糖コントロールの達成が困難となる場合もある。

被験者には、Bolus インスリン投与による反応と Basal インスリン投与による反応を区別するため、Bolus インスリンを腹部に、Basal インスリンを大腿部又は三角筋部に皮下注射するよう指導した。

2.7.4.2.3.4.1　評価方法

4131 及び 4101 試験において、付録 2.7.4.7.8、Trial 4131（M 5.3.5.1）Appendix 16.2.7、 Listing 16.2.7.13 及び Trial 4101（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.14 に示す一覧の基本語を用いた基本語検索に基づき、注射部位反応に関連する有害事象を特定した。

Bolus インスリン及び／又は Basal インスリンに関連する注射部位反応は、有害事象として「AE form」に記録し、さらに「AE form」では報告されない追加的な情報を入手するため、注射部位反応専用フォームにも報告することとした。基本語検索で特定された有害事象の中には治験責任医師により注射部位反応として記録されていないものも含まれており、また、治験責任医師が注射部位反応として記録していても基本語検索では特定されなかった事象もあった。

また、リポジストロフィーに関連する有害事象についても、付録 2.7.4.7.8、Trial 4131（M 5.3.5.1）Appendix 16.2.7、 Listing 16.2.7.13 及び Trial 4101（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.14 に示す一覧の基本語を用いた基本語検索に基づき特定した。

2.7.4.2.3.4.2　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

注射部位反応

注射部位反応はいずれの投与群においても同程度の頻度で報告され、1%超の被験者において報告された有害事象（基本語）はなかった（表 2.7.4.2-17）。基本語検索により、21 例 31 件の有害事象が特定され、内訳は faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 8 例（2.3%）9 件、8 例（2.3%）12 件及び 5 例（1.5%）10 件であった。いずれの注射部位反応も非重篤で、軽度又は中等度であった〔Trial 4131（M 5.3.5.1）Memo Appendix 16.2.7、Listing 16.2.7.1〕。

31 件中 15 件の注射部位反応が、faster aspart 又はノボラピッド®注との因果関係が「あり」又は「可能性あり」と判定された。これらの有害事象の発現に、投与群間〔faster aspart（食前投与）群で、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 4、9 及び 2 件〕及び有害事象（基本語）間で特段の偏りは認められなかった〔Trial 4131（M 5.3.5.1）Memo EOT Table 14.3.1.30〕。治験薬との因果関係が「あり」又は「可能性あり」と判定された注射部位反応に関連する有害事象は、以下の 2 例 2 件を除いていずれも回復した：1 件は軽度の注射部位肥厚で回復したが後遺症あり〔faster aspart（食前投与）群〕、1 件は軽度の投与部位硬結で未回復〔faster aspart（食後投与）群〕〔Trial 4131（M 5.3.5.1）Memo Appendix 16.2.7、Listing 16.2.7.3〕。

基本語検索では特定されたが、治験責任医師により注射部位反応専用フォームでの報告がされていない事象が 2 件あった。1 件は注射部位内出血〔faster aspart（食後投与）群〕、1 件は注射部位肥厚〔faster aspart（食前投与）群〕であった。また、基本語検索により特定されなかったが、注射部位反応専用フォームで報告された事象が 4 件あった。このうち、3 件は脂肪肥大症〔faster aspart（食後投与）群で 1 例及び faster aspart（食前投与）群で 2 例〕、1 件は挫傷〔faster aspart（食後投与）群で 1 例〕であった。詳細については、Trial 4131（M 5.3.5.1）Section 12.5.5 を参照のこと。試験の中止や治験薬の投与中止に至った注射部位反応はなかった〔Trial 4131（M 5.3.5.1）Appendix 16.2.1、 Listing 16.2.1.3 及び 16.2.1.5。被験者番号は、Safety Appendix 5（M 5.3.5.1）Listing 5.1 参照〕。

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表 2.7.4.2-17　器官別大分類及び基本語別の注射部位反応－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	342				341				342			
Total exposure (yrs)	171.3				170.2				170.2			
Total events	8	(2.3)	9	5.3	8	(2.3)	12	7.1	5	(1.5)	10	5.9
一般・全身障害および投与部位の状態												
注射部位血腫	2	(0.6)	2	1.2	2	(0.6)	4	2.4	2	(0.6)	4	2.4
注射部位内出血	1	(0.3)	2	1.2	2	(0.6)	2	1.2	0			
注射部位疼痛	1	(0.3)	1	0.6	1	(0.3)	1	0.6	2	(0.6)	2	1.2
注射部位反応	0				1	(0.3)	1	0.6	2	(0.6)	3	1.8
注射部位肥厚	2	(0.6)	2	1.2	1	(0.3)	1	0.6	0			
投与部位硬結	0				1	(0.3)	1	0.6	0			
注射部位出血	1	(0.3)	1	0.6	0				0			
注射部位過敏反応	0				1	(0.3)	1	0.6	0			
注射部位硬結	0				0				1	(0.3)	1	0.6
注射部位発疹	0				1	(0.3)	1	0.6	0			
注射部位腫脹	1	(0.3)	1	0.6	0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Events included are selected based on preferred terms.
MedDRA version 20.0.

リポジストロフィー

基本語検索により、6 例（0.6%）6 件のリポジストロフィーに関連する有害事象が特定された〔faster aspart（食前投与）群及び faster aspart（食後投与）群で各 3 例〕。リポジストロフィーに関連する有害事象の大部分（6 件中 5 件）は脂肪肥大症として報告され、残りの有害事象は後天性リポジストロフィーとして報告された（表 2.7.4.2-18）。いずれも非重篤、軽度であり〔Trial 4131（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.1〕、試験の中止や治験薬の投与中止に至った事象はなかった〔Safety Appendix 5（M 5.3.5.1）Listing 5.4、ならびに Trial 4131（M 5.3.5.1）Appendix 16.2.1、Listing 16.2.1.3 及び 16.2.1.5〕。

表 2.7.4.2-18　器官別大分類及び基本語別のリポジストロフィー－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	342				341				342			
Total exposure (yrs)	171.3				170.2				170.2			
Total events	3	(0.9)	3	1.8	3	(0.9)	3	1.8	0			
皮膚および皮下組織障害												
脂肪肥大症	2	(0.6)	2	1.2	3	(0.9)	3	1.8	0			
後天性リポジストロフィー	1	(0.3)	1	0.6	0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Events included are selected based on preferred terms.
MedDRA version 20.0.

2.7.4.2.3.4.3　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

注射部位反応

基本語検索により、33 例 59 件の注射部位反応が特定され、内訳は faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 8 例 11 件、14 例 31 件及び 11 例 17 件であった（表 2.7.4.2-19）。

最も高頻度（1%以上の被験者）で報告された注射部位反応は、注射部位出血、注射部位内出血、注射部位疼痛及び注射部位反応であった。

注射部位出血は 26 件であったが、うち 25 件は同一の治験実施医療機関で組み入れられた 5 例の被験者で報告された（当該治験実施医療機関のすべての被験者において注射部位出血が発現した）。当該治験実施医療機関で組み入れられた 5 例の被験者のうち、3 例が faster aspart（食後投与）群に無作為割り付けされ、この 3 例の被験者で 19 件の注射部位出血が報告された。他に faster aspart（食前投与）群の 1 例で 4 件、ノボラピッド®注群の 1 例では 2 件の注射部位出血が報告された。これら 25 件の注射部位出血について、医師により報告された事象名はいずれも「注射手技による（腹部、脚又は腕の）斑状出血（ecchymosis on abdomen/leg/arm due to injection technique）」であった〔Trial 4101（M 5.3.5.1）Appendix 16.2.7、Table 16.2.7.1〕。

注射部位反応のうち、注射部位出血以外の報告件数は少なく、いずれの投与群においても同程度に認められた（表 2.7.4.2-19）。

全体で 59 件の注射部位反応のうち、14 件で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。これらの事象はいずれの投与群においても同程度の頻度で認められた。治験薬との因果関

係が「あり」又は「可能性あり」と判定された事象に、注射部位出血は含まれなかった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.42 及び 14.3.1.44〕。

基本語検索では注射部位反応として特定されたが、治験責任医師により注射部位反応専用フォームでの報告がされていない事象が 33 件あった。内訳は、faster aspart（食前投与）群で 5 件、faster aspart（食後投与）群で 23 件、ノボラピッド®注群で 5 件であった。一方、基本語検索では注射部位反応として特定されなかったが、注射部位反応専用フォームでの報告がされた事象は 14 件あり、うち 8 件は脂肪肥大症〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 3 例 4 件、1 例 1 件及び 3 例 3 件〕、4 件は肥大〔faster aspart（食前投与）群、faster aspart（食後投与）群、ノボラピッド®注群でそれぞれ 1 例 1 件、1 例 1 件及び 2 例 2 件〕、1 件は挫傷〔faster aspart（食後投与）群 1 例〕、1 件は血腫〔faster aspart（食後投与）群 1 例〕であった。詳細については、Trial 4101（M 5.3.5.1）Section 12.3.5 参照。

試験の中止や治験薬投与の中止に至った注射部位反応はなかった〔Trial 4101（M 5.3.5.1）Appendix 16.2.1、 Listing 16.2.1.3 及び 16.2.1.5。被験者番号は、Safety Appendix 5（M 5.3.5.1）Listing 5.2 参照〕。

表 2.7.4.2-19　器官別大分類及び基本語別の注射部位反応－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	261			258			258		
Total exposure (yrs)	128.4			127.7			127.7		
Total events	8 (3.1)	11	8.6	14 (5.4)	31	24.3	11 (4.3)	17	13.3
一般・全身障害および投与部位の状態									
注射部位出血	1 (0.4)	4	3.1	4 (1.6)	20	15.7	1 (0.4)	2	1.6
注射部位内出血	0			3 (1.2)	4	3.1	2 (0.8)	2	1.6
注射部位疼痛	3 (1.1)	3	2.3	0			2 (0.8)	3	2.3
注射部位反応	0			5 (1.9)	5	3.9	1 (0.4)	1	0.8
注射部位血腫	1 (0.4)	1	0.8	0			2 (0.8)	4	3.1
注射部位肥厚	0			1 (0.4)	1	0.8	2 (0.8)	2	1.6
注射部位腫脹	1 (0.4)	1	0.8	0			1 (0.4)	1	0.8
注射部位変色	1 (0.4)	1	0.8	0			0		
注射部位紅斑	0			0			1 (0.4)	1	0.8
注射部位腫瘤	0			0			1 (0.4)	1	0.8
注射部位結節	0			1 (0.4)	1	0.8	0		
注射部位浮腫	1 (0.4)	1	0.8	0			0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

リポジストロフィー

基本語検索により、15 例（1.9%）17 件のリポジストロフィーが特定され、内訳は faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 7 例 8 件、4 例 5 件及び 4 例 4 件であった（表 2.7.4.2-20）。リポジストロフィーに関連する事象の大部分（17 件中 15 件）が脂肪肥大症として、残りの 2 件は後天性リポジストロフィーとして報告された〔2 件とも faster aspart（食後投与）群〕〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.45〕。

リポジストロフィーに関連する事象はいずれも非重篤で、重症度は中等度であった 1 件〔faster aspart（食前投与）群〕を除き、すべて軽度であった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.20、14.3.1.34 及び 14.3.1.36〕。

全体で、8 件の脂肪肥大症が、治験薬との因果関係が「あり」又は「可能性あり」と判定され、内訳は faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 3 例（1.1%）4 件、1 例（0.4%）1 件及び 3 例（1.2%）3 件であった。後天性リポジストロフィーで治験薬との因果関係が「あり」又は「可能性あり」と判定されたものはなかった〔Safety Appendix 5（M 5.3.5.1）Listing 5.5 及び Trial 4101（M 5.3.5.1）EOT Table 14.3.1.25〕。

表 2.7.4.2-20　器官別大分類及び基本語別のリポジストロフィー－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	261			258			258		
Total exposure (yrs)	128.4			127.7			127.7		
Total events	7 (2.7)	8	6.2	4 (1.6)	5	3.9	4 (1.6)	4	3.1
皮膚および皮下組織障害									
脂肪肥大症	7 (2.7)	8	6.2	3 (1.2)	3	2.4	4 (1.6)	4	3.1
後天性リポジストロフィー	0			1 (0.4)	2	1.6	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.2.3.4.4　結論

4131 試験の注射部位反応はいずれの投与群においても同程度の頻度で報告されたが、4101 試験では注射部位反応の発現件数は faster aspart（食前投与）群及びノボラピッド®注群と比較して、faster aspart（食後投与）群で多く報告された。注射部位反応の発現件数が faster aspart（食後投与）群で多かったことは、注射部位出血の発現件数が多いことに起因する。注射部位出血は 26 件であったが、うち 25

件は同一の治験実施医療機関で組み入れられた 5 例の被験者で報告された（当該治験実施医療機関のすべての被験者において注射部位出血が発現した）。当該治験実施医療機関で組み入れられた 5 例の被験者のうち、3 例が faster aspart（食後投与）群に無作為割り付けされ、この 3 例の被験者で 19 件の注射部位出血が報告されたことが、投与群間の偏りの原因であると考えられた。

4131 試験において、リポジストロフィーは faster aspart 群でのみ報告され、faster aspart（食前投与）群及び faster aspart（食後投与）群でそれぞれ 3 例 3 件ずつであった。4101 試験では、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 7 例 8 件、4 例 5 件及び 4 例 4 件報告された。

注射部位反応やリポジストロフィーに関連する有害事象はいずれも非重篤で、重症度は 4101 試験で 1 件のリポジストロフィーが中等度であったことを除き、すべて軽度であった。

結論として、ノボラピッド®注と比較して、faster aspart による注射部位反応やリポジストロフィーのリスクの増加は示唆されず、このことは海外併合データに基づく結果と一致した（2.7.4.2.3.11 項）。

2.7.4.2.3.5　末梢性浮腫

インスリンは、ナトリウム再吸収や毛細血管透過性の亢進により、末梢性浮腫を引き起こすことがある。インスリンによる末梢性浮腫は、インスリン治療において稀にみられる合併症で、主に 1 型糖尿病患者で認められ、インスリン療法を開始した直後や、コントロール不良の糖尿病患者がインスリン治療を強化した直後の発現が一般的である[9]。このため、末梢性浮腫を特に注目すべき安全性領域とした。

2.7.4.2.3.5.1　評価方法

4131 及び 4101 試験において、付録 2.7.4.7.8 に示す一覧の基本語を用いた基本語検索に基づき、末梢性浮腫に関連する有害事象を特定した。

2.7.4.2.3.5.2　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

基本語による検索により、5 例 6 件の末梢性浮腫に関連する有害事象が特定され、内訳は faster aspart（食前投与）群で 1 例 1 件、faster aspart（食後投与）群で 2 例 3 件、ノボラピッド®注群で 2 例 2 件であった（表 2.7.4.2-21）。いずれも軽度又は中等度で、治験薬の減量、治験薬投与の中止又は試験の中止に至った有害事象はなかった〔付録 2.7.4.7.2.1、表 2.7.4.7.2.1-26 ならびに Trial 4131（M 5.3.5.1）Appendix 16.2.1、Listing 16.2.1.3 及び 16.2.1.5〕。6 件中 1 件〔ノボラピッド®注群の 1 例で報告された末梢性浮腫（中等度）〕が、治験責任医師により治験薬との因果関係が「あり」と判定された。本有害事象の転帰は回復であった〔付録 2.7.4.7.2.1、表 2.7.4.7.2.1-26 及び Trial 4131（M 5.3.5.1）Memo Appendix 16.2.7、Listing 16.2.7.3〕。残りの 5 件は、治験薬との因果関係は「なし」と判定された。

表 2.7.4.2-21　器官別大分類及び基本語別の末梢性浮腫に関連する有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	342				341				342			
Total exposure (yrs)	171.3				170.2				170.2			
Total events	1	(0.3)	1	0.6	2	(0.6)	3	1.8	2	(0.6)	2	1.2
一般・全身障害および投与部位の状態	1	(0.3)	1	0.6	2	(0.6)	3	1.8	2	(0.6)	2	1.2
末梢性浮腫	1	(0.3)	1	0.6	2	(0.6)	2	1.2	2	(0.6)	2	1.2
浮腫	0				1	(0.3)	1	0.6	0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.2.3.5.3　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

4101 試験では、末梢性浮腫に関連する有害事象は報告されなかった（付録 2.7.4.7.2.1、表 2.7.4.7.2.1-27 及び 2.7.4.7.2.1-28）。

2.7.4.2.3.5.4　結論

末梢性浮腫に関連する有害事象の発現件数はわずかであった。ノボラピッド®注と比較して、faster aspart による末梢性浮腫のリスクの増加は示唆されず、このことは海外併合データに基づく結果と一致した（2.7.4.2.3.11 項）。

2.7.4.2.3.6　眼障害（糖尿病網膜症及び屈折障害）

長期的な血糖コントロールの改善は、糖尿病網膜症の発症・進行リスクを低下させる。しかしながら、インスリン療法の強化によって急激に血糖コントロールが改善すると、糖尿病網膜症が一時的に悪化する場合がある[10]。このことから、糖尿病網膜症を特に注目すべき安全性領域とした。

また、急激な血糖コントロールの変化（コントロール不良の被験者における悪化や急激な改善）により屈折障害が生じ、視力に影響することがある。このことから faster aspart においても、他のインスリン製剤と同様、屈折障害を特に注目すべき安全性領域とした。

2.7.4.2.3.6.1　評価方法

4131 及び 4101 試験において、付録 2.7.4.7.8 に示す一覧の基本語を用いた基本語検索に基づき、糖尿病網膜症及び屈折障害に関連する有害事象を特定した。

2.7.4.2.3.6.2　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

基本語検索により、42 例 45 件の糖尿病網膜症に関連する眼障害に関連する有害事象が特定され、内訳は faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 12 例（3.5%）12 件、16 例（4.7%）18 件及び 14 例（4.1%）15 件であった（表 2.7.4.2-22）。これら事象の大部分は、治験責任医師により軽度又は中等度、治験薬との因果関係は「なし」と判定された。増量があった 1 例 1 件を除き、投与量の変更に至った有害事象はなかった〔付録 2.7.4.7.2.1、表 2.7.4.7.2.1-8 及び Trial 4131（M 5.3.5.1）Memo Appendix 16.2.7、Listing 16.2.7.1〕。最も多く報告された有害事象（基本語）は、3 つの投与群のいずれにおいても糖尿病網膜症であった。それ以外の有害事象（基本語）は 1 例又は数例で報告された事象であり、特定の事象が多く発現することはなかった。

2 例〔いずれも faster aspart（食後投与）群〕3 件の事象が重度と判定されたが、治験薬との因果関係は「なし」と判定された。当該事象による投与量の変更はなかった。

Faster aspart（食後投与）群の 1 例において屈折障害に関連する眼障害の事象が 2 件報告された（表 2.7.4.2-23）。いずれの事象も治験責任医師により、軽度で治験薬との因果関係は「なし」と判定された。当該事象による投与量の変更はなかった〔付録 2.7.4.7.2.1、表 2.7.4.7.2.1-14 及び Trial 4131（M 5.3.5.1）Memo Appendix 16.2.7、Listing 16.2.7.1〕。

治験薬の投与中止や試験の中止に至った眼障害の事象はなかった〔Trial 4131（M 5.3.5.1）Appendix 16.2.1、Listing 16.2.1.3 及び 16.2.1.5〕。

表 2.7.4.2-22　器官別大分類及び基本語別の糖尿病網膜症に関連する有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	342			341			342		
Total exposure (yrs)	171.3			170.2			170.2		
Total events	12 (3.5)	12	7.0	16 (4.7)	18	10.6	14 (4.1)	15	8.8
眼障害	12 (3.5)	12	7.0	16 (4.7)	18	10.6	14 (4.1)	15	8.8
糖尿病網膜症	7 (2.0)	7	4.1	12 (3.5)	12	7.1	7 (2.0)	7	4.1
黄斑浮腫	0			2 (0.6)	2	1.2	2 (0.6)	2	1.2
網膜症	2 (0.6)	2	1.2	0			2 (0.6)	2	1.2
増殖性網膜症	0			1 (0.3)	1	0.6	1 (0.3)	1	0.6
硝子体出血	0			2 (0.6)	2	1.2	0		
嚢胞様黄斑浮腫	0			0			1 (0.3)	1	0.6
黄斑症	0			0			1 (0.3)	1	0.6
網膜滲出物	0			1 (0.3)	1	0.6	0		
網膜出血	1 (0.3)	1	0.6	0			0		
網膜虚血	0			0			1 (0.3)	1	0.6
一過性視力低下	1 (0.3)	1	0.6	0			0		
硝子体剥離	1 (0.3)	1	0.6	0			0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

表 2.7.4.2-23　器官別大分類及び基本語別の屈折障害に関連する有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	342			341			342		
Total exposure (yrs)	171.3			170.2			170.2		
Total events	0			1 (0.3)	2	1.2	0		
眼障害	0			1 (0.3)	2	1.2	0		
乱視	0			1 (0.3)	1	0.6	0		
近視	0			1 (0.3)	1	0.6	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure,yrs: Years.
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.2.3.6.3　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

4101 試験において、糖尿病網膜症に関連する有害事象は報告されなかった（付録 2.7.4.7.2.1、表 2.7.4.7.2.1-9 及び 2.7.4.7.2.1-10）。

屈折障害に関連した眼障害が、faster aspart（食前投与）群で 2 例 3 件及び faster aspart（食後投与）群で 1 例 1 件報告された。Faster aspart（食前投与）群の 1 件（近視）が中等度と判定されたことを除いては、すべての事象が治験責任医師により軽度と判定された。いずれの事象も治験薬との因果関係は「なし」と判定され、当該事象による投与量の変更はなかった。転帰が回復であった被験者はいなかった〔付録 2.7.4.7.2.1、表 2.7.4.7.2.1-16 及び Trial 4101（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.1〕。

治験薬の投与中止や試験の中止に至った眼障害の事象はなかった〔Trial 4101（M 5.3.5.1）Appendix 16.2.1、Listing 16.2.1.3 及び 16.2.1.5〕。

表 2.7.4.2-24　器官別大分類及び基本語別の屈折障害に関連する有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	261			258			258		
Total exposure (yrs)	128.4			127.7			127.7		
Total events	2 (0.8)	3	2.3	1 (0.4)	1	0.8	0		
眼障害	2 (0.8)	3	2.3	1 (0.4)	1	0.8	0		
乱視	2 (0.8)	2	1.6	1 (0.4)	1	0.8	0		
近視	1 (0.4)	1	0.8	0			0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure,yrs: Years.
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.2.3.6.4　結論

糖尿病網膜症及び屈折障害の発現件数はいずれの群においても少なく、いずれの投与群においても同程度であった。大部分の事象が軽度又は中等度で、治験薬との因果関係は「なし」と判定された。ノボラピッド®注と比較して、faster aspart による眼障害のリスクの増加は示唆されず、このことは海外併合データに基づく結果と一致した（2.7.4.2.3.11 項）。

2.7.4.2.3.7　末梢性ニューロパチー

長期的な血糖コントロールの改善は、末梢性ニューロパチーの発症・進行リスクを低下させる。しかしながら、急激に血糖コントロールが改善すると、急性有痛性ニューロパチーが発現したり、併発

している末梢性ニューロパチーが一時的に悪化する場合がある（いずれも通常は可逆的）[11]。このため、末梢性ニューロパチーを特に注目すべき安全性領域とした。

2.7.4.2.3.7.1　評価方法

4131 及び 4101 試験において、付録 2.7.4.7.8 に示す一覧の基本語を用いた基本語検索に基づき、末梢性ニューロパチーに関連する有害事象を特定した。

2.7.4.2.3.7.2　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

基本語検索により、13 例 13 件の末梢性ニューロパチーが特定され、内訳は faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 4 例（1.2%）4 件、7 例（2.1%）7 件及び 2 例（0.6%）2 件であった（表 2.7.4.2-25）。いずれの事象も治験責任医師により軽度又は中等度と判定された。治験薬との因果関係が「あり」又は「可能性あり」と報告された事象はなく、当該事象により投与量が変更された報告もなかった〔付録 2.7.4.7.2.1、表 2.7.4.7.2.1-20 及び Trial 4131（M 5.3.5.1）Memo Appendix 16.2.7、Listing 16.2.7.1〕。いずれの有害事象（基本語）も 1 例又は数例での報告であり、特定の事象が多く発現することはなかった。

治験薬の投与中止や試験の中止に至った事象はなかった〔Trial 4131（M 5.3.5.1）Appendix 16.2.1 Listing 16.2.1.3 及び 16.2.1.5〕。

表 2.7.4.2-25　器官別大分類及び基本語別の末梢性ニューロパチーに関連する有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	342				341				342			
Total exposure (yrs)	171.3				170.2				170.2			
Total events	4	(1.2)	4	2.3	7	(2.1)	7	4.1	2	(0.6)	2	1.2
神経系障害	4	(1.2)	4	2.3	6	(1.8)	6	3.5	2	(0.6)	2	1.2
糖尿病性ニューロパチー	3	(0.9)	3	1.8	0				0			
感覚鈍麻	0				2	(0.6)	2	1.2	1	(0.3)	1	0.6
錯感覚	1	(0.3)	1	0.6	1	(0.3)	1	0.6	1	(0.3)	1	0.6
多発ニューロパチー	0				2	(0.6)	2	1.2	0			
反射減弱	0				1	(0.3)	1	0.6	0			
筋骨格系および結合組織障害	0				1	(0.3)	1	0.6	0			
筋力低下	0				1	(0.3)	1	0.6	0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.2.3.7.3　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

4101 試験では、基本語検索により、faster aspart（食前投与）群において 1 件の事象が特定された。本事象は器官別大分類「一般・全身障害および投与部位の状態」に含まれる歩行障害であった（付録 2.7.4.7.2.1、表 2.7.4.7.2.1-21 及び 2.7.4.7.2.1-22）。

2.7.4.2.3.7.4　結論

全体として、末梢性ニューロパチーの発現件数は少なく、いずれの投与群においても同程度であった。いずれの事象も軽度又は中等度で、因果関係が報告された事象に関しては、治験薬との因果関係は「なし」とされた。ノボラピッド®注と比較して、faster aspart による末梢性ニューロパチーのリスクの増加は示唆されず、このことは海外併合データに基づく結果と一致した（2.7.4.2.3.11 項）。

2.7.4.2.3.8　高血糖（4101 試験のみ）

食後高血糖は HbA1c 値に大きな影響を及ぼすため、HbA1c の目標値を達成する上で、食後高血糖のコントロールは重要である[12]。

2.7.4.2.3.8.1　評価方法

体調が優れず、「血糖自己測定値が 250 mg/dL（14.0 mmol/L）超かつ血中ケトン体が 1.5 mmol/L 超」又は「血糖自己測定値が 250 mg/dL（14.0 mmol/L）超かつ尿ケトン体が『中等度』超」の高血糖が認められた場合、被験者はそれを被験者日誌に記録し、可能な限り速やかに治験実施医療機関のスタッフに連絡して投与量調節の指示を受けることとした。

2.7.4.2.3.8.2　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

12 例（1.5%）に 12 件の高血糖が報告され、内訳は faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 4 例（1.5%）4 件、1 例（0.4%）1 件及び 7 例（2.7%）7 件であった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.106〕。高血糖を発現した被験者数及び発現件数は少なく、発現パターンに投与群間で違いは認められなかった。

2.7.4.2.3.9　稀な事象

2.7.4.2.3.9.1　評価方法

有害事象のなかにはごく稀にしか発現しないものの、事象の性質上重篤なものや、医薬品との関連性が知られているものがある。このため、4131 及び 4101 試験において、4131 及び 4101 試験において、付録 2.7.4.7.8 に示す一覧の基本語を用いた基本語検索に基づき、稀な有害事象を特定した。

2.7.4.2.3.9.2　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

本試験では 15 例 16 件の稀な事象が報告され、内訳は faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 5 例（1.5%）5 件、6 例（1.8%）6 件及び 4 例（1.2%）5 件であった（表 2.7.4.2-26）。治験責任医師により 16 件のうち 2 件が中等度、残りは軽度と判定された。因果関係が報告されていない事例が数例あったものの、報告のあった事象についてはいずれも治験薬との因果関係は「なし」と判定された。稀な事象のうち、重篤と判定されたものはなく〔付録 2.7.4.7.2.1、表 2.7.4.7.2.1-32 及び Trial 4131（M 5.3.5.1）Memo Appendix 16.2.7、Listing 16.2.7.1 及び Appendix 16.2.7、Listing 16.2.7.2〕、治験薬の投与中止や試験の中止に至ったものもなかった〔Trial 4131（M 5.3.5.1）Appendix 16.2.1、Table 16.2.1.3 及び 16.2.1.5〕。

表 2.7.4.2-26　器官別大分類及び基本語別の稀な事象に関連する有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	342				341				342			
Total exposure (yrs)	171.3				170.2				170.2			
Total events	5	(1.5)	5	2.9	6	(1.8)	6	3.5	4	(1.2)	5	2.9
心臓障害	1	(0.3)	1	0.6	3	(0.9)	3	1.8	1	(0.3)	1	0.6
動悸	0				1	(0.3)	1	0.6	1	(0.3)	1	0.6
期外収縮	0				1	(0.3)	1	0.6	0			
洞性徐脈	1	(0.3)	1	0.6	0				0			
心室性期外収縮	0				1	(0.3)	1	0.6	0			
肝胆道系障害	0				1	(0.3)	1	0.6	1	(0.3)	1	0.6
脂肪肝	0				1	(0.3)	1	0.6	1	(0.3)	1	0.6
臨床検査	0				0				1	(0.3)	2	1.2
心電図変化	0				0				1	(0.3)	1	0.6
心拍数増加	0				0				1	(0.3)	1	0.6
神経系障害	1	(0.3)	1	0.6	0				1	(0.3)	1	0.6
失神	1	(0.3)	1	0.6	0				1	(0.3)	1	0.6
腎および尿路障害	1	(0.3)	1	0.6	1	(0.3)	1	0.6	0			
急性腎障害	1	(0.3)	1	0.6	0				0			
腎不全	0				1	(0.3)	1	0.6	0			
血液およびリンパ系障害	1	(0.3)	1	0.6	0				0			
白血球減少症	1	(0.3)	1	0.6	0				0			
先天性、家族性および遺伝性障害	1	(0.3)	1	0.6	0				0			
副脾	1	(0.3)	1	0.6	0				0			
眼障害	0				1	(0.3)	1	0.6	0			
眼瞼浮腫	0				1	(0.3)	1	0.6	0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years.
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.2.3.9.3　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

本試験では 11 例 14 件の稀な事象が報告され、内訳は faster aspart（食前投与）群で 3 例（1.1%）3 件、faster aspart（食後投与）群で 5 例（1.9%）6 件、ノボラピッド®注群で 3 例（1.2%）5 件であった（表 2.7.4.2-27）。治験責任医師により 14 件のうち 3 件が中等度、残りの 11 件が軽度と判定された。

因果関係は 12 件において報告され、このうち 11 件で治験薬との因果関係は「なし」と判定された。Faster aspart（食後投与）群の肝炎（軽度）1 件が、治験薬との因果関係が「可能性あり」と判定された。稀な事象のうち、重篤と判定されたものは、ネフローゼ症候群 1 件及び動悸 1 件〔いずれも faster aspart（食後投与）群〕であった〔付録 2.7.4.7.2.1、表 2.7.4.7.2.1-34 及び Trial 4101（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.1 及び Lising 16.2.7.2〕、治験薬の投与中止や試験の中止に至ったものもなかった〔Trial 4101（M 5.3.5.1）Appendix 16.2.1、Table 16.2.1.3 及び 16.2.1.5〕。

表 2.7.4.2-27　器官別大分類及び基本語別の稀な事象に関連する有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	261				258				258			
Total exposure (yrs)	128.4				127.7				127.7			
Total events	3	(1.1)	3	2.3	5	(1.9)	6	4.7	3	(1.2)	5	3.9
神経系障害	2	(0.8)	2	1.6	0				1	(0.4)	2	1.6
失神	2	(0.8)	2	1.6	0				1	(0.4)	2	1.6
心臓障害	0				2	(0.8)	2	1.6	0			
動悸	0				2	(0.8)	2	1.6	0			
肝胆道系障害	0				1	(0.4)	1	0.8	1	(0.4)	1	0.8
肝炎	0				1	(0.4)	1	0.8	0			
高ビリルビン血症	0				0				1	(0.4)	1	0.8
腎および尿路障害	0				1	(0.4)	1	0.8	1	(0.4)	1	0.8
ネフローゼ症候群	0				1	(0.4)	1	0.8	1	(0.4)	1	0.8
先天性、家族性および遺伝性障害	0				1	(0.4)	1	0.8	0			
皮様嚢腫	0				1	(0.4)	1	0.8	0			
胃腸障害	0				1	(0.4)	1	0.8	0			
口唇腫脹	0				1	(0.4)	1	0.8	0			
臨床検査	1	(0.4)	1	0.8	0				0			
白血球数減少	1	(0.4)	1	0.8	0				0			
皮膚および皮下組織障害	0				0				1	(0.4)	1	0.8
顔面腫脹	0				0				1	(0.4)	1	0.8

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years,
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.2.3.9.4　結論

予想されたとおり、稀な事象の検索で特定された有害事象（基本語）の大部分は、投与群あたり 1 例ずつの報告であった。いずれの事象も軽度又は中等度であり、1 件のみが治験薬との因果関係が「可能性あり」と判定された。海外併合データに基づく結果と一致して（2.7.4.2.3.11 項、付録 2.7.4.7.2.2、表 2.7.4.7.2.2-13 及び 2.7.4.7.2.2-14）、faster aspart とノボラピッド®注との間に臨床的に意味のある違いは認められなかった。

2.7.4.2.3.10　治験薬による病原体感染の疑い

2.7.4.2.3.10.1 評価方法

万一、不完全な滅菌環境下で製造された治験薬によって感染症が伝播することがあれば、当該治験薬の使用上の安全性に問題が生じる。ただし治験薬による病原体感染と、治験薬が患者の免疫系を変化させ感染症にかかりやすくさせる潜在的なリスクを有することを示唆する事象とは、区別すべきである。

4131 及び 4101 試験において、付録 2.7.4.7.8 に示す一覧の基本語を用いた基本語検索に基づき、治験薬による病原体感染の疑いに関連する有害事象を特定した。

2.7.4.2.3.10.2 4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

本試験において、治験薬による病原体感染の疑いに関連する有害事象は報告されなかった（付録 2.7.4.7.2.1、表 2.7.4.7.2.1-37）。

2.7.4.2.3.10.3 4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

本試験において、治験薬による病原体感染の疑いに関連する有害事象は報告されなかった（付録 2.7.4.7.2.1、表 2.7.4.7.2.1-39）。

2.7.4.2.3.10.4 結論

4131 及び 4101 試験において、治験薬による病原体感染の疑いに関連する有害事象は報告されず、このことは海外併合データに基づく結果と一致した（表 2.7.4.2-28）。

2.7.4.2.3.11　海外併合データにおける特に注目すべき安全性領域

海外併合データのより大規模データセットにおける、特に注目すべき安全性領域の要約を表 2.7.4.2-28 に示す。海外併合データを用いた評価方法は付録 2.7.4.7.7 に提示する。

特に注目すべき安全性領域における有害事象の件数及び単位時間あたりの発現件数は、faster aspart 群と対照群で同程度であった。投与部位反応（注射部位反応／注入部位反応）に関連する有害事象の単位時間あたりの発現件数は少なかったものの、対照群と比較して faster aspart 群で多かった。投与部位反応に関連する有害事象で重篤と判定されたものはなく、いずれも軽度又は中等度であった（付録 2.7.4.7.2.3、表 2.7.4.7.2.3-7）。

海外併合データの結果から、特に注目すべき安全性領域のいずれについても、対照薬と比較して、faster aspart によるリスクの増加は示唆されなかった。

表 2.7.4.2-28　治験薬投与下で発現した特に注目すべき有害事象の概観－安全性解析対象集団－海外併合データ

	Faster aspart			**Comparator**		
	N	**%**	**E** **R**	**N**	**%**	**E** **R**
Number of subjects	1244			853		
Total exposure (PYE)	741.21			566.26		
Events:						
Positively adjudicated cardiovascular events	9	(0.7)	12 1.5	9	(1.0)	9 1.3
Medication errors	59	(4.2)	72 9.3	31	(4.1)	39 7.2
Immunogenicity-related events (allergic reactions)	39	(2.9)	46 6.1	30	(3.8)	34 6.2
Injection site reactions[a]	21	(1.6)	29 3.8	8	(1.0)	12 2.0
Lipodystrophy	6	(0.4)	6 0.8	3	(0.4)	3 0.6
Peripheral oedema	10	(0.8)	10 1.4	6	(0.6)	6 1.0
Diabetic retinopathy	39	(2.9)	41 5.5	22	(2.7)	24 4.3
Refraction disorders	2	(0.1)	4 0.5	7	(0.9)	11 2.0
Peripheral neuropathy	21	(1.6)	24 3.3	18	(2.2)	19 3.3
Rare events	19	(1.5)	22 3.0	20	(2.3)	23 3.8
Suspected transmission of an infectious agent via trial product	0			0		

Abbreviations: N: Number of subjects, PYE: patient years of exposure, %: Percentage of subjects, E: Number of events, R: Event rate per 100 patient years of exposure from treatment start to follow up. Cochran-Mantel-Haenszel adjusted, Treatment-emergent: AE that has an onset date on or after the first day of exposure to randomised treatment, and no later than 7 days after the last day of randomised treatment. The ‘overseas diabetes pool' consists of trials 3852(52w), 3853, 4049 and 3931. Faster aspart: a pool of the mealtime and postmeal faster aspart groups.
[a] Injection site reactions are based on a pool of trials 3852 (52 weeks), 3853 and 4049 (total exposure: 738.30 PYE (faster aspart) and 564.85 PYE (NovoRapid®))

2.7.4.2.4　低血糖

2.7.4.2.4.1　評価方法

低血糖は、糖尿病治療の新薬のベネフィット／リスクプロファイルを評価する上で、検討すべき重要なエンドポイントの一つであるため、詳細な評価を実施した。低血糖は、糖尿病の治療において良好な血糖コントロールを得る上で最大の障害の一つであり[13,14]、血糖コントロールの改善は、低血糖発現リスクの潜在的な増加を常に考慮しつつ検討すべきものである。

治験薬投与開始日から投与終了 1 日後までに発現した低血糖を、治験薬投与下で発現した低血糖と定義した。

2.7.4.2.4 項では、4131 及び 4101 試験における低血糖の評価について提示する。3918 試験における低血糖の評価は、Module 2.7.6.1 及び Module 5.3.4.2 を参照。インスリンポンプ使用時の低血糖に関する評価は、2.7.4.5.12.2.12 項を参照。

2.7.4.2.4.1.1　低血糖の報告

低血糖は専用の「hypoglycaemic episode form」に記録し、基本的に有害事象としては報告されないこととした。しかしながら、重篤な有害事象の基準に合致する低血糖（定義は 2.7.4.2.2.1.1 項）については重篤な有害事象としても報告するため、「hypoglycaemic episode form」、「AE form」及び「safety information form」とも記載することとした（図 2.7.4.2-1）。

低血糖の疑われる場合には常に血糖値を測定することとした。被験者には、低血糖症状が発現している間の血糖値を被験者日誌に記録するよう指導した。

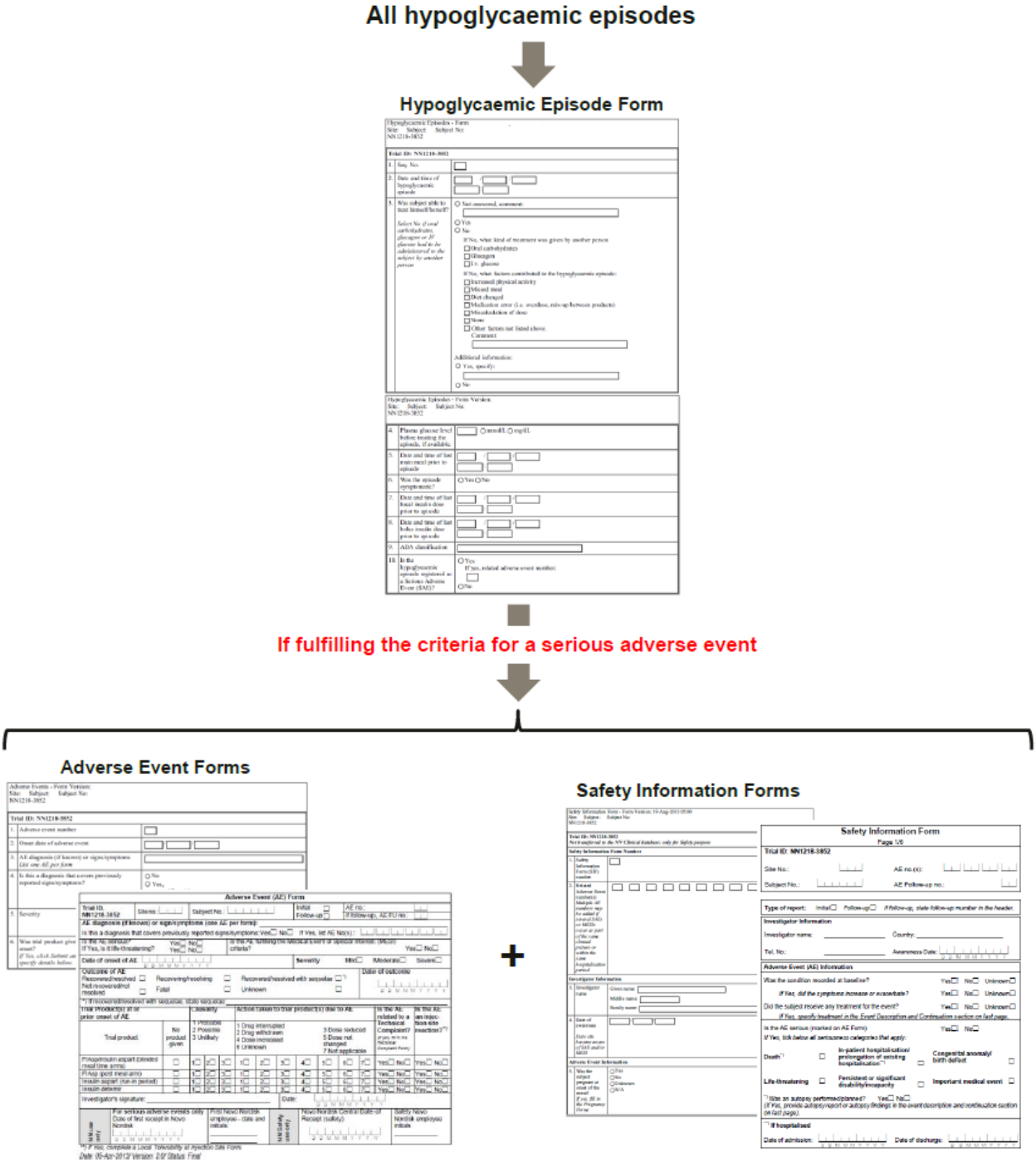


図 2.7.4.2-1　　低血糖の報告

2.7.4.2.4.1.2　低血糖の分類

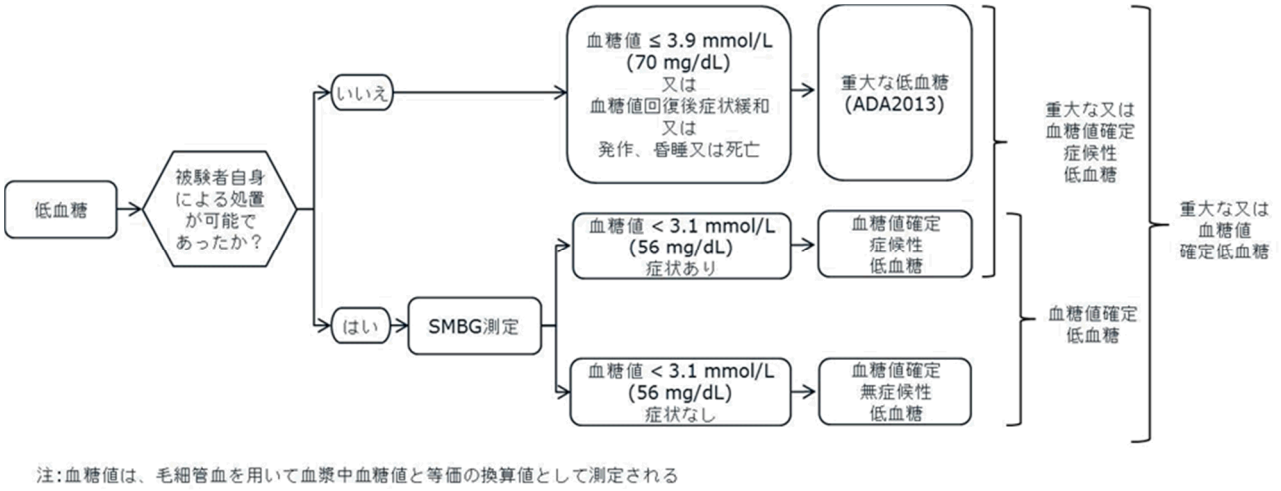
4131 試験（1 型糖尿病成人患者）

低血糖は図 2.7.4.2-2 及び図 2.7.4.2-3 に示すとおり、ノボ ノルディスク社及び米国糖尿病学会（ADA）の定義に従って分類した。ノボ ノルディスク社による「重大な低血糖」の定義は、ADA による定義と同一であった。追加の分類として、重大でない低血糖でかつ血糖値が 56～70 mg/dL の事象、血糖値確定性でない事象、ならびにデータの不足により分類不可の場合の事象は「ノボ ノルディスク社分類不能（Novo Nordisk unclassifiable）」として扱った。被験者自身による処置は可能でなかったが重大な低血糖に定義されない事象は、「自己治療不可 – ADA 分類不能（Not able to self-treat – unclassifiable）」として扱った。さらに、被験者自身による処置が可能であり、かつ血糖値が 70 mg/dL 超又は不明な場合、あるいは症状に関する情報のない事象は「ADA 分類不能（ADA unclassifiable）」として扱った。

ノボ ノルディスク社は低血糖の定義に際し、臨床現場における血糖値の cut-off 値として、ADA の分類で用いられる「70 mg/dL 以下」よりも「56 mg/dL 未満」の使用を推奨している。これは、56 mg/dL の cut-off 値は低血糖の特定及び定義における特異度が非常に高い[15]ためである。「70 mg/dL 以下」の cut-off 値は、コントロールの良好な糖尿病患者にとっては、低血糖症状が発現する値よりも高い血糖値の範囲が含まれる[16]。このような高い cut-off 値と比較すると「56 mg/dL 未満」は、生理的カウンターレギュレーションが作動し始める血糖値の範囲と、患者が症状を報告する血糖値の範囲とのバランスがより考慮された値である。さらに 56 mg/dL 未満の cut-off 値は、複数の検証的試験で事前に規定した食前血糖値の目標値 71～108 mg/dL（3931 試験では 108 mg/dL 未満）を十分に下回っており、これら食前血糖値の目標値にはわずかに届かないものの臨床的重要性の低い事例が、低血糖として頻繁に報告されることを回避できる。

すべての低血糖は、以下の基準に従って分類した：

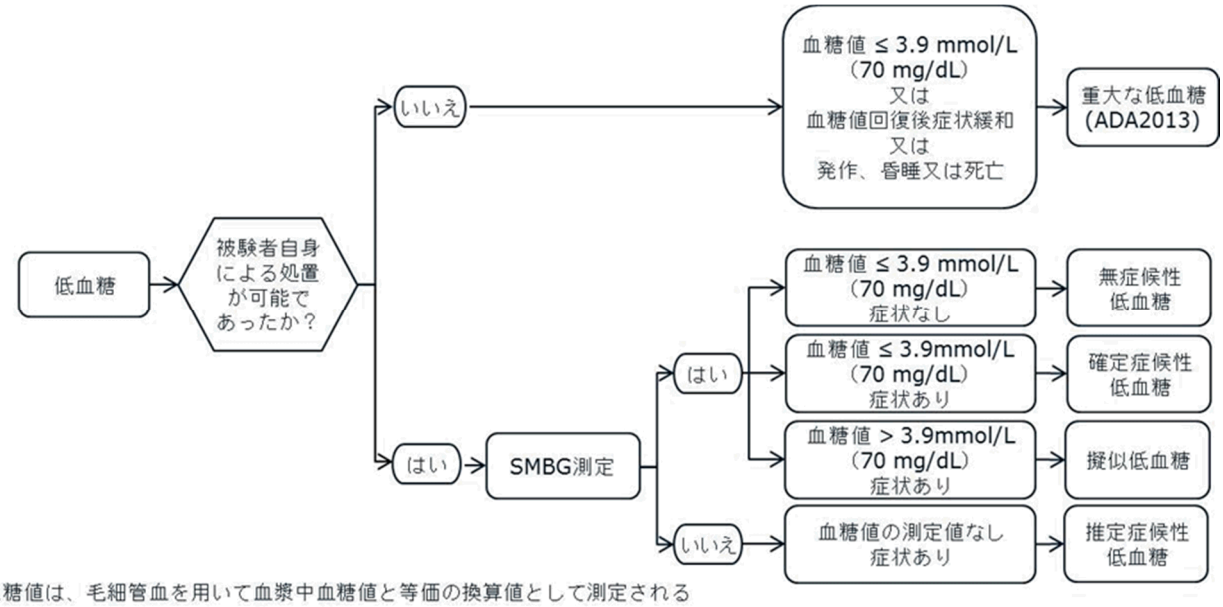
- **日中**低血糖〔06:00 から 00:00 まで（両時刻を含む）〕か、**夜間**低血糖〔00:01 から 05:59 まで（両時刻を含む）〕か：
  - 発現時刻が不明な場合は、日中の事象とみなした
- **食事との関連性**の有無（事象の発現時刻及び食事の日時の情報が得られる場合のみ）：
  - 食事開始後 1 時間、2 時間又は 4 時間以内に発現した事象
  - 食事開始後 1～2 時間、2～3 時間、2～4 時間又は 3～4 時間に発現した事象（ちょうど 2 時間目に発現した事象は 1～2 時間のグループに含める；以降の各時間区分も同様）。



注: 重大でない低血糖でかつ血糖値が 56～70 mg/dL の事象、血糖値確定性でない事象、ならびにデータの不足により分類不可の場合の事象は「ノボ ノルディスク社分類不能」として扱った

略語: SMBG: self-measured blood glucose.

図 2.7.4.2-2　　成人の低血糖におけるノボ ノルディスク社の分類（4131 試験）



注: 被験者自身による処置は可能でなかったが重大な低血糖に定義されない事象は、「自己治療不可 – ADA 分類不能」として扱った。さらに、被験者自身による処置が可能であり、かつ血糖値が 70 mg/dL 超又は不明な場合、あるいは症状に関する情報のない事象は「ADA 分類不能」として扱った

略語: SMBG: self-measured blood glucose.

図 2.7.4.2-3　　成人の低血糖における ADA の分類（4131 試験）

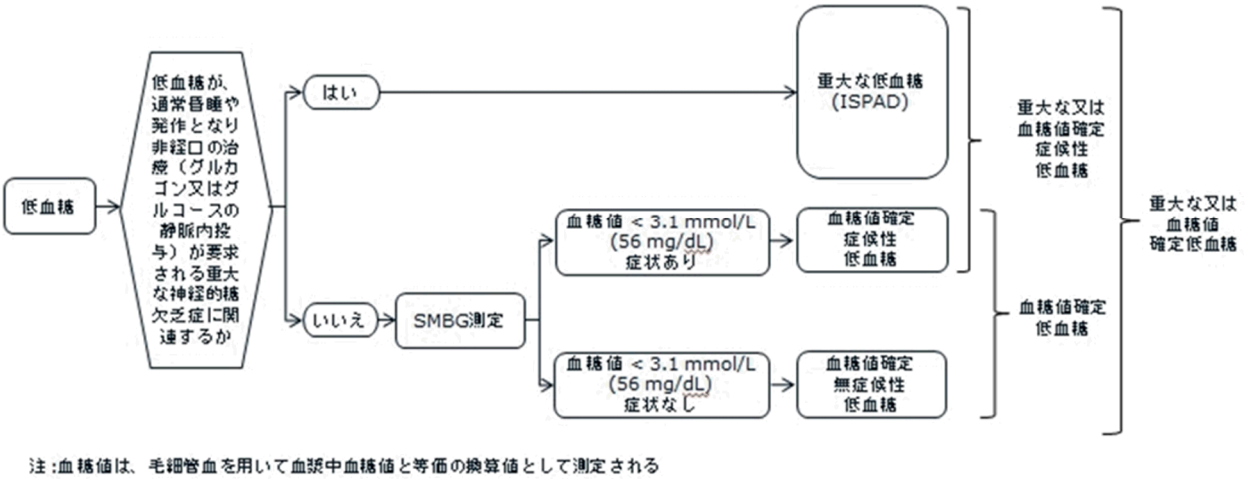
4101 試験（1 型糖尿病の小児被験者及び青年期被験者）

低血糖は国際小児思春期糖尿病学会（ISPAD）による重大な低血糖の定義[17]、ノボ ノルディスク社による小児の低血糖の分類（図 2.7.4.2-4）、及び ADA による低血糖の分類[18]（図 2.7.4.2-5）に従って分類した。

さらに、すべての低血糖を以下の基準に従って分類した：

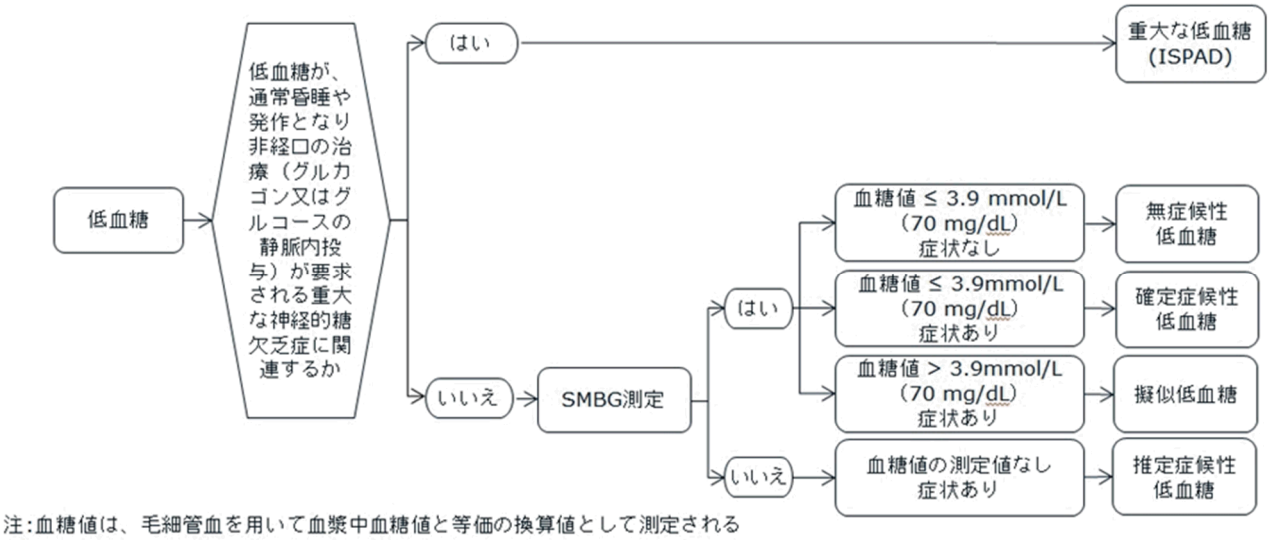
- **日中**低血糖〔07:01 から 22:59 まで（両時刻を含む）〕か、**夜間**低血糖〔23:00 から 07:00 まで（両時刻を含む）〕か
  - 発現時刻が不明な場合は、日中の事象とみなした
- **食事との関連性**の有無（事象の発現時刻及び食事の日時の情報が得られる場合のみ）
  - 食事開始後 1 時間、2 時間又は 4 時間以内に発現した事象
  - 食事開始後 1～2 時間、2～3 時間、2～4 時間又は 3～4 時間に発現した事象（ちょうど 2 時間目に発現した事象は 1～2 時間のグループに含める；以降の各時間区分も同様）。

特記しない限り、すべての低血糖は治験薬投与下で発現した事象である。



略語: ISPAD: International Society for Paediatric and Adolescent Diabetes; SMBG: self-measured blood glucose.

図 2.7.4.2-4　　小児の低血糖におけるノボ ノルディスク社の分類（4101 試験）



注: 推定症候性低血糖は、発現時に低血糖の症状は認められたが、血糖値の測定が実施されず、血糖値は 70 mg/dL 以下であると推察される低血糖
略語: ISPAD: International Society for Paediatric and Adolescent Diabetes; SMBG: self-measured blood glucose.
図 2.7.4.2-5　　小児の低血糖における ADA／ISPAD の分類（4101 試験）

2.7.4.2.4.1.3　低血糖の統計解析

治験薬投与下で発現した重大な又は血糖値確定低血糖の発現件数〔全体、日中、夜間、食事開始後 1 時間、2 時間又は 4 時間以内、1～2 時間（開始時刻は含まず終了時刻を含む：以降の各時間区分も同様）、2～3 時間、3～4 時間、及び 2～4 時間〕は、対数リンク関数を仮定し、低血糖が治験薬投与下として考えられる期間の対数をオフセット項とする負の二項分布回帰モデルを用いて解析した。当該モデルには治療、地域及び Bolus インスリンの投与量調節方法を因子として含めた。データが許す範囲で、重大な低血糖（全体）について別途解析を実施した。

4101 試験では、モデルに層別因子を因子として含めたが、Bolus インスリンの投与量調節方法は因子として含めなかった。

低血糖のすべての統計解析は、最大の解析対象集団における on-treatment 観察期間のデータに基づいて実施した。なお特記しない限り、図表内のデータは安全性解析対象集団に基づくものである。

低血糖の総合的な概観を提示するため、年齢グループ別（小児及び思春期）ならびに各内因性及び外因性民族的要因別の低血糖の結果を 2.7.4.2.4.3 項に提示した。さらに、faster aspart（食前投与）群及び faster aspart（食後投与）群間の比較を、2.7.4.2.4.2.1 項に提示した。

2.7.4.2.4.1.1 項で述べたように、重篤な有害事象の基準に合致した低血糖は「AE form」及び「safety information form」にも記入され、有害事象として報告された。試験中に報告された低血糖の総合的な概観を提示するため、これ以降の各項には、各試験で有害事象として報告された低血糖も併せて提示

する。該当する事象は専用の「hypoglycaemic episode form」により報告された低血糖の一部に含まれている。

2.7.4.2.4.2　検証的試験

2.7.4.2.4.2.1　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

治験薬投与下で発現したすべての低血糖の概要

4131 試験の 26 週の投与期間を通じて発現したすべての低血糖の概要を、ノボ ノルディスク社の分類別及び ADA の分類別に、投与群ごとに表 2.7.4.2-29 に提示する。これらの分類は定義が重複しているため（2.7.4.2.4.1 項）、同一事象が複数の分類に含まれている。

全体として、低血糖を報告した被験者の割合及び単位時間あたりの発現件数は、投与群間で同程度であった。低血糖の分類にも投与群間で顕著な違いはみられず、また 3 つの投与群いずれにおいても重大な低血糖の発現件数は少なかった（表 2.7.4.2-29）。

表 2.7.4.2-29 低血糖（分類別）－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	342				341				342			
Total exposure (yrs)	171.3				170.2				170.2			
Total events	332	(97.1)	15760	9201	324	(95.0)	16579	9740	329	(96.2)	16520	9708
NN classification												
BG confirmed	303	(88.6)	5793	3382	292	(85.6)	6678	3923	299	(87.4)	6773	3980
Severe or BG confirmed symptomatic	282	(82.5)	4006	2339	270	(79.2)	4890	2873	269	(78.7)	4858	2855
Severe or BG confirmed	304	(88.9)	5839	3409	295	(86.5)	6707	3940	302	(88.3)	6820	4008
NN unclassifiable	329	(96.2)	9919	5791	319	(93.5)	9872	5800	326	(95.3)	9698	5699
ADA												
Severe	32	(9.4)	46	27	19	(5.6)	29	17	31	(9.1)	47	28
Documented symptomatic	308	(90.1)	9348	5458	289	(84.8)	10429	6127	288	(84.2)	10083	5925
Asymptomatic	268	(78.4)	6102	3563	259	(76.0)	5820	3419	264	(77.2)	6114	3593
Probable symptomatic	50	(14.6)	121	71	42	(12.3)	211	124	56	(16.4)	184	108
Pseudo-hypoglycaemia	10	(2.9)	15	9	15	(4.4)	52	31	11	(3.2)	24	14
ADA unclassifiable	20	(5.8)	126	74	23	(6.7)	38	22	23	(6.7)	66	39
Not able to selftreat - unclassifiable	2	(0.6)	2	1	0				2	(0.6)	2	1

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <56 mg/dL.
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <56 mg/dL) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

重大な低血糖

すべての重大な低血糖に関する叙述は、Trial 4131（M 5.3.5.1）Section 14.3.3 に示す。

重大な低血糖（ADA の定義）を報告した被験者の割合は、faster aspart（食前投与）群で 9.4%、faster aspart（食後投与）群で 5.6%及びノボラピッド®注群で 9.1%であった（表 2.7.4.2-29 ）。3 つの投与群における単位時間あたりの発現件数は、それぞれ順に 27、17 及び 28 件/100 人・年であり、事象の件数は 46、29 及び 47 件であった（表 2.7.4.2-29）。単位時間あたりの発現件数の比の推定値は、faster aspart（食前投与）群／ノボラピッド®注群で 1.01（95%信頼区間： 0.58; 1.78）、faster aspart（食後投与）群／ノボラピッド®注群で 0.74（95%信頼区間：0.40; 1.35）であり、投与群間に統計的な有意差はみられなかった（表 2.7.4.2-30）。

いずれの投与群においても、重大な低血糖を発現した被験者のうち、その報告件数が 1 件のみの被験者の割合は 70%を上回った〔Trial 4131（M 5.3.5.1）EOT Figure 14.3.1.54 及び Appendix 16.2.7、Listing 16.2.7.11〕。被験者あたりの発現件数で最も多かったのは、faster aspart（食前投与）群の 1 例の被験者により報告された 6 件であった。重大な低血糖は、3 つの投与群それぞれにおいて、26 週の投与期間を通じて一定の頻度で報告された〔Trial 4131（M 5.3.5.1）EOT Figure 14.3.1.55〕。

表 2.7.4.2-30　低血糖－治験薬投与下で発現－統計解析－on-treatment 観察期間－最大の解析対象集団（4131 試験）

	Full analysis set	N	Estimate	95% CI	p-value*
Severe or BG confirmed hypoglycaemic episodes (NN classification)					
LSmeans, events per 100 PYE					
Faster aspart (meal)	342	342	3372.44		
Faster aspart (post)	341	341	3883.87		
NovoRapid (meal)	342	342	4000.48		
Treatment ratio					
Faster aspart (meal) / NovoRapid (meal)			0.84	[0.70; 1.01]	0.065
Faster aspart (post) / NovoRapid (meal)			0.97	[0.81; 1.16]	0.750
Severe hypoglycaemic episodes (ADA classification)					
LSmeans, events per 100 PYE					
Faster aspart (meal)	342	342	19.55		
Faster aspart (post)	341	341	14.23		
NovoRapid (meal)	342	342	19.27		
Treatment ratio					
Faster aspart (meal) / NovoRapid (meal)			1.01	[0.58; 1.78]	0.960
Faster aspart (post) / NovoRapid (meal)			0.74	[0.40; 1.35]	0.325

ADA: American Diabetes Association, BG: Blood glucose, CI: Confidence interval, N: Number of subjects, PYE: Patient years of exposure
*p-values are from the 2-sided test for treatment ratio evaluated at the 5% level.
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period. Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <56 mg/dL. Number of hypoglycaemic episodes is analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model includes treatment, region and bolus adjusting method at randomisation as factors.

重大な又は血糖値確定低血糖

重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、faster aspart の各群とノボラピッド®注群間で統計的な有意差はみられなかった〔投与群間の比の推定値：faster aspart（食前投与）群／ノボラピッド®注群で 0.84（95%信頼区間：0.70; 1.01）、faster aspart（食後投与）群／ノボラピッド®注群で 0.97（95%信頼区間：0.81; 1.16）〕（表 2.7.4.2-30）。

重大な又は血糖値確定低血糖は、3 つの投与群それぞれにおいて、26 週の投与期間を通じて一定の頻度で報告された（図 2.7.4.2-6）。

重大な又は血糖値確定低血糖でみられたように、重大な又は血糖値確定症候性低血糖も、3 つの投与群で同様に、26 週の投与期間を通じて一定の頻度で報告された〔Trial 4131（M 5.3.5.1）EOT Figure 14.3.1.80〕。

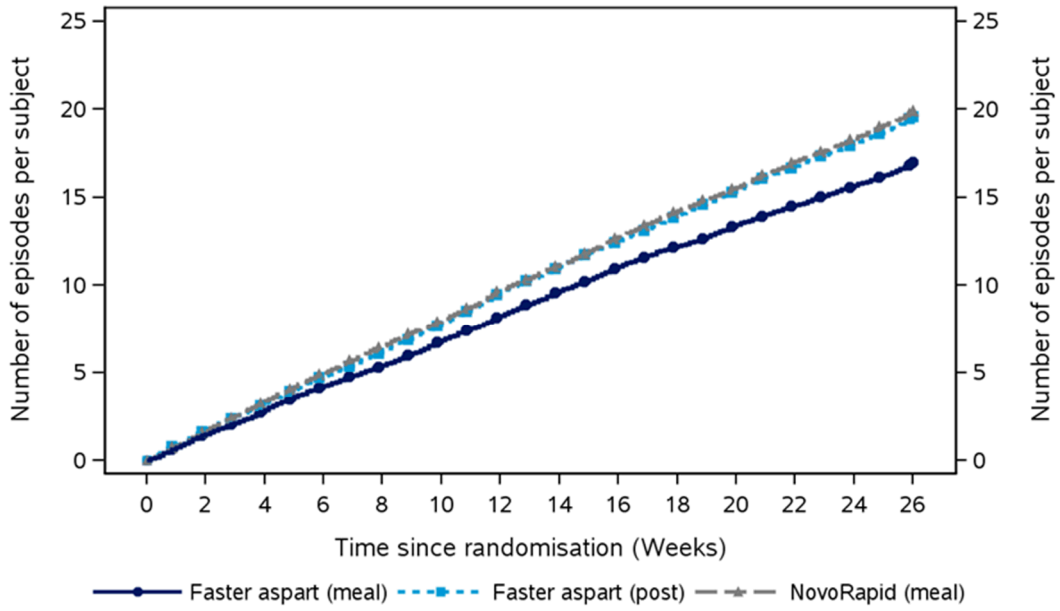


図 2.7.4.2-6　重大な又は血糖値確定低血糖－治験薬投与下で発現－平均累積関数－on-treatment 観察期間－安全性解析対象集団（4131 試験）

重大な又は血糖値確定低血糖は 26 週の投与期間を通じて一定の頻度で報告され、投与群間で違いはみられなかった〔Trial 4131（M 5.3.5.1）EOT Table 14.3.1.44〕。

有害事象として報告された低血糖

重篤な有害事象として報告された低血糖は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 8 例（2.3%）8 件、3 例（0.9%）6 件及び 6 例（1.8%）6 件であった〔Trial 4131（M 5.3.5.1）EOT Table 14.3.1.13〕。ノボラピッド®注群で報告された 1 件を除き、すべて

の事象は治験責任医師により治験薬との因果関係が「可能性あり」又は「あり」と判定された〔Trial 4131（M 5.3.5.1）EOT Table 14.3.1.17〕。

重篤な有害事象として報告された低血糖性意識消失は、faster aspart（食前投与）群で 2 例（0.6%）2 件、faster aspart（食後投与）群で 3 例（0.9%）3 件、及びノボラピッド®注群で 2 例（0.6%）2 件であった。ノボラピッド®注群で報告された 1 件を除き、すべての事象は治験責任医師により治験薬との因果関係が「可能性あり」又は「あり」と判定された。

低血糖（各投与群で 6 件）及び低血糖性意識消失〔faster aspart（食前投与）群で 2 件、faster aspart（食後投与）群で 3 件及びノボラピッド®注群で 2 件〕は、本試験で報告された重度の有害事象の中で、最も高頻度の事象であった。さらに、いずれも重度の有害事象として、3 件の低血糖性痙攣〔faster aspart（食前投与）群 2 例 2 件、faster aspart（食後投与）群 1 件〕、1 件の無自覚性低血糖〔faster aspart（食後投与）群〕、及び 1 件の低血糖昏睡（ノボラピッド®注群）が報告された〔Trial 4131（M 5.3.5.1）EOT Table 14.3.1.19〕。これらのうち、低血糖 1 件、低血糖昏睡 1 件及び低血糖性意識消失 1 件（いずれもノボラピッド®注群で報告）を除いたすべての事象は、治験責任医師により治験薬との因果関係が「可能性あり」又は「あり」と判定された〔Trial 4131（M 5.3.5.1）EOT Table 14.3.1.20〕。

食事に関連した低血糖

重大な低血糖、ならびに重大な又は血糖値確定低血糖につき、食事開始後の経過時間との関連性を評価した。投与群ごと及び低血糖の分類別の要約を表 2.7.4.2-31 に、重大な又は血糖値確定低血糖の単位時間あたりの発現件数に関する投与群間の違いを図 2.7.4.2-7 に提示する。

表 2.7.4.2-31　食事に関連した低血糖－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	342				341				342			
Total exposure (yrs)	171.3				170.2				170.2			
Severe or BG confirmed												
Total	304	(88.9)	5839	3409	295	(86.5)	6707	3940	302	(88.3)	6820	4008
Within 1 hour after meal	84	(24.6)	255	149	88	(25.8)	265	156	88	(25.7)	217	128
Within 2 hours after meal	143	(41.8)	555	324	153	(44.9)	708	416	147	(43.0)	624	367
Within 4 hours after meal	210	(61.4)	1555	908	220	(64.5)	2137	1256	215	(62.9)	1914	1125
Between 1-2 hours after meal	111	(32.5)	300	175	110	(32.3)	443	260	111	(32.5)	407	239
Between 2-3 hours after meal	135	(39.5)	512	299	160	(46.9)	745	438	156	(45.6)	609	358
Between 2-4 hours after meal	176	(51.5)	1000	584	194	(56.9)	1429	840	189	(55.3)	1290	758
Between 3-4 hours after meal	149	(43.6)	488	285	165	(48.4)	684	402	156	(45.6)	681	400
Severe												
Total	32	(9.4)	46	27	19	(5.6)	29	17	31	(9.1)	47	28
Within 1 hour after meal	3	(0.9)	9	5	2	(0.6)	2	1	3	(0.9)	7	4
Within 2 hours after meal	5	(1.5)	11	6	3	(0.9)	3	2	3	(0.9)	7	4
Within 4 hours after meal	10	(2.9)	16	9	5	(1.5)	5	3	4	(1.2)	8	5
Between 1-2 hours after meal	2	(0.6)	2	1	1	(0.3)	1	1	0			
Between 2-3 hours after meal	2	(0.6)	2	1	1	(0.3)	1	1	0			
Between 2-4 hours after meal	5	(1.5)	5	3	2	(0.6)	2	1	1	(0.3)	1	1
Between 3-4 hours after meal	3	(0.9)	3	2	1	(0.3)	1	1	1	(0.3)	1	1

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period. Episodes with missing time stamps or with missing main meal time are not included. Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <56 mg/dL.

食事開始後 1 時間以内では、重大な又は血糖値確定低血糖の単位時間あたりの発現件数は少なかったものの、ノボラピッド®注群と比較して faster aspart（食前投与）群及び faster aspart（食後投与）群でわずかに多かった。3 つの投与群いずれにおいても、食事開始後 1～2 時間よりも 2～3 時間で低血糖の単位時間あたりの発現件数が多かった。Faster aspart（食前投与）群及び faster aspart（食後投与）群では、食事開始後 2～3 時間と比較して 3～4 時間で低血糖の単位時間あたりの発現件数がわずかに少なく、ノボラピッド®注群ではやや多かった（表 2.7.4.2-31）。

重大な又は血糖値確定低血糖の単位時間あたりの発現件数の違いが最も顕著であったのは、食事開始後 3～4 時間における faster aspart（食前投与）群とノボラピッド®注群の間であり、その違いは統計的に有意であった〔単位時間あたりの発現件数の比の推定値 0.72（95%信頼区間：0.54; 0.96）〕（図 2.7.4.2-7）。食事開始後 1 時間、2 時間及び 4 時間以内、ならびに食事開始後 1～2 時間、2～3 時間及び 2～4 時間の時間間隔における重大な又は血糖値確定低血糖の単位時間あたりの発現件数については、faster aspart（食前投与）群とノボラピッド®注群間に統計的な有意差はみられなかった（図 2.7.4.2-7）。

Faster aspart（食後投与）群とノボラピッド®注群間の比較では、食後 4 時間までのいずれの時間枠においても、重大な又は血糖値確定低血糖の単位時間あたりの発現件数に、統計的な有意差はみられなかった（図 2.7.4.2-7）。

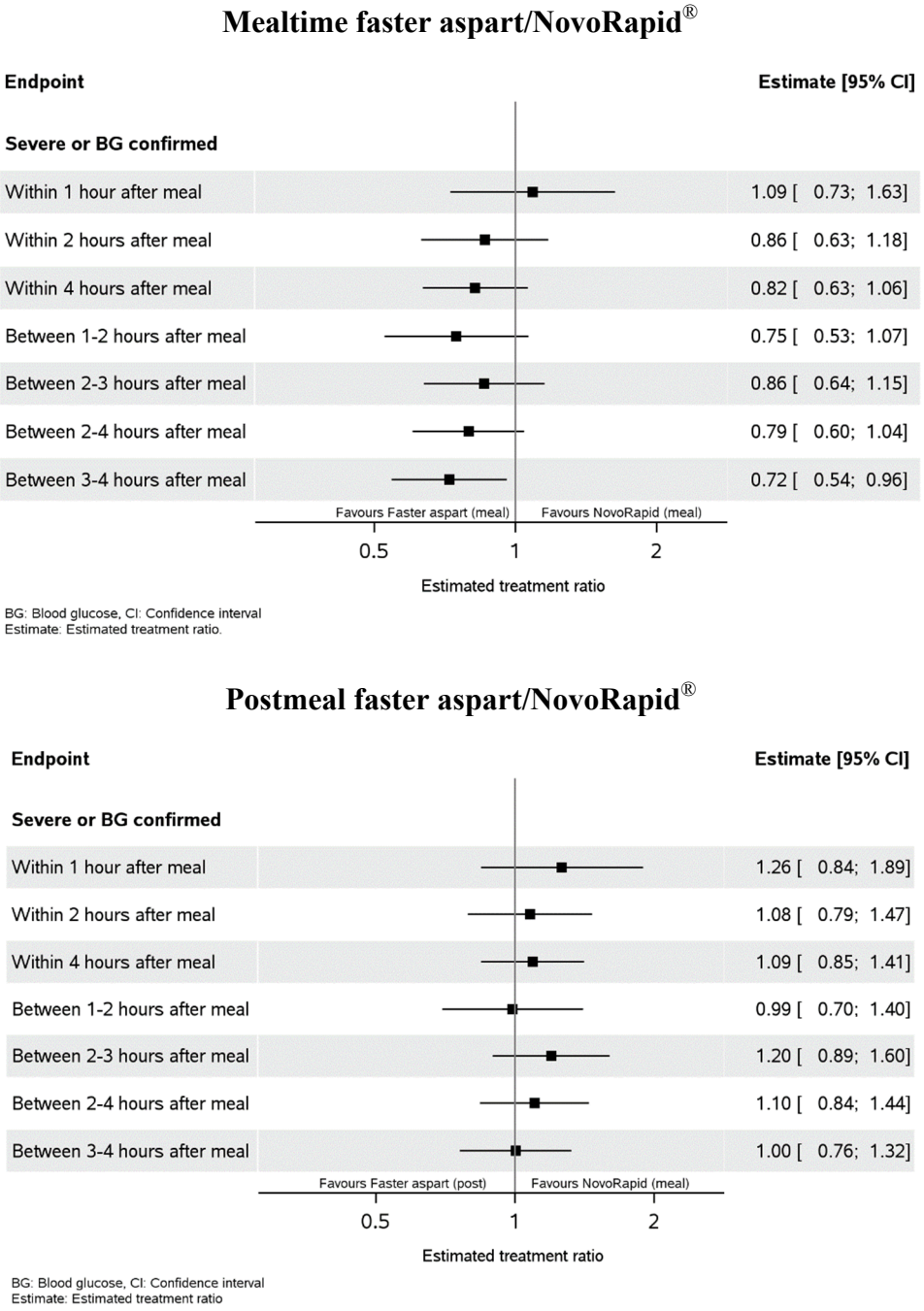


図 2.7.4.2-7　食事に関連した重大な又は血糖値確定低血糖－治験薬投与下で発現－統計解析－フォレストプロット－on-treatment 観察期間－最大の解析対象集団（4131 試験）

食事に関連した重大な低血糖の発現件数は、すべての投与群で非常に少なかった。いずれの投与群においても、重大な低血糖の発現に明らかな違いはみられなかった（表 2.7.4.2-31）。

低血糖の発現時刻の分布 （日中又は夜間、ならびに 24 時間）

3 つの投与群いずれにおいても、重大な又は血糖値確定低血糖の大部分は日中、すなわち 06:00 から 00:00 までに発現した〔Trial 4131（M 5.3.5.1）EOT Table 14.3.1.39 及び 14.3.1.41〕。その他の事象は夜間、すなわち 00:01 から 05:59 までに発現した〔Trial 4131（M 5.3.5.1）EOT Table 14.3.1.42〕。日中及び夜間それぞれの重大な又は血糖値確定低血糖の単位時間あたりの発現件数に関して、faster aspart（食前投与）群とノボラピッド®注群間、ならびに faster aspart（食後投与）群とノボラピッド®注群間に統計的な有意差はみられなかった（表 2.7.4.2-32）。

表 2.7.4.2-32　日中及び夜間における低血糖－治験薬投与下で発現－統計解析－on-treatment 観察期間－最大の解析対象集団（4131 試験）

	Full analysis set	N	Estimate	95% CI	p-value*
Daytime severe or BG confirmed hypoglycaemia					
LSMeans, events per 100 PYE					
Faster aspart (meal)	342	342	3044.14		
Faster aspart (post)	341	341	3536.63		
NovoRapid (meal)	342	342	3619.64		
Treatment ratio					
Faster aspart (meal) / NovoRapid (meal)			0.84	[0.70;1.01]	0.065
Faster aspart (post) / NovoRapid (meal)			0.98	[0.81;1.17]	0.805
Nocturnal severe or BG confirmed hypoglycaemia					
LSMeans, events per 100 PYE					
Faster aspart (meal)	342	342	318.06		
Faster aspart (post)	341	341	339.59		
NovoRapid (meal)	342	342	378.65		
Treatment ratio					
Faster aspart (meal) / NovoRapid (meal)			0.84	[0.65;1.09]	0.188
Faster aspart (post) / NovoRapid (meal)			0.90	[0.69;1.16]	0.410

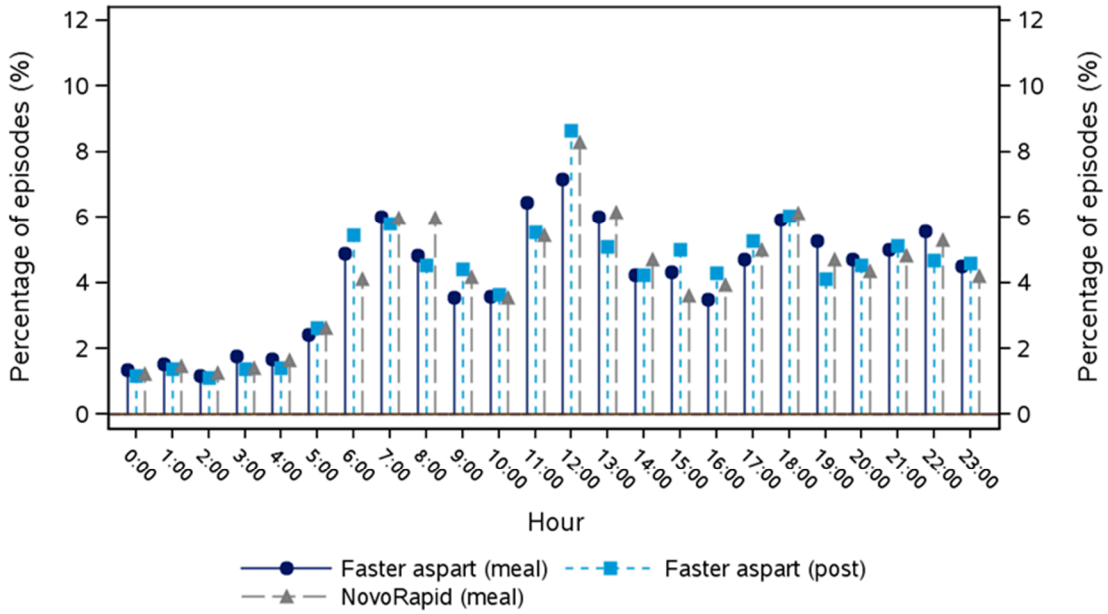
BG: Blood glucose, CI: Confidence interval, N: Number of subjects,PYE: Patient years of exposure.
*p-values are from the 2-sided test for treatment ratio evaluated at the 5% level.
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period. Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <56 mg/dL. Number of hypoglycaemic episodes is analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model includes treatment, region and bolus adjusting method at randomisation as factors.

日中及び夜間の重大な又は血糖値確定低血糖は、3 つの投与群間で同様かつ 26 週の投与期間を通じて一定の頻度で報告された〔Trial 4131（M 5.3.5.1）EOT Figure 14.3.1.65 及び 14.3.1.66〕。

重大な低血糖の発現時刻（24 時間）分布は、Trial 4131（M 5.3.5.1）EOT Figure 14.3.1.56 に提示する。

重大な又は血糖値確定低血糖の発現時刻（24 時間）の分布は、3 つの投与群を通じて同様であった（図 2.7.4.2-8）。いずれの投与群においても、重大な又は血糖値確定低血糖が最も高頻度で報告されたのは、正午付近（12:00～12:59）であった。

重大な又は血糖値確定症候性低血糖の発現時刻（24 時間）の分布は、総括報告書〔Trial 4131（M 5.3.5.1）EOT Figure 14.3.1.87〕に提示する。重大な又は血糖値確定低血糖と同様に、重大な又は血糖値確定症候性低血糖の大部分は日中に発現した。



Hour x:00 [x:00; x:59].
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Episodes with missing time stamps are excluded.
Percentage is based on the total number of episodes in each treatment group.

図 2.7.4.2-8　重大な又は血糖値確定低血糖－治験薬投与下で発現－発現時刻（24 時間）の分布－on-treatment 観察期間－安全性解析対象集団（4131 試験）

他の低血糖分類同様、3 つの投与群いずれにおいても、重大な低血糖の大部分は日中（すなわち 06:00 から 00:00 まで）に発現した〔Trial 4131（M 5.3.5.1）EOT Table 14.3.1.41〕。

Bolus インスリンの投与量調節方法と低血糖

4131 試験において、各被験者の Bolus インスリン投与量の調節は、食事の炭水化物含有量に基づくフレキシブルな Bolus インスリンの用量調節法（カーボカウント）、もしくは事前に規定した Bolus インスリン投与量調節アルゴリズムに基づく方法のいずれかにより実施した。スクリーニング以前にフレキシブルな Bolus インスリンの用量調節法（カーボカウント）を使用していた被験者、ならびに同法

について適切な指導を受けたと治験責任医師が判断した被験者は、試験の投与期間中もカーボカウントによる Bolus インスリン投与量の調節を継続した。その他の被験者は、事前に規定した Bolus インスリン投与量調節アルゴリズムにより Bolus 投与量を調節した。詳細は Trial 4131（M 5.3.5.1）の総括報告書を参照。

3 つの投与群ごとに、各方法を使用した被験者の数を表 2.7.4.2-33 に提示する。

全体として、カーボカウントを使用した被験者と、事前に規定した Bolus インスリン投与量調節アルゴリズムを使用した被験者の間で、重大な又は血糖値確定低血糖の発現に違いはみられなかった（表 2.7.4.2-33）。なお、本試験において、2 つの Bolus インスリン投与量の調節方法に対する被験者の無作為割り付けは実施していない（スクリーニング以前にフレキシブルな Bolus インスリンの用量調節法を使用していた被験者、ならびに同法について適切な指導を受けたと治験責任医師が判断した被験者は、投与期間中も本調節法を継続した。その他の被験者は、Bolus インスリン投与量調節アルゴリズムにより調節した）。

表 2.7.4.2-33 分類別の低血糖－カーボカウント又は Bolus インスリン投与量調節アルゴリズムの被験者－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal)				Faster aspart (post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Carbohydrate counting												
Number of subjects	142				150				136			
Total exposure (yrs)	70.6				75.2				67.8			
Total events	141	(99.3)	6503	9215	145	(96.7)	7028	9345	133	(97.8)	6971	10282
Severe or BG confirmed	131	(92.3)	2394	3392	134	(89.3)	2731	3631	126	(92.6)	2869	4232
Severe (ADA)	11	(7.7)	13	18	4	(2.7)	4	5	7	(5.1)	7	10
Bolus dosing algorithm												
Number of subjects	200				191				206			
Total exposure (yrs)	100.7				95.0				102.4			
Total events	191	(95.5)	9257	9192	179	(93.7)	9551	10053	196	(95.1)	9549	9328
Severe or BG confirmed	173	(86.5)	3445	3421	161	(84.3)	3976	4185	176	(85.4)	3951	3860
Severe (ADA)	21	(10.5)	33	33	15	(7.9)	25	26	24	(11.7)	40	39

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <56 mg/dL.

Faster aspart（食前投与）群と faster aspart（食後投与）群の低血糖

Faster aspart（食前投与）群と faster aspart（食後投与）群の重大な又は血糖値確定低血糖を比較する検討を行った。

重大な又は血糖値確定低血糖について、faster aspart（食前投与）群及び faster aspart（食後投与）群の間に顕著な違いは認められなかった。

重大な又は血糖値確定低血糖を報告した被験者の割合は、faster aspart（食前投与）群（88.9%）及び faster aspart（食後投与）群（86.5%）で同程度であった。重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、faster aspart（食前投与）群で 3409 件/100 人・年、faster aspart（食後投与）群で 3940 件/100 人・年と、faster aspart（食前投与）群が少なかった（表 2.7.4.2-29）。

重大な低血糖の単位時間あたりの発現件数は、faster aspart（食前投与）群で数値的に多かった〔faster aspart（食前投与）群で 27 件/100 人・年、faster aspart（食後投与）群で 17 件/100 人・年〕（表 2.7.4.2-29）。

2.7.4.2.4.2.2　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

治験薬投与下で発現したすべての低血糖の概要

4101 試験の 26 週の投与期間に発現したすべての低血糖の概要を、ノボ ノルディスク社の分類及び ADA／ISPAD の分類に従い、投与群ごとに表 2.7.4.2-34 に提示する。これらの分類は定義が重複しているため、同一事象が複数の分類に含まれている。

全体として、低血糖を報告した被験者の割合及び単位時間あたりの発現件数は、いずれの投与群においても同程度であった。投与群間で低血糖の分類に顕著な違いはみられず、またいずれの投与群においても重大な低血糖の発現件数は少なかった（表 2.7.4.2-34）。

表 2.7.4.2-34 低血糖（分類別）－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	261				258				258			
Total exposure (yrs)	128.4				127.7				127.7			
Total events	251	(96.2)	9701	7556	250	(96.9)	9550	7481	249	(96.5)	8902	6973
BG confirmed	228	(87.4)	3580	2788	227	(88.0)	3586	2809	217	(84.1)	3272	2563
Severe or BG confirmed symptomatic	192	(73.6)	2242	1746	194	(75.2)	2427	1901	185	(71.7)	2194	1719
Severe or BG confirmed	228	(87.4)	3583	2791	227	(88.0)	3594	2815	217	(84.1)	3276	2566
NN unclassifiable	251	(96.2)	6118	4765	244	(94.6)	5956	4666	245	(95.0)	5626	4407
ADA/ISPAD												
Severe (ISPAD 2014)	3	(1.1)	3	2	8	(3.1)	8	6	4	(1.6)	4	3
Documented symptomatic	210	(80.5)	5391	4199	213	(82.6)	5712	4475	207	(80.2)	5170	4050
Asymptomatic	215	(82.4)	4255	3314	214	(82.9)	3781	2962	211	(81.8)	3656	2864
Probable symptomatic	8	(3.1)	12	9	6	(2.3)	10	8	9	(3.5)	24	19
Pseudo-hypoglycaemia	19	(7.3)	35	27	9	(3.5)	37	29	13	(5.0)	47	37
ADA unclassifiable	5	(1.9)	5	4	1	(0.4)	2	2	1	(0.4)	1	1

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, ISPAD: International Society for Pediatric and Adolescent Diabetes, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years

Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.

Severe or BG confirmed: Severe according to the ISPAD 2014 classification and/or have a recorded PG <56 mg/dL.

NN unclassifiable: Includes non-severe episodes (ISPAD 2014) that are not BG confirmed (PG <56 mg/dL) as well as non-severe episodes (ISPAD 2014) that cannot be classified due to missing data.

重大な低血糖

すべての重大な低血糖に関する叙述は、Trial 4101（M 5.3.5.1）Section 14.3.3 に示す。

全体として、重大な低血糖を報告した被験者の数及び重大な低血糖の発現件数は、3 つの投与群いずれにおいても少なかった〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド® 注群でそれぞれ 3 例 3 件、8 例 8 件及び 4 例 4 件（表 2.7.4.2-34）〕。

単位時間あたりの発現件数の比の推定値は、faster aspart（食前投与）群／ノボラピッド®注群で 0.77（95%信頼区間：0.17; 3.45）、faster aspart（食後投与）群／ノボラピッド®注群で 2.11（95%信頼区間：0.63; 7.02）であり、投与群間で統計的な有意差はみられなかった（表 2.7.4.2-35）。

表 2.7.4.2-35 低血糖－治験薬投与下で発現－統計解析－on-treatment 観察期間－最大の解析対象集団（4101 試験）

	Full analysis set	N	Estimate	95% CI	p-value*
Severe or BG confirmed hypoglycaemic episodes					
LSmeans, events per 100 PYE					
Faster aspart (meal)	260	260	2737.41		
Faster aspart (post)	259	259	2733.36		
NovoRapid (meal)	258	258	2463.85		
Treatment ratio					
Faster aspart (meal) / NovoRapid (meal)			1.11	[0.90; 1.37]	0.329
Faster aspart (post) / NovoRapid (meal)			1.11	[0.90; 1.37]	0.334
Severe hypoglycaemic episodes					
LSmeans, events per 100 PYE					
Faster aspart (meal)	260	260	0.26		
Faster aspart (post)	259	259	0.72		
NovoRapid (meal)	258	258	0.34		
Treatment ratio					
Faster aspart (meal) / NovoRapid (meal)			0.77	[0.17; 3.45]	0.734
Faster aspart (post) / NovoRapid (meal)			2.11	[0.63; 7.02]	0.225

ADA: American Diabetes Association, BG: Blood glucose, CI: Confidence interval, ISPAD: International Society for Pediatric and Adolescent Diabetes, N: Number of subjects, PYE: Patient years of exposure *p-values are from the 2-sided test for treatment ratio evaluated at the 5% level. Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period. Severe or BG confirmed: Severe according to the ISPAD 2014 classification and/or have a recorded PG <56 mg/dL. Number of hypoglycaemic episodes is analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model includes treatment, region and strata (age group) as factors.

重大な又は血糖値確定低血糖

重大な又は血糖値確定低血糖を報告した被験者の割合は、投与期間中、いずれの投与群においても同程度であった〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 87.4、88.0 及び 84.1%〕。同様に、重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、いずれの投与群においても同程度であった〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 2791、2815 及び 2566 件/100 人・年〕（表 2.7.4.2-34）。

重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、faster aspart の各群とノボラピッド®注群間で統計的な有意差はみられなかった〔投与群間の比の推定値：faster aspart（食前投与）群／ノボラピッド®注群で 1.11（95%信頼区間：0.90; 1.37）、faster aspart（食後投与）群／ノボラピッド®注群で 1.11（95%信頼区間：0.90; 1.37）〕〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.68〕。

重大な又は血糖値確定低血糖の単位時時間あたりの発現件数は、26 週の投与期間を通じて変動なく、投与群間でも違いはみられなかった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.64〕。重大な又は血糖値確定低血糖は、3 つの投与群で同様に、26 週の投与期間を通じて一定の頻度で報告された（図 2.7.4.2-9）。

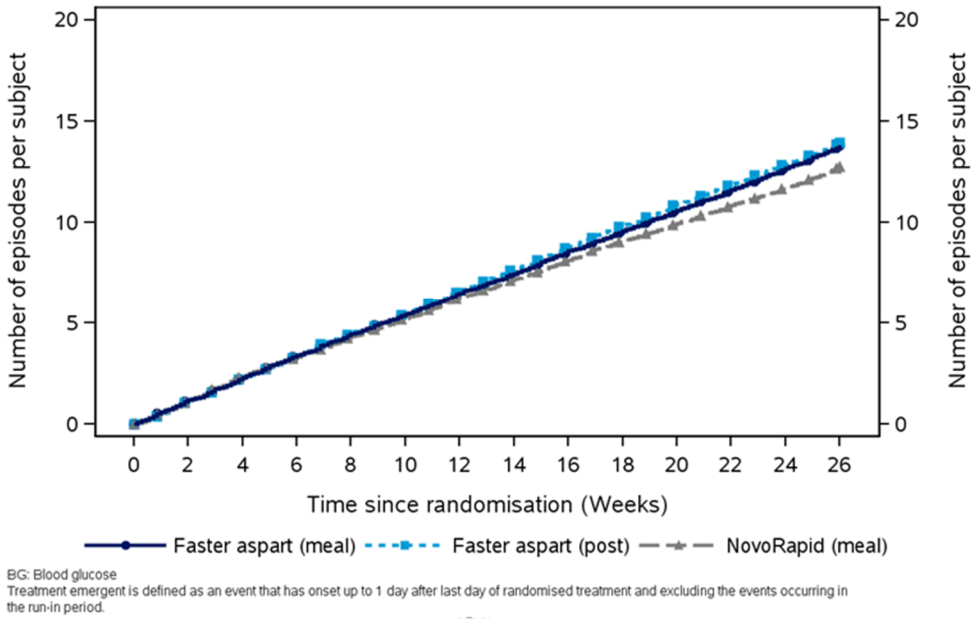


図 2.7.4.2-9　重大な又は血糖値確定低血糖－治験薬投与下で発現－平均累積関数－on-treatment 観察期間－安全性解析対象集団（4101 試験）

重大な又は血糖値確定低血糖の過半数（10453 件中 6863 件）は症候性の事象であった。重大な又は血糖値確定低血糖でみられたように、重大な又は血糖値確定症候性低血糖を報告した被験者の割合は

いずれの投与群においても同程度であり、また重大な又は血糖値確定症候性低血糖の分布は 3 つの投与群とも同様であった。単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 1746、1901 及び 1719 件/100 人・年であった（表 2.7.4.2-34）。

有害事象として報告された低血糖

重篤な有害事象として報告された低血糖は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 1 例（0.4%）1 件、2 例（0.8%）2 件及び 1 例（0.4%）1 件であった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.20〕。Faster aspart（食後投与）群で報告された 2 件を除き、他の 2 件はいずれも治験責任医師により治験薬との因果関係が「可能性あり」又は「あり」と判定された〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.30〕。

Faster aspart（食後投与）群の 2 例（0.8%）で、2 件の低血糖性意識消失が重篤な有害事象として報告された。いずれの事象も、治験責任医師により治験薬との因果関係が「可能性あり」又は「あり」と判定された〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.30〕。

2 件の低血糖が重度の有害事象として報告され、内訳は faster aspart（食前投与）群 1 件、faster aspart（食後投与）群 1 件であった。これらのうち、faster aspart（食前投与）群の 1 件は、治験責任医師により治験薬との因果関係が「あり」と判定された。また 1 件の低血糖性意識消失が重度の有害事象として faster aspart（食後投与）群から報告され、治験責任医師により治験薬との因果関係が「あり」と判定された〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.32 及び Appendix 16.2.7、Listing 16.2.7.4〕。

食事に関連した低血糖

重大な低血糖、ならびに重大な又は血糖値確定低血糖につき、食事開始後の経過時間との関連性を評価した。投与群ごと及び低血糖の分類別の要約を表 2.7.4.2-36 に、重大な又は血糖値確定低血糖の単位時間あたりの発現件数に関する投与群間の違いを図 2.7.4.2-10 に提示する。

表 2.7.4.2-36　食事に関連した低血糖－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal)				Faster aspart (post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	261				258				258			
Severe or BG confirmed												
Total	228	(87.4)	3583	2791	227	(88.0)	3594	2815	217	(84.1)	3276	2566
Within 1 hour after meal	64	(24.5)	119	93	46	(17.8)	66	52	62	(24.0)	105	82
Within 2 hours after meal	161	(61.7)	717	558	136	(52.7)	505	396	147	(57.0)	601	471
Within 4 hours after meal	200	(76.6)	1777	1384	201	(77.9)	1782	1396	191	(74.0)	1668	1307
Between 1-2 hours after meal	151	(57.9)	598	466	124	(48.1)	439	344	136	(52.7)	496	389
Between 2-3 hours after meal	151	(57.9)	666	519	157	(60.9)	742	581	145	(56.2)	601	471
Between 2-4 hours after meal	179	(68.6)	1060	826	190	(73.6)	1277	1000	169	(65.5)	1067	836
Between 3-4 hours after meal	135	(51.7)	394	307	150	(58.1)	535	419	132	(51.2)	466	365
Severe (ISPAD 2014)												
Total	3	(1.1)	3	2	8	(3.1)	8	6	4	(1.6)	4	3
Within 1 hour after meal	0				0				0			
Within 2 hours after meal	2	(0.8)	2	2	1	(0.4)	1	1	1	(0.4)	1	1
Within 4 hours after meal	3	(1.1)	3	2	1	(0.4)	1	1	2	(0.8)	2	2
Between 1-2 hours after meal	2	(0.8)	2	2	1	(0.4)	1	1	1	(0.4)	1	1
Between 2-3 hours after meal	1	(0.4)	1	1	0				0			
Between 2-4 hours after meal	1	(0.4)	1	1	0				1	(0.4)	1	1
Between 3-4 hours after meal	0				0				1	(0.4)	1	1

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, ISPAD: International Society for Pediatric and Adolescent Diabetes, N: Number of subjects, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Episodes with missing time stamps or with missing main meal time are not included.
Severe or BG confirmed: Severe according to the ISPAD 2014 classification and/or have a recorded PG <56 mg/dL.

食事開始後 1 時間以内では、重大な又は血糖値確定低血糖の単位時間あたりの発現件数は 3 つの投与群すべてで少なかったものの、faster aspart（食前投与）群（93 件/100 人・年）及びノボラピッド®注群（82 件/100 人・年）と比較して faster aspart（食後投与）群（52 件/100 人・年）で少なかった。3 つの投与群いずれにおいても、食事開始後 1～2 時間よりも 2～3 時間で低血糖の単位時間あたりの発現件数が多かった。一方、いずれの投与群においても、食事開始後 2～3 時間と比較して 3～4 時間で低血糖の単位時間あたりの発現件数が少なかった（表 2.7.4.2-36）。

Faster aspart（食前投与）群とノボラピッド®注群間の比較では、食事開始後 1 時間、2 時間及び 4 時間以内、ならびに食事開始後 1～2 時間、2～3 時間、2～4 時間及び 3～4 時間のいずれにおいても、重大な又は血糖値確定低血糖の単位時間あたりの発現件数に統計的な有意差はみられず、比の推定値は 1 に近かった（図 2.7.4.2-10）。

Faster aspart（食後投与）群とノボラピッド®注群間の比較では、食事開始後 1 時間以内の重大な又は血糖値確定低血糖の単位時間あたりの発現件数が、faster aspart（食後投与）群で低く、その違いは統計的に有意であった〔単位時間あたりの発現件数の比の推定値 0.64（95%信頼区間：0.42; 0.96）〕。食事開始後 2 時間及び 4 時間以内、ならびに食事開始後 1～2 時間、2～3 時間、2～4 時間及び 3～4 時間については、faster aspart（食後投与）群とノボラピッド®注群間に統計的な有意差はみられなかった（図 2.7.4.2-10）。

食事に関連した重大な低血糖の発現件数は、すべての投与群で非常に少なかった。いずれの投与群においても、重大な低血糖の発現に明らかな違いはみられなかった（表 2.7.4.2-36）。

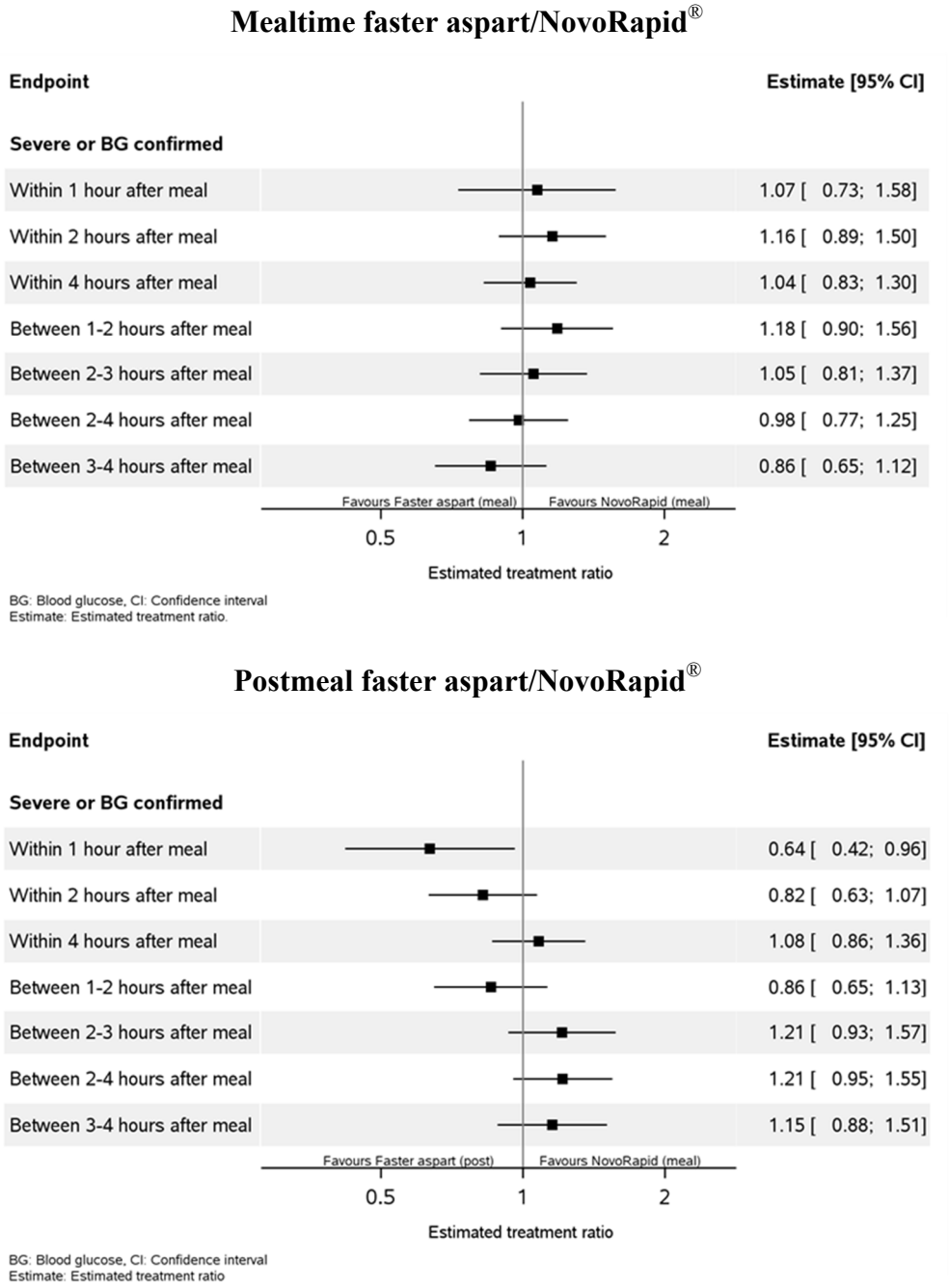


図 2.7.4.2-10　食事に関連した重大な又は血糖値確定低血糖－治験薬投与下で発現－統計解析－フォレストプロット－on-treatment 観察期間－最大の解析対象集団（4101 試験）

低血糖の発現時刻の分布 （日中又は夜間、ならびに 24 時間）

重大な又は血糖値確定低血糖の大部分（10453 件中 9267 件）は日中、すなわち 07:01 から 22:59 までに発現した〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.61 及び 14.3.1.53〕。他の事象は夜間、すなわち

23:00 から 07:00 までの事象であった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.62〕。日中の重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、いずれの投与群においても同程度であり〔faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 2482、2442 及び 2321 件/100 人・年〕、faster aspart（食前投与）群とノボラピッド®注群間、ならびに faster aspart（食後投与）群とノボラピッド®注群間に統計的な有意差はみられなかった（表 2.7.4.2-37）。

重大な又は血糖値確定夜間低血糖を報告した被験者の割合は、faster aspart（食前投与）群（42.9%）及びノボラピッド®注群（40.3%）と比較して、faster aspart（食後投与）群（48.4%）で高かった。さらに、夜間の重大な又は血糖値確定低血糖の単位時間あたりの発現件数も、faster aspart（食前投与）群（308 件/100 人・年）及びノボラピッド®注群（245 件/100 人・年）と比較して faster aspart（食後投与）群（374 件/100 人・年）で高かった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.62〕。夜間の重大な又は血糖値確定低血糖の単位時間あたりの発現件数に関し、faster aspart（食前投与）群とノボラピッド®注群の比較では統計的な有意差はみられなかったが、faster aspart（食後投与）群とノボラピッド®注群の比較では統計的な有意差が認められた（表 2.7.4.2-37）。

表 2.7.4.2-37　日中及び夜間における低血糖－治験薬投与下で発現－統計解析－on-treatment 観察期間－最大の解析対象集団（4101 試験）

	Full analysis set	N	Estimate	95% CI	p-values*
Daytime severe or BG confirmed hypoglycaemia					
LSmeans, events per 100 PYE					
Faster aspart (meal)	260	260	2437.72		
Faster aspart (post)	259	259	2370.43		
NovoRapid (meal)	258	258	2225.14		
Treatment ratio					
Faster aspart (meal) / NovoRapid (meal)			1.10	[0.89;1.35]	0.397
Faster aspart (post) / NovoRapid (meal)			1.07	[0.86;1.32]	0.556
Nocturnal severe or BG confirmed hypoglycaemia					
Faster aspart (meal)	260	260	298.84		
Faster aspart (post)	259	259	348.66		
NovoRapid (meal)	258	258	231.79		
Treatment ratio					
Faster aspart (meal) / NovoRapid (meal)			1.29	[0.93;1.79]	0.130
Faster aspart (post) / NovoRapid (meal)			1.50	[1.09;2.08]	0.014

ADA: American Diabetes Association, BG: Blood glucose, CI: Confidence interval, ISPAD: International Society for Pediatric and Adolescent Diabetes, N: Number of subjects, PG: Plasma glucose, PYE: Patient years of exposure
*p-values are from the 2-sided test for treatment ratio evaluated at the 5% level.
Daytime period: The period between 07:01 and 22:59 (both included). Episodes with missing time stamps are considered as daytime episodes. Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period. Severe or BG confirmed: Severe according to the ISPAD 2014 classification and/or have a recorded PG <56 mg/dL. Number of hypoglycaemic episodes is analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model includes treatment, region and strata (age group) as factors.

重大な又は血糖値確定低血糖の発現時刻（24 時間）の分布は、3 つの投与群とも同様であった（図 2.7.4.2-11）。いずれの投与群においても、重大な又は血糖値確定低血糖が最も高頻度で報告されたのは、正午付近（12:00～12:59）であった。

重大な又は血糖値確定症候性低血糖の発現時刻（24 時間）の分布は、総括報告書〔Trial 4101（M 5.3.5.2）EOT Figure 14.3.1.104〕に提示する。重大な又は血糖値確定低血糖と同様に、重大な又は血糖値確定症候性低血糖の大部分は、日中に発現した。

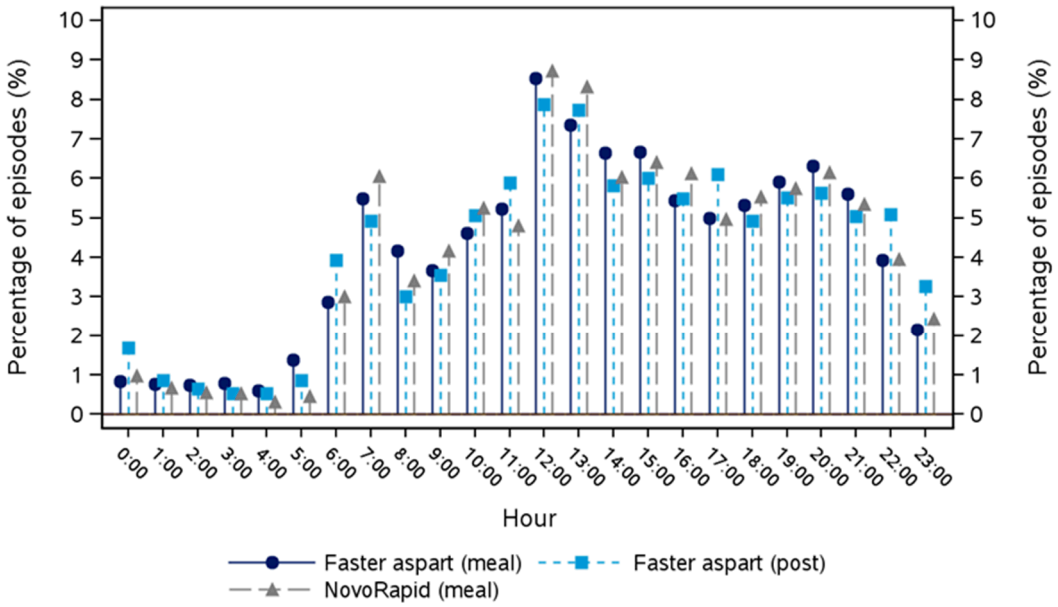


図 2.7.4.2-11　重大な又は血糖値確定低血糖－治験薬投与下で発現－発現時刻（24 時間）の分布－on-treatment 観察期間－安全性解析対象集団（4101 試験）

重大な低血糖の大部分は日中に発現した。faster aspart（食前投与）群では 3 件すべて、faster aspart（食後投与）群では 8 件中 5 件、ノボラピッド®注群では 4 件中 3 件が日中に発現した事象であった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.61 及び 14.3.1.62〕。重大な低血糖の発現時刻（24 時間）の分布は、総括報告書〔Trial 4101（M 5.3.5.1）EOT Figure 14.3.1.73〕に提示する。

Faster aspart（食前投与）群と faster aspart（食後投与）群の低血糖

重大な又は血糖値確定低血糖を報告した被験者の割合は、faster aspart（食前投与）群（87.4%）及び faster aspart（食後投与）群（88.0%）で同程度であった。同様に、重大な又は血糖値確定低血糖の単位時間あたりの発現件数も、faster aspart（食前投与）群（2791 件/100 人・年）及び faster aspart（食後投与）群（2815 件/100 人・年）で同程度であった（表 2.7.4.2-34）。

重大な低血糖を報告した被験者の数及び低血糖の発現件数は、faster aspart（食前投与）群（3 例 3 件）及び faster aspart（食後投与）群（8 例 8 件）とも少なかった。同様に、重大な低血糖の単位時間あたりの発現件数も 2 つの群で少なかった〔faster aspart（食前投与）群で 2 件/100 人・年、faster aspart（食後投与）群で 6 件/100 人・年であった〕（表 2.7.4.2-34）。

2.7.4.2.4.2.3　結論

4131 及び 4101 試験では、faster aspart（食前投与）群とノボラピッド®注群間、ならびに faster aspart（食後投与）群とノボラピッド®注群間のいずれにおいても、重大な又は血糖値確定低血糖の単位時間あたりの発現件数に統計的な有意差はみられなかった。

全体として、4131 及び 4101 試験における食事開始後の重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、faster aspart（食前投与）群とノボラピッド®注群間、ならびに faster aspart（食後投与）群とノボラピッド®注群間で同程度であった。

4131 及び 4101 試験のいずれにおいても、重大な又は血糖値確定低血糖の大部分は日中に発現した。Faster aspart（食前投与）群とノボラピッド®注群間の比較においては、日中の重大な又は血糖値確定低血糖の単位時間あたりの発現件数に統計的な有意差はみられなかった。4101 試験では、夜間の重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、ノボラピッド®注群と比較して faster aspart（食後投与）群で統計的に有意に高かった。

重大な低血糖の単位時間あたりの発現件数について、faster aspart（食前投与）群とノボラピッド®注群間、ならびに faster aspart（食後投与）群とノボラピッド®注群間に統計的な有意差はみられなかった。なお、重大な低血糖の発現件数はいずれの投与群においても少なかった。

2.7.4.2.4.3　内因性／外因性民族的要因別又は年齢グループ別の低血糖

2.7.4.2.4.3.1　4131 試験における内因性／外因性民族的要因別の重大な又は血糖値確定低血糖

評価方法

重大な又は血糖値確定低血糖の発現に対する、人口統計学的特性（内因性民族的要因）及び環境（外因性民族的要因）による潜在的な影響の探索を、4131 試験で得られた 1 型糖尿病成人患者のデータを用いて実施した。なお内因性及び外因性民族的要因別の検討のうち、重大な又は血糖値確定低血糖に関する検討は faster aspart（食前投与）群と faster aspart（食後投与）群を区別して実施したが、その他全般的な検討については、投与のタイミングによる発現件数への影響が予想されなかったため、faster aspart の両投与群を併合して実施した。

重大な又は血糖値確定低血糖の発現に対する、内因性及び外因性民族的要因による潜在的な影響の検討は、単位時間あたりの発現件数について faster aspart の両投与群とノボラピッド®注群間の違いを評価すること、ならびに各民族的要因に基づく部分集団間での違いを評価することで実施した。

4131 試験（1 型糖尿病成人患者）

検討した要因に基づく部分集団の概観、ならびに部分集団ごとの重大な又は血糖値確定低血糖の単位時間あたりの発現件数のうち、内因性民族的要因に関するものを表 2.7.4.2-38 に提示する。詳細は付録 2.7.4.7.3.1 を参照。外因性民族的要因別（Bolus インスリン投与量の調節方法として、カーボカウン

ト法に従ったか、事前に規定した Bolus インスリン投与量調節アルゴリズムに従ったか）の低血糖に関する検討は、2.7.4.2.4.2.1 項を参照。

全体として、4131 試験では、単位時間あたりの発現件数が、ノボラピッド®注群と比較して faster aspart（食前投与）群で少なく、faster aspart（食後投与）群とノボラピッド®注群で同程度であるという重大な又は血糖値確定低血糖の発現傾向は、ほとんどの部分集団において同様に認められた。ごく一部の部分集団間では重大な又は血糖値確定低血糖の単位時間あたりの発現件数に多少の違いがみられたが、これは多数の比較を実施したこと、ならびに一部の部分集団では該当する被験者の数が比較的少なかったことを考慮すると、予測されたとおりの所見であった（表 2.7.4.2-38）。

表 2.7.4.2-38 重大な又は血糖値確定低血糖－治験薬投与下で発現－内因性民族的要因別－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Age at baseline ≥18-<65 years			
Number of subjects	322	319	323
Total exposure (yrs)	161.4	159.5	160.6
Severe or BG confirmed	285 (88.5) 5510 3413	275 (86.2) 6366 3990	284 (87.9) 6530 4066
Age at baseline >=65 years			
Number of subjects	20	22	19
Total exposure (yrs)	9.8	10.7	9.6
Severe or BG confirmed	19 (95.0) 329 3344	20 (90.9) 341 3195	18 (94.7) 290 3032
Females			
Number of subjects	158	155	163
Total exposure (yrs)	78.7	77.5	80.1
Severe or BG confirmed	146 (92.4) 2822 3584	137 (88.4) 3222 4157	152 (93.3) 3547 4429
Males			
Number of subjects	184	186	179
Total exposure (yrs)	92.5	92.7	90.1
Severe or BG confirmed	158 (85.9) 3017 3260	158 (84.9) 3485 3760	150 (83.8) 3273 3633
BMI at baseline <25 kg/m^2			
Number of subjects	190	185	194
Total exposure (yrs)	95.1	92.7	95.6
Severe or BG confirmed	170 (89.5) 3499 3678	167 (90.3) 3670 3961	176 (90.7) 4284 4480
BMI at baseline ≥25-<30 kg/m^2			
Number of subjects	105	104	99
Total exposure (yrs)	52.7	51.3	50.2
Severe or BG confirmed	94 (89.5) 1584 3004	88 (84.6) 2020 3941	80 (80.8) 1674 3336
BMI at baseline >= 30 kg/m^2			
Number of subjects	47	52	49
Total exposure (yrs)	23.4	26.3	24.4
Severe or BG confirmed	40 (85.1) 756 3229	40 (76.9) 1017 3867	46 (93.9) 862 3538

Continues next page

Severe or BG confirmed hypoglycaemic episodes - treatment emergent – by intrinsic factor - summary - on-treatment - trial 4131 - safety analysis set

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
HbA1c at baseline <8%												
Number of subjects	265				280				276			
Total exposure (yrs)	132.7				139.7				137.1			
Severe or BG confirmed	232	(87.5)	4691	3535	242	(86.4)	5561	3981	245	(88.8)	5707	4163
HbA1c at baseline >=8%												
Number of subjects	77				61				66			
Total exposure (yrs)	38.6				30.5				33.1			
Severe or BG confirmed	72	(93.5)	1148	2975	53	(86.9)	1146	3754	57	(86.4)	1113	3363
Duration of diabetes at baseline <15 yrs												
Number of subjects	177				190				175			
Total exposure (yrs)	88.6				93.9				86.8			
Severe or BG confirmed	156	(88.1)	2705	3053	160	(84.2)	3029	3227	145	(82.9)	3029	3491
Duration of diabetes at baseline ≥15 yrs												
Number of subjects	165				151				167			
Total exposure (yrs)	82.7				76.3				83.4			
Severe or BG confirmed	148	(89.7)	3134	3791	135	(89.4)	3678	4817	157	(94.0)	3791	4546
Hepatic impairment at baseline: no												
Number of subjects	318				320				318			
Total exposure (yrs)	159.0				159.6				158.1			
Severe or BG confirmed	282	(88.7)	5374	3380	282	(88.1)	6507	4078	280	(88.1)	6371	4030
Hepatic impairment at baseline: yes												
Number of subjects	24				21				24			
Total exposure (yrs)	12.3				10.6				12.1			
Severe or BG confirmed	22	(91.7)	465	3786	13	(61.9)	200	1881	22	(91.7)	449	3716
Renal impairment at baseline: normal												
Number of subjects	272				263				277			
Total exposure (yrs)	136.2				131.5				138.1			
Severe or BG confirmed	239	(87.9)	4550	3340	226	(85.9)	5402	4108	242	(87.4)	5536	4008

Continues next page

Severe or BG confirmed hypoglycaemic episodes - treatment emergent – by intrinsic factor - summary - on-treatment - trial 4131 - safety analysis set

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Renal impairment at baseline: mild												
Number of subjects	69				68				58			
Total exposure (yrs)	34.6				34.1				28.5			
Severe or BG confirmed	64	(92.8)	1276	3692	61	(89.7)	1086	3181	54	(93.1)	1150	4035
Renal impairment at baseline: moderate												
Number of subjects	1				10				7			
Total exposure (yrs)	0.5				4.6				3.5			
Severe or BG confirmed	1	(100.0)	13	2581	8	(80.0)	219	4778	6	(85.7)	134	3803
Renal impairment at baseline: severe												
Number of subjects	0				0				0			

%: Percentage of subjects, BG: Blood glucose, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <56 mg/dL.

2.7.4.2.4.3.2　4101 試験における年齢グループ別の重大な又は血糖値確定低血糖

重大な又は血糖値確定低血糖を報告した被験者の割合について、年齢グループ間及び投与群間で顕著な違いはみられなかった。単位時間あたりの発現件数は、いずれの群においても、6 歳以上 12 歳未満及び 12 歳以上 18 歳未満の年齢グループで同程度であった。1 歳以上 6 歳未満の年齢グループでは、重大な又は血糖値確定低血糖の単位時間あたりの発現件数が faster aspart の各群と比較してノボラピッド®注群でわずかに少なかった。なお、1 歳以上 6 歳未満の年齢グループに含まれる被験者数は少なかった（表 2.7.4.2-39）。

表 2.7.4.2-39　年齢グループ別の重大な又は血糖値確定低血糖－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal)			**Faster aspart (post)**			**NovoRapid (meal)**		
	N (%)	**E**	**R**	**N (%)**	**E**	**R**	**N (%)**	**E**	**R**
1 to <6 years									
Number of subjects	16			16			14		
Total exposure (years)	8.0			8.0			7.0		
Severe or BG confirmed[a]	15 (93.8)	243	3031	15 (93.8)	289	3616	12 (85.7)	163	2331
6 to <12 years									
Number of subjects	101			99			101		
Total exposure (years)	50.6			49.4			50.0		
Severe or BG confirmed[a]	88 (87.1)	1540	3042	93 (93.9)	1490	3018	83 (82.2)	1472	2942
12 to <18 years									
Number of subjects	144			143			143		
Total exposure (years)	69.8			70.3			70.6		
Severe or BG confirmed[a]	125 (86.8)	1800	2580	119 (83.2)	1815	2582	122 (85.3)	1641	2323

[a] Severe according to the ISPAD 2014 classification and/or have a recorded plasma glucose <56 mg/dL.
Abbreviations: % = percentage of subjects within age group; BG = blood glucose; E = number of events; N = number of subjects; R: event rate per 100 patient years of exposure within age group

2.7.4.2.4.3.3　結論

4131 試験における内因性及び外因性民族的要因別の重大な又は血糖値確定低血糖の発現、ならびに 4101 試験における年齢グループ別の低血糖の発現について、総じて投与群間に顕著な違いは認められなかった。

2.7.4.2.5　　個別有害事象の叙述

完了した試験の以下の項目に関する叙述は、各試験のデータベースロック時点の安全性データベースに基づいて作成し、試験ごとの総括報告書（Module 5）に提示する。

- 死亡
- その他の重篤な有害事象
- 試験の中止に至った有害事象
- 治験薬投与の中止に至った有害事象
- 妊娠

2.7.4.3 臨床検査値の評価

2.7.4.3.1 臨床検査値の概観

2.7.4.3 項では、4131 及び 4101 試験における臨床検査値の評価について要約する。3918 試験については Module 2.7.6.1 及び総括報告書〔Trial 3918（M 5.3.4.2）〕を参照。

臨床検査値はそれぞれの基準範囲と比較の上、範囲から外れた値には、検査報告書上で臨床検査機関により印が付けられた。基準範囲から外れた値はすべて、臨床的に有意か否か治験責任医師がを評価した。治験責任医師が臨床的に有意な臨床検査値の異常と判断した事象は有害事象として報告することとしたため、2.7.4.2 項に示した有害事象の一部にも含まれている。なお、スクリーニング来院時の臨床的に有意な臨床検査値の異常は、既往歴／併発疾患として記録することとした。

4131 及び 4101 試験では、抗インスリン アスパルト抗体を評価したが、ベースライン、投与後 12 週及び 26 週とも、3 つの投与群間で臨床的に意味のある違いは認められなかった。

血液生化学的検査、血液学的検査及び脂質検査、ならびに尿検査（4131 試験のみ）については、ベースライン及び無作為割り付け後 26 週とも、3 つの投与群間で臨床的に意味のある違いは認められなかった。

2.7.4.3.2 抗インスリン アスパルト抗体

2.7.4.3.2.1 評価方法

薬剤の免疫原性は様々な要因〔例：投与経路、患者の年齢、ヒト白血球抗原（HLA）の種類〕によって影響を受け、抗薬物抗体は薬剤の有効性と安全性の両方に影響を及ぼし得る[19]。免疫原性反応は必ずしも薬剤の中和能と相関するわけではないため、抗体価そのものが臨床的に問題となるかどうかは不明である。しかし薬剤が抗体によって中和されると、曝露量が減少して有効性が低下し、有効性を維持するために増量が必要となる場合がある。このため、抗体が糖尿病治療薬の臨床的な有効性及び安全性に及ぼす影響について検討する必要がある。

両試験において、ベースライン（0 週）、投与期間の概ね中間時点の来院（12 週）及び投与終了来院（26 週）で抗体測定用の採血を実施した。抗体測定への影響を最小限に抑えるため、これらの来院日には、被験者は朝のインスリンを投与せずに来院した。抗体測定法については Module 2.7.1 参照。

どのようなインスリン製剤も、程度の違いはあれ、抗体産生を誘導する [19]。各来院時点の抗インスリン アスパルト抗体陽性の被験者数（抗体発現率）を特定するため、インスリン治療歴のない健康な 50 人の検体を測定した際の 99 パーセンタイルを抗体陽性のカットポイントとし、また基準値の上限として扱った（Module 2.7.1.1.3.2.3）。

各抗体価のカットポイントは以下のとおりである。

- インスリン アスパルト特異抗体：1.9% B/T 超

- ヒトインスリンと交叉反応するインスリン アスパルト抗体（以下、ヒトインスリン交叉抗体）：0.7% B/T 超
- 総インスリン アスパルト抗体：1.9% B/T 超

抗体の評価は、以下に基づいて実施した。

- インスリン アスパルト特異抗体又はヒトインスリン交叉抗体が、ベースラインで陽性であった被験者の数、
- インスリン アスパルト特異抗体又はヒトインスリン交叉抗体が、on-treatment 観察期間中（ベースラインを含む）のいずれかの時点で陽性であった被験者の数、あるいは
- インスリン アスパルト特異抗体又はヒトインスリン交叉抗体が、持続的に陽性であった（ベースラインから on-treatment 観察期間中に 2 回以上陽性と判定されたか、もしくは投与終了時に陽性と判定された場合と定義）被験者の数

また、アレルギー反応、注射部位反応、血糖コントロール（HbA1c）及びインスリン投与量に対する抗体産生の影響についてもさらに探索した。4131 及び 4101 試験の有効性評価項目（HbA1c 及びインスリン投与量）に対する抗体の影響については Module 2.7.3.5.2 を参照のこと。

抗体価〔インスリン アスパルト特異抗体、ヒトインスリン交叉抗体、ならびに両抗体価の合計から求めた総インスリン アスパルト抗体〕は、各検体採取時点における、全体の放射能（T）に対する結合した放射能（B）の割合（% B/T）で示す。

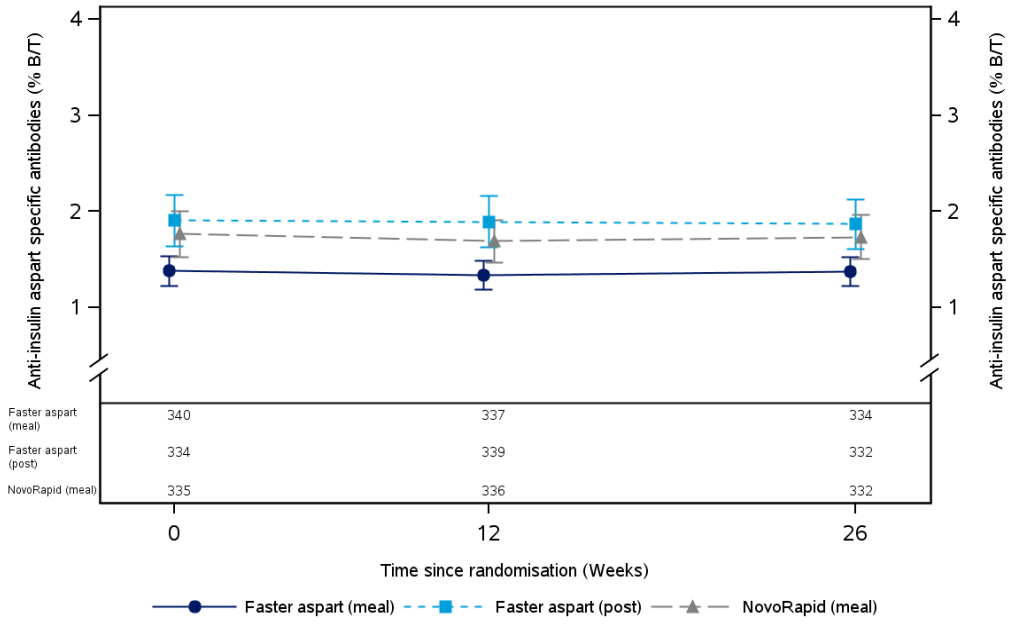
2.7.4.3.2.2　検証的試験

2.7.4.3.2.2.1　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

抗体産生

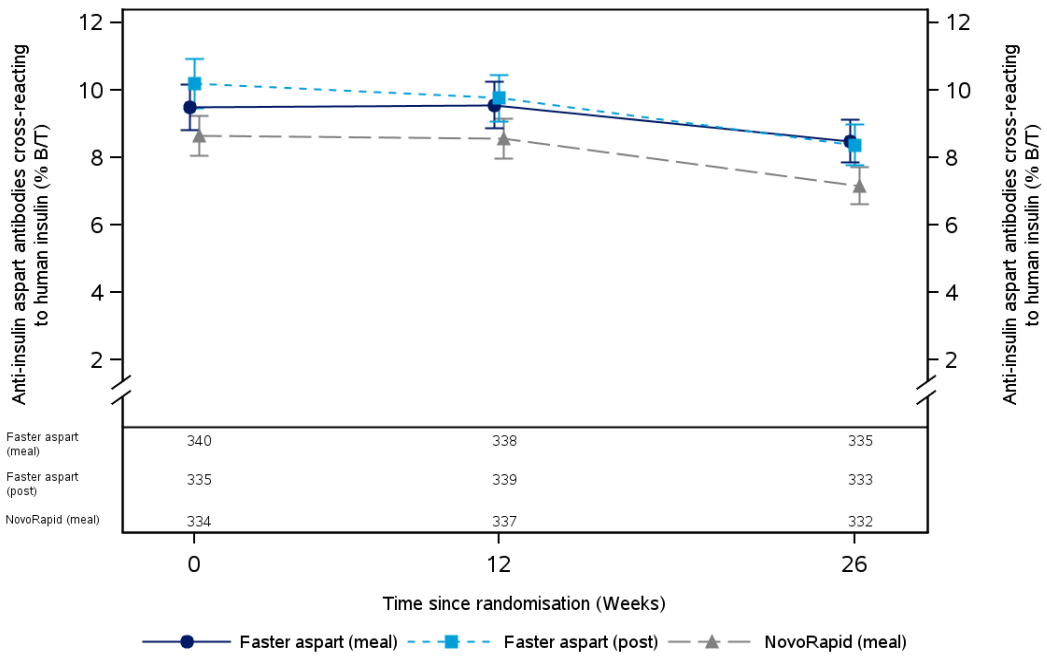
インスリン アスパルト特異抗体、ヒトインスリン交叉抗体、ならびに総インスリン アスパルト抗体（インスリン アスパルト特異抗体＋ヒトインスリン交叉抗体）それぞれの抗体価の平均から、ベースライン、投与後 12 週及び 26 週において、投与群間で臨床的に意味のある違いは認められなかった（図 2.7.4.3-1 及び表 2.7.4.3-1）。

Anti-insulin aspart specific antibodies



Error bars: +/- Standard error (mean)
Observed data.

Anti-insulin aspart antibodies cross-reacting to human insulin



Error bars: +/- Standard error (mean)
Observed data.

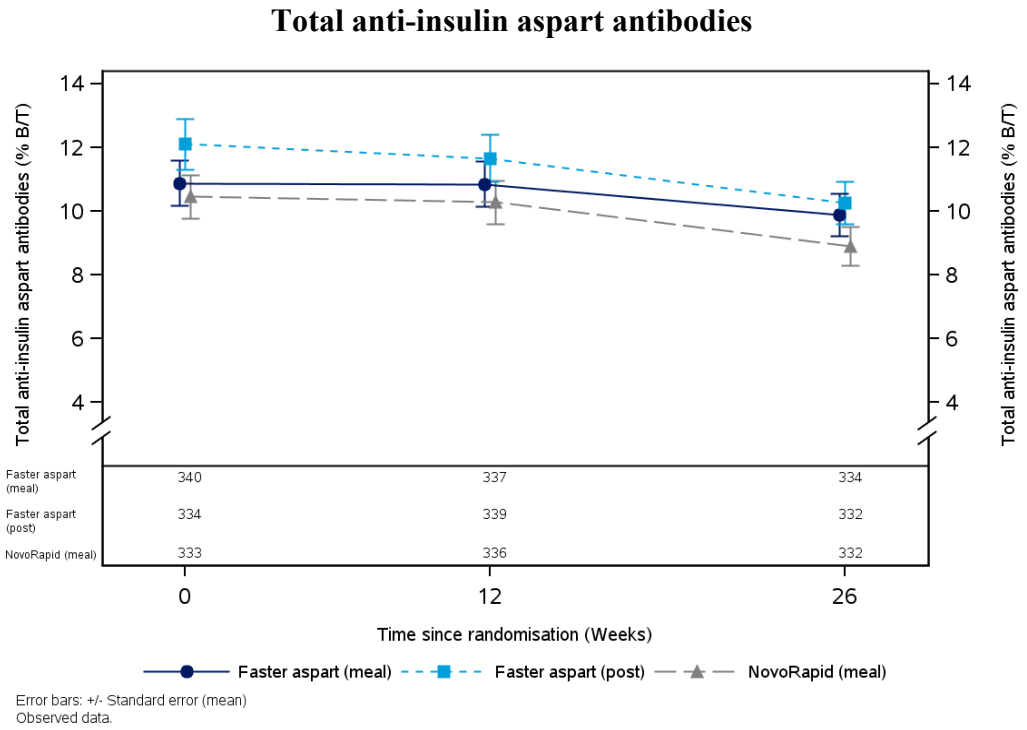


図 2.7.4.3-1　　各種インスリン アスパルト抗体価の平均（4131 試験）

表 2.7.4.3-1　　投与週別の各種インスリン アスパルト抗体価（4131 試験）

	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)
Number of subjects	342	341	342
Anti-insulin aspart specific antibodies (% B/T)			
Visit 10 (Week 0)			
N	340	334	335
Mean (SD)	1.379 (2.840)	1.904 (4.944)	1.763 (4.337)
Median	0.410	0.405	0.390
Min ; Max	-1.18 ; 23.18	-2.02 ; 47.14	-0.48 ; 41.87
Visit 22 (Week 12)			
N	337	339	336
Mean (SD)	1.336 (2.744)	1.891 (4.898)	1.689 (4.004)
Median	0.440	0.430	0.380
Min ; Max	-1.25 ; 25.30	-1.97 ; 48.98	-0.82 ; 39.82
Visit 36 (Week 26)			
N	334	332	332
Mean (SD)	1.374 (2.784)	1.867 (4.688)	1.733 (4.192)
Median	0.465	0.410	0.395
Min ; Max	-3.66 ; 22.69	-4.78 ; 42.52	-0.40 ; 44.35

Table continues next page

Table continued from previous page

	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)
Anti-insulin aspart antibodies cross-reacting to human insulin (% B/T)			
Visit 10 (Week 0)			
N	340	335	334
Mean (SD)	9.500 (12.598)	10.196 (13.353)	8.654 (10.948)
Median	4.700	4.730	4.065
Min ; Max	-0.16 ; 66.96	-1.28 ; 87.73	-0.40 ; 62.12
Visit 22 (Week 12)			
N	338	339	337
Mean (SD)	9.556 (12.592)	9.766 (12.728)	8.568 (10.957)
Median	4.090	4.680	4.380
Min ; Max	-0.58 ; 61.32	-1.63 ; 87.96	-0.43 ; 74.72
Visit 36 (Week 26)			
N	335	333	332
Mean (SD)	8.492 (11.670)	8.374 (11.074)	7.173 (9.863)
Median	3.670	4.040	3.430
Min ; Max	-0.80 ; 67.61	-0.53 ; 87.44	-0.80 ; 77.86
Total anti-insulin aspart antibodies (% B/T)			
Visit 10 (Week 0)			
N	340	334	333
Mean (SD)	10.879 (13.192)	12.109 (14.568)	10.453 (12.357)
Median	6.030	6.280	5.480
Min ; Max	0.00 ; 68.29	-0.62 ; 89.07	-0.13 ; 83.45
Visit 22 (Week 12)			
N	337	339	336
Mean (SD)	10.853 (13.186)	11.656 (13.589)	10.280 (12.458)
Median	6.050	5.890	5.315
Min ; Max	-0.32 ; 64.90	-0.13 ; 87.83	0.07 ; 85.35
Visit 36 (Week 26)			
N	334	332	332
Mean (SD)	9.889 (12.303)	10.262 (12.285)	8.906 (11.219)
Median	5.330	5.215	4.625
Min ; Max	-2.33 ; 67.91	0.23 ; 87.35	-0.13 ; 83.94

Note: Minimum value contains the smallest value measured across available visits including retest. Maximum value contains the largest value measured across available visits including retest.
Abbreviations: N: Number of subjects, SD: Standard deviation

インスリン アスパルト特異抗体及びヒトインスリン交叉抗体の陽性の頻度

インスリン アスパルト特異抗体

インスリン アスパルト特異抗体陽性と判定された被験者の割合は、検体採取時点や、陽性反応が持続的か単発的かに関わらず、いずれの投与群においても同程度（17.5～21.1%）であった（表 2.7.4.3-2）。

ヒトインスリン交叉抗体

インスリン アスパルト特異抗体の結果と同様に、ヒトインスリン交叉抗体陽性と判定された被験者の割合は、検体採取時期や、陽性反応が持続的か単発的かに関わらず、いずれの投与群においても同

程度であった。ベースラインでヒトインスリン交叉抗体陽性と判定された被験者の割合は 82.7～84.2%であり、被験者の 90.6～91.8%が on-treatment 観察期間中に 1 回は陽性と判定された。陽性反応が持続的に認められた被験者の割合は、on-treatment 観察期間中に 1 回は陽性反応が認められた被験者の割合よりわずかに低かった（表 2.7.4.3-2）。

表 2.7.4.3-2　抗インスリン アスパルト抗体陽性の被験者の頻度－要約－on-treatment 観察期間－安全性解析対象集団（4131 試験）

		Anti-insulin aspart antibody positive		
	Safety Set	Baseline N (%)	Anytime N (%)	Sustained N (%)
Anti-insulin aspart antibodies cross-reacting to human insulin (% B/T)				
Faster aspart (meal)	342	288 (84.2)	314 (91.8)	295 (86.3)
Faster aspart (post)	341	285 (83.6)	309 (90.6)	303 (88.9)
Faster aspart (meal+post)	683	573 (83.9)	623 (91.2)	598 (87.6)
NovoRapid (meal)	342	283 (82.7)	313 (91.5)	296 (86.5)
Anti-insulin aspart specific antibodies (% B/T)				
Faster aspart (meal)	342	65 (19.0)	71 (20.8)	66 (19.3)
Faster aspart (post)	341	60 (17.6)	72 (21.1)	68 (19.9)
Faster aspart (meal+post)	683	125 (18.3)	143 (20.9)	134 (19.6)
NovoRapid (meal)	342	60 (17.5)	69 (20.2)	66 (19.3)
Total anti-insulin aspart antibodies (% B/T)				
Faster aspart (meal)	342	254 (74.3)	279 (81.6)	263 (76.9)
Faster aspart (post)	341	263 (77.1)	287 (84.2)	278 (81.5)
Faster aspart (meal+post)	683	517 (75.7)	566 (82.9)	541 (79.2)
NovoRapid (meal)	342	262 (76.6)	283 (82.7)	274 (80.1)

%: Percentage of subjects, N: Number of subjects
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
Limits: Cross-reacting antibodies > 0.7 % B/T, Specific antibodies > 1.9 % B/T, Total antibodies > 1.9 % B/T. Baseline: antibody sample above limit at baseline. Anytime: at least one antibody sample above limit during the on-treatment period including the baseline visit. Sustained: More than one antibody sample above limit during the on-treatment period including the baseline visit or above at last on-treatment observation.

抗体陽性とアレルギー反応に関連する有害事象

アレルギー反応の単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群間で同程度であった（2.7.4.2.3.3 項）。この結果と一致して、抗体陽性の被験者におけるアレルギー反応の単位時間あたりの発現件数は、いずれの投与群においても同程度であった（表 2.7.4.3-3 及び表 2.7.4.3-4）（なお、アレルギー反応の発現時に抗体価を測定したわけではない）。

インスリン アスパルト特異抗体が 1 回以上陽性の被験者、インスリン アスパルト特異抗体が陽性にならなかった被験者、ヒトインスリン交叉抗体が 1 回以上陽性の被験者、及びヒトインスリン交叉抗体が陽性にならなかった被験者それぞれにおいて、アレルギー反応の単位時間（100 人・年）あたりの発現件数は、いずれの投与群においても同程度であった（表 2.7.4.3-3 及び表 2.7.4.3-4）。以上の結果か

ら、いずれの投与群においても、抗体産生とアレルギー反応との関連性は示唆されなかった。このことは、各被験者の抗体価（%B/T）とアレルギー反応の発現の有無を示す散布図によっても裏付けられており、それら散布図からは、ベースラインから投与終了時までの抗体産生（抗体価高値ないし陽性）と、アレルギー反応との間に明らかな関連性は認められなかった〔Safety Appendix 4（M 5.3.5.1）Figure 47～49 及び 53～55〕。

表 2.7.4.3-3　インスリン アスパルト特異抗体が 1 回以上陽性であった／なかった被験者別（カットポイント 1.9%B/T）アレルギー反応（4131 試験）

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects positive	71	72	69
Total exposure (yrs)	35.3	36.0	34.4
Total events	1 (1.4) 2 5.7	4 (5.6) 4 11.1	4 (5.8) 4 11.6
Number of subjects not positive	271	269	273
Total exposure (yrs)	135.9	134.2	135.8
Total events	8 (3.0) 11 8.1	10 (3.7) 12 8.9	7 (2.6) 7 5.2

Note: Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. **Abbreviations:** %: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years

表 2.7.4.3-4　ヒトインスリン交叉抗体が 1 回以上陽性であった／なかった被験者別（カットポイント 0.7%B/T）アレルギー反応（4131 試験）

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects positive	314	309	313
Total exposure (yrs)	157.2	154.8	156.2
Total events	8 (2.5) 12 7.6	12 (3.9) 14 9.0	10 (3.2) 10 6.4
Number of subjects not positive	28	32	29
Total exposure (yrs)	14.0	15.4	14.0
Total events	1 (3.6) 1 7.1	2 (6.3) 2 13.0	1 (3.4) 1 7.1

Note: Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. **Abbreviations:** %: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years

抗体陽性と注射部位反応に関連する有害事象

注射部位反応の単位時間あたりの発現件数は、いずれの投与群においても同程度であった（2.7.4.2.3.4 項）。この結果と一致して、抗体陽性の被験者における注射部位反応の単位時間あたりの発現件数は、いずれの投与群においても同程度であった（表 2.7.4.3-5 及び表 2.7.4.3-6）（なお、注射部位反応の発現時に抗体価を測定したわけではない）。

インスリン アスパルト特異抗体が 1 回以上陽性の被験者、インスリン アスパルト特異抗体が陽性にならなかった被験者、ヒトインスリン交叉抗体が 1 回以上陽性の被験者及びヒトインスリン交叉抗体が陽性にならなかった被験者それぞれにおいて、注射部位反応の単位時間（100 人・年）あたりの発現件数は、いずれの投与群においても同程度であった（表 2.7.4.3-5 及び表 2.7.4.3-6）。

注射部位反応に関連する有害事象を報告した被験者はすべて、投与群に関わらず、ヒトインスリン交叉抗体が 1 回以上陽性であった（表 2.7.4.3-6）。しかしながら、全被験者の 90.6～91.8%が試験期間中のいずれかの時点でヒトインスリン交叉抗体陽性だった（表 2.7.4.3-2）ため、いずれの投与群においても、抗体産生と注射部位反応との間に明らかな関連性は認められなかった。このことは、各被験者の抗体価（%B/T）と注射部位反応の発現の有無を示す散布図によっても裏付けられており、それら散布図からは、ベースラインから投与終了時までの抗体産生（抗体価高値ないし陽性）と、注射部位反応との間に明らかな関連性は認められなかった〔Safety Appendix 4（M 5.3.5.1）Figure 29～31 及び Figure 35～37〕。

表 2.7.4.3-5 インスリン アスパルト特異抗体が 1 回以上陽性であった／なかった被験者別（カットポイント 1.9%B/T）注射部位反応（4131 試験）

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects positive	71	72	69
Total exposure (yrs)	35.3	36.0	34.4
Total events	2 (2.8) 2 5.7	3 (4.2) 4 11.1	1 (1.4) 2 5.8
Number of subjects not positive	271	269	273
Total exposure (yrs)	135.9	134.2	135.8
Total events	6 (2.2) 7 5.1	5 (1.9) 8 6.0	4 (1.5) 8 5.9

Note: Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. **Abbreviations:** %: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years

表 2.7.4.3-6 ヒトインスリン交叉抗体が 1 回以上陽性であった／なかった被験者別（カットポイント 0.7%B/T）注射部位反応（4131 試験）

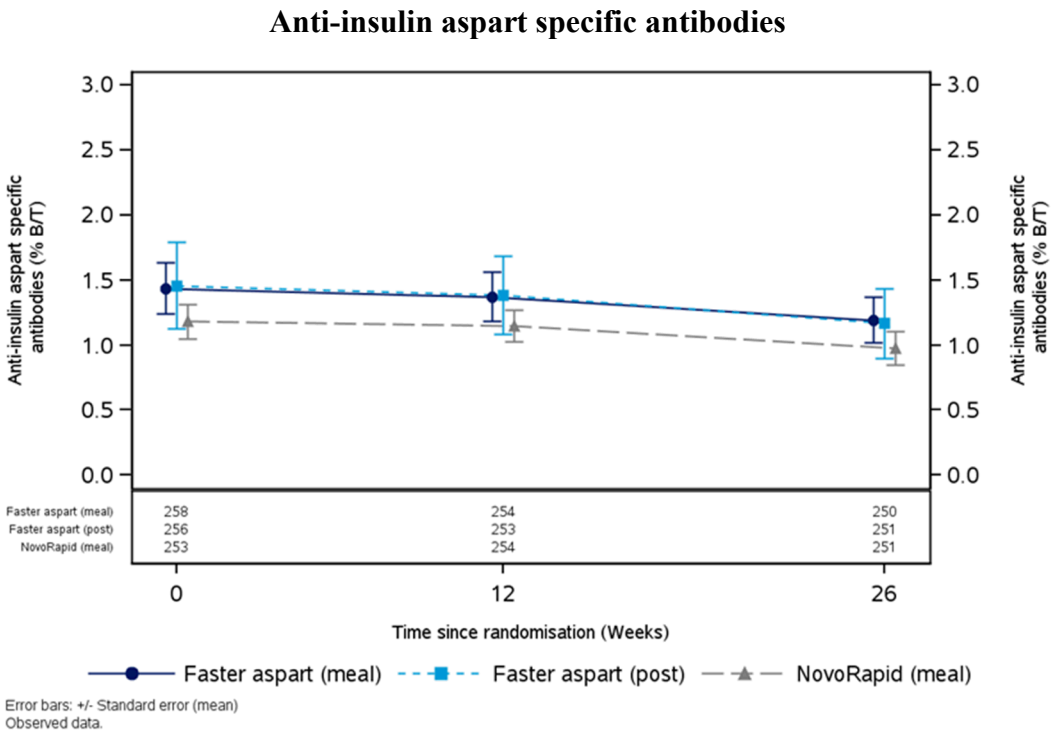
	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects positive	314	309	313
Total exposure (yrs)	157.2	154.8	156.2
Total events	8 (2.5) 9 5.7	8 (2.6) 12 7.8	5 (1.6) 10 6.4
Number of subjects not positive	28	32	29
Total exposure (yrs)	14.0	15.4	14.0
Total events	0	0	0

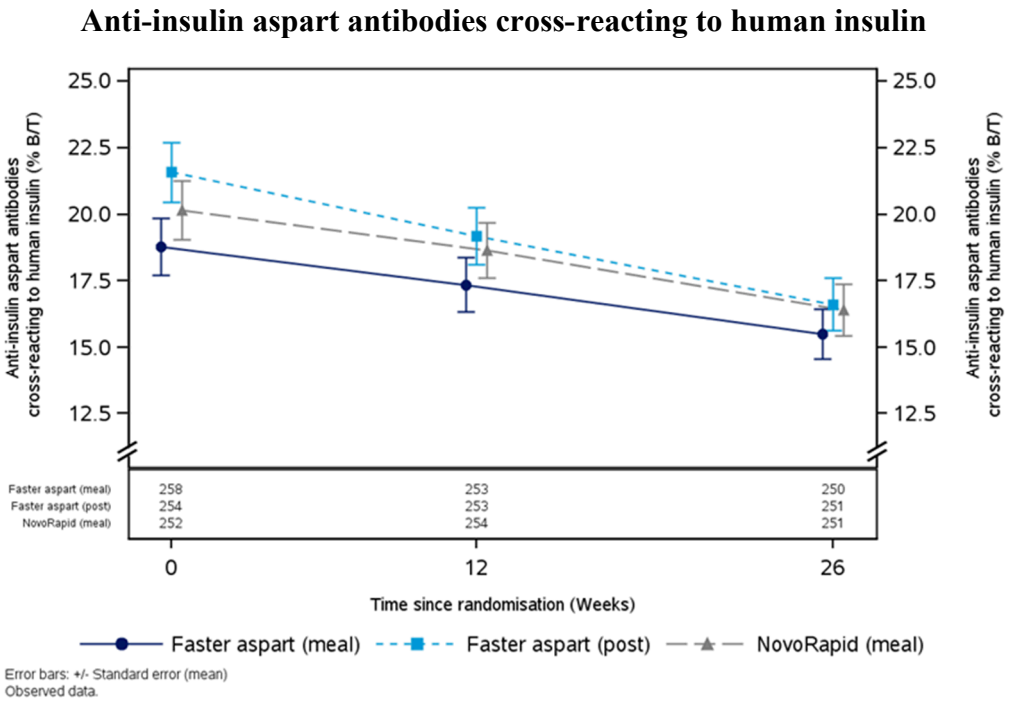
Note: Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. **Abbreviations:** %: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years

2.7.4.3.2.2.2　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

抗体産生

全体として、インスリン アスパルト特異抗体、ヒトインスリン交叉抗体、総インスリン アスパルト抗体それぞれの抗体価の平均値から、ベースライン、投与後 12 週及び 26 週において、投与群間で差は認められなかった（図 2.7.4.3-2 及び表 2.7.4.3-7）。





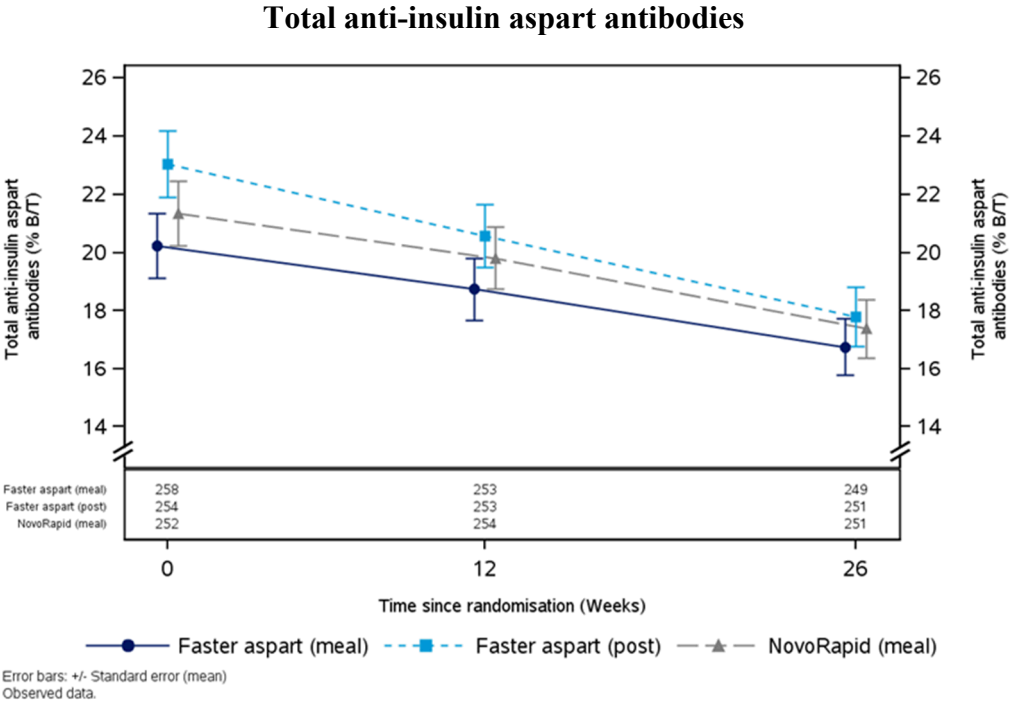


図 2.7.4.3-2　　各種インスリン アスパルト抗体価の平均値（4101 試験）

表 2.7.4.3-7　　投与週別の各種インスリン アスパルト抗体価（4101 試験）

	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)
Anti-insulin aspart specific antibodies (% B/T)			
Visit 14 (Week 0)			
N	258	256	253
Mean (SD)	1.436 (3.159)	1.459 (5.313)	1.183 (2.134)
Median	0.460	0.410	0.370
Min ; Max	-0.35 ; 23.01	-6.54 ; 61.05	-0.48 ; 13.84
Visit 26 (Week 12)			
N	254	253	254
Mean (SD)	1.374 (3.010)	1.388 (4.776)	1.151 (1.941)
Median	0.465	0.340	0.400
Min ; Max	-4.03 ; 20.76	-1.61 ; 55.32	-0.42 ; 12.02
Visit 40 (Week 26)			
N	250	251	251
Mean (SD)	1.196 (2.808)	1.170 (4.241)	0.981 (2.036)
Median	0.395	0.340	0.340
Min ; Max	-2.47 ; 25.15	-6.36 ; 53.75	-5.79 ; 16.02
Anti-insulin aspart antibodies cross-reacting to human insulin (% B/T)			
Visit 14 (Week 0)			
N	258	254	252
Mean (SD)	18.794 (17.189)	21.576 (17.721)	20.156 (17.315)
Median	13.325	17.765	15.155
Min ; Max	0.00 ; 81.42	-1.35 ; 83.75	0.13 ; 84.66
Visit 26 (Week 12)			
N	253	253	254
Mean (SD)	17.358 (16.164)	19.192 (16.984)	18.654 (16.600)
Median	11.810	13.680	14.845
Min ; Max	-0.82 ; 82.27	-1.63 ; 90.16	-0.76 ; 84.19
Visit 40 (Week 26)			
N	250	251	251
Mean (SD)	15.514 (14.871)	16.621 (15.572)	16.409 (15.438)
Median	10.230	13.010	12.150
Min ; Max	0.10 ; 81.74	-0.17 ; 81.97	0.01 ; 80.26
Total anti-insulin aspart antibodies (% B/T)			
Visit 14 (Week 0)			
N	258	254	252
Mean (SD)	20.230 (17.795)	23.044 (18.070)	21.344 (17.825)
Median	14.290	19.260	15.770
Min ; Max	0.26 ; 89.20	-6.08 ; 85.07	0.15 ; 89.79
Visit 26 (Week 12)			
N	253	253	254
Mean (SD)	18.737 (17.029)	20.580 (17.226)	19.805 (16.964)
Median	13.660	16.010	15.440
Min ; Max	0.05 ; 90.18	-2.17 ; 91.84	0.16 ; 90.37
Visit 40 (Week 26)			
N	249	251	251
Mean (SD)	16.741 (15.610)	17.790 (16.017)	17.391 (15.888)
Median	11.620	13.910	13.170
Min ; Max	-0.03 ; 89.86	-3.50 ; 82.87	-0.40 ; 89.43

N: Number of subjects, SD: Standard deviation, period. Minimum value contains the smallest value measured across available visits including retest. Maximum value contains the largest value measured across available visits including retest.

インスリン アスパルト特異抗体及びヒトインスリン交叉抗体の陽性の頻度

インスリン アスパルト特異抗体

インスリン アスパルト特異抗体陽性と判定された被験者の割合は、検体採取時期や、陽性反応が持続的か単発的かに関わらず、いずれの投与群においても同程度（13.6～20.5%）であった（表 2.7.4.3-8）。

ヒトインスリン交叉抗体

インスリン アスパルト特異抗体の結果と同様に、ヒトインスリン交叉抗体陽性と判定された被験者の割合は、検体採取時期や、陽性反応が持続的か単発的かに関わらず、いずれの投与群においても同程度であった。ベースラインでヒトインスリン交叉抗体陽性と判定された被験者の割合は 93.0～96.2%であり、被験者の 96.1～98.1%が on-treatment 観察期間中に 1 回は陽性と判定された。陽性反応が持続的に認められた被験者の割合は、on-treatment 観察期間中に 1 回以上陽性反応が認められた被験者の割合よりわずかに低く、ベースラインでヒトインスリン交叉抗体陽性と判定された被験者の割合と同程度であった（表 2.7.4.3-8）。

表 2.7.4.3-8　抗インスリン アスパルト抗体陽性の被験者の発現頻度－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

		Anti-insulin aspart antibody positive		
	Safety Set	Baseline N (%)	Anytime N (%)	Sustained N (%)
Anti-insulin aspart antibodies cross-reacting to human insulin (% B/T)				
Faster aspart (meal)	261	251 (96.2)	256 (98.1)	252 (96.6)
Faster aspart (post)	258	240 (93.0)	248 (96.1)	241 (93.4)
Faster aspart (meal+post)	519	491 (94.6)	504 (97.1)	493 (95.0)
NovoRapid (meal)	258	244 (94.6)	251 (97.3)	246 (95.3)
Anti-insulin aspart specific antibodies (% B/T)				
Faster aspart (meal)	261	41 (15.7)	48 (18.4)	41 (15.7)
Faster aspart (post)	258	42 (16.3)	51 (19.8)	35 (13.6)
Faster aspart (meal+post)	519	83 (16.0)	99 (19.1)	76 (14.6)
NovoRapid (meal)	258	44 (17.1)	53 (20.5)	43 (16.7)
Total anti-insulin aspart antibodies (% B/T)				
Faster aspart (meal)	261	241 (92.3)	250 (95.8)	240 (92.0)
Faster aspart (post)	258	234 (90.7)	241 (93.4)	236 (91.5)
Faster aspart (meal+post)	519	475 (91.5)	491 (94.6)	476 (91.7)
NovoRapid (meal)	258	238 (92.2)	248 (96.1)	244 (94.6)

%: Percentage of subjects, N: Number of subjects
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
Limits: Cross-reacting antibodies > 0.7 % B/T, Specific antibodies > 1.9 % B/T, Total antibodies > 1.9 % B/T. Baseline: antibody sample above limit at baseline. Anytime: at least one antibody sample above limit during the on-treatment period including the baseline visit. Sustained: More than one antibody sample above limit during the on-treatment period including the baseline visit or above at last on-treatment observation.

抗体陽性とアレルギー反応に関連する有害事象

抗体が 1 回以上陽性であった／なかった被験者別に、アレルギー反応に関連する有害事象の単位時間あたりの発現件数を表 2.7.4.3-9 及び表 2.7.4.3-10 に提示する（なお、アレルギー反応の発現時に抗体を測定したわけではない）。

アレルギー反応の単位時間あたりの発現件数は、インスリン アスパルト特異抗体が 1 回以上陽性の被験者において、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 4.2、7.9 及び 11.3 件/100 人・年であった。また、インスリン アスパルト特異抗体が陽性にならなかった被験者においては、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 15.3、5.9 及び 9.9 件/100 人・年であった（表 2.7.4.3-9）。アレルギー反応に関連する有害事象を報告した被験者はすべて、ヒトインスリン交叉抗体が 1 回以上陽性であり、単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 13.5、6.5 及び 10.5 件/100 人・年であった（表 2.7.4.3-10）。

各被験者の抗体価（%B/T）とアレルギー反応の発現の有無を示す散布図からは、ベースラインから投与終了時までの抗体産生（抗体価高値ないし陽性）と、アレルギー反応との間に明らかな関連性は認められなかった〔Safety Appendix 4（M 5.3.5.1）Figure 50～52 及び Figure 56～58〕。以上の結果から、いずれの投与群においても、抗体産生とアレルギー反応との関連性は示唆されなかった。

表 2.7.4.3-9　インスリン アスパルト特異抗体が 1 回以上陽性であった／なかった被験者別（カットポイント 1.9%B/T）アレルギー反応（4101 試験）

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects positive	48	51	53
Total exposure (yrs)	23.8	25.3	26.6
Total events	1 (2.1) 1 4.2	2 (3.9) 2 7.9	2 (3.8) 3 11.3
Number of subjects not positive	213	207	204
Total exposure (yrs)	104.6	102.3	100.6
Total events	12 (5.6) 16 15.3	6 (2.9) 6 5.9	7 (3.4) 10 9.9

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.

表 2.7.4.3-10　ヒトインスリン交叉抗体が 1 回以上陽性であった／なかった被験者別（カットポイント 0.7%B/T）アレルギー反応（4101 試験）

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects positive	256	248	251
Total exposure (yrs)	125.9	123.1	124.2
Total events	13 (5.1) 17 13.5	8 (3.2) 8 6.5	9 (3.6) 13 10.5
Number of subjects not positive	5	10	6
Total exposure (yrs)	2.5	4.5	3.0
Total events	0	0	0

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.

抗体陽性と注射部位反応に関連する有害事象

抗体が 1 回以上陽性であった／なかった被験者別に、注射部位反応に関連する有害事象の単位時間あたりの発現件数を表 2.7.4.3-11 及び表 2.7.4.3-12 に提示する（なお、注射部位反応の発現時に抗体を測定したわけではない）。

注射部位反応に関連する有害事象の単位時間あたりの発現件数は、インスリン アスパルト特異抗体が 1 回以上陽性の被験者において、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 8.4、43.4 及び 18.8 件/100 人・年であった。インスリン アスパルト特異抗体が陽性にならなかった被験者においては、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 8.6、19.5 及び 11.9 件/100 人・年であった。また、ヒトインスリン交叉抗体が 1 回以上陽性の被験者においては、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 8.7、18.7 及び 12.1 件/100 人・年であり、ヒトインスリン交叉抗体検体が陽性にならなかった被験者においては、それぞれ 0 件、176.8 及び 66.9 件/100 人・年であった（表 2.7.4.3-11 及び表 2.7.4.3-12）。なお、いずれも faster aspart（食後投与）群で単位時間あたりの発現件数が多い原因は、同一医療機関の 3 例において 19 件の事象（注射部位出血）が報告されたためである（詳細は 2.7.4.2.3.4.3 項）。

各被験者の抗体価（%B/T）と注射部位反応の発現の有無を示す散布図からは、ベースラインから投与終了時までの抗体産生（抗体価高値ないし陽性）と、注射部位反応との間に明らかな関連性は認められなかった〔Safety Appendix 4（M 5.3.5.1）Figure 32～34 及び Figure 38～40〕。以上の結果から、いずれの投与群においても、抗体産生と注射部位反応との関連性は示唆されなかった。

表 2.7.4.3-11 インスリン アスパルト特異抗体が 1 回以上陽性であった／なかった被験者別（カットポイント 1.9%B/T）注射部位反応（4101 試験）

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects positive	48	51	53
Total exposure (yrs)	23.8	25.3	26.6
Total events	2 (4.2) 2 8.4	5 (9.8) 11 43.4	3 (5.7) 5 18.8
Number of subjects not positive	213	207	204
Total exposure (yrs)	104.6	102.3	100.6
Total events	6 (2.8) 9 8.6	9 (4.3) 20 19.5	8 (3.9) 12 11.9

Note: Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. **Abbreviations:** %: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years

表 2.7.4.3-12 ヒトインスリン交叉抗体が 1 回以上陽性であった／なかった被験者別（カットポイント 0.7%B/T）注射部位反応（4101 試験）

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects positive	256	248	251
Total exposure (yrs)	125.9	123.1	124.2
Total events	8 (3.1) 11 8.7	13 (5.2) 23 18.7	10 (4.0) 15 12.1
Number of subjects not positive	5	10	6
Total exposure (yrs)	2.5	4.5	3.0
Total events	0	1 (10.0) 8 176.8	1 (16.7) 2 66.9

Note: Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. **Abbreviations:** %: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years

2.7.4.3.2.3 結論

4131 及び 4101 試験では、ベースライン、投与後 12 週及び 26 週のいずれの時点においても、抗体に関して投与群間で臨床的に意味のある違いは認められなかった。総インスリン アスパルト抗体の抗体価の平均値はベースラインにおいて低く、いずれの投与群においても投与後 12 週から 26 週にかけてわずかに減少した。インスリン アスパルト特異抗体及びヒトインスリン交叉抗体が陽性と判定された被験者の割合は、いずれの投与群においても同程度であった。抗体産生とアレルギー反応又は注射部位反応に関連する有害事象との間に関連性は認められなかった。

2.7.4.3.3 血液学的検査及び血液生化学的検査

2.7.4.3.3.1 評価方法

4131 及び 4101 試験において検討した血液生化学的検査項目及び血液学的検査項目の概要を表 2.7.4.3-13 に提示する。

表 2.7.4.3-13 血液学的検査及び血液生化学的検査の評価項目の概観（4131 及び 4101 試験）

Clinical laboratory assessment	Parameters
Biochemistry	Albumin, ALP, ALT, AST, creatinine, sodium, potassium, albumin, total bilirubin and total protein[a]
Haematology	Haemoglobin, haematocrit, erythrocytes, thrombocytes and leucocytes

[a] Only trial 4131
Abbreviations: ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

スクリーニング、ベースライン、投与期間の概ね中間時点の来院（12 週）及び投与終了来院（26 週）で血液生化学的検査項目及び血液学的検査項目の採血を実施した。

血液生化学的検査項目及び血液学的検査項目の臨床的に有意な異常は、有害事象として報告されたため、2.7.4.2 項に示した有害事象の一部にも含まれている、

さらに、4131 及び 4101 試験では、Hy's law[20]に基づいて薬物性肝障害の可能性のあるすべての症例を検出できるよう、以下の事例を調査した。

- アラニンアミノトランスフェラーゼ（ALT）又はアスパラギン酸アミノトランスフェラーゼ（AST）が基準値上限の 3 倍超及び総ビリルビンが基準値上限の 2 倍超で、治験薬以外の要因が存在しない。

2.7.4.3.3.2　検証的試験

2.7.4.3.3.2.1　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

血液生化学的検査項目及び血液学的検査項目の平均値は試験期間を通して安定しており、試験期間中の平均値や平均変化量に投与群間で明らかな違いは認められなかった。大部分の被験者において、血液生化学的検査及び血液学的検査の値は試験期間を通して正常であった。正常値から高値又は低値への変化がみられた被験者はわずかであり、いずれの検査項目においても投与群間で違いは認められなかった〔Trial 4131（M 5.3.5.1）EOT Table 14.3.5.1～14.3.5.4 及び 14.3.5.23～14.3.5.26、ならびに EOT Figure 14.3.5.5～14.3.5.22 及び 14.3.5.27～14.3.5.36〕。

2.7.4.3.3.2.2　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

血液生化学的検査項目及び血液学的検査項目の平均値は試験期間を通して安定しており、試験期間中の平均値や平均変化量に投与群間で明らかな違いは認められなかった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.5.1～14.3.5.4 及び 14.3.5.21～14.3.5.24、ならびに EOT Figure 14.3.5.5～14.3.5.20、14.3.5.25～14.3.5.34〕。

2.7.4.3.3.3　結論

4131 及び 4101 試験において、血液生化学的検査項目及び血液学的検査項目の平均値は試験中を通して安定しており、試験期間中の平均値や平均変化量に投与群間で明らかな違いは認められなかった。

2.7.4.3.4　脂質

2.7.4.3.4.1　評価方法

4131 試験において、脂質検査項目〔総コレステロール、高比重リポタンパク（HDL）コレステロール、低比重リポタンパク（LDL）コレステロール〕のベースラインからの変化量は、有効性評価項目の一部であった。しかしながら、本臨床概要ではこれらの結果についても、4101 試験の脂質検査項目（同試験では安全性評価項目）の結果とともに提示する。統計解析については、総括報告書（Module 5.3.5.1）を参照のこと。

両試験とも、スクリーニング、ベースライン、投与期間の概ね中間時点の来院（12 週）及び投与終了来院（26 週）で脂質測定用の採血を実施した。

4101 試験では、脂質検査項目の臨床的に有意な異常は有害事象として報告されたため、2.7.4.2 項に示した有害事象の一部にも含まれている、

脂質測定用の検体を分析し、以下の項目のベースラインからの変化量を求めた。

- 総コレステロール

- HDL コレステロール
- LDL コレステロール

2.7.4.3.4.2　検証的試験

2.7.4.3.4.2.1　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

全体として、無作為割り付け後 26 週において、3 つの投与群のいずれにおいても、総コレステロール、HDL コレステロール及び LDL コレステロールの幾何平均（実測値）にベースラインからの顕著な変化は認められなかった〔Trial 4131（M 5.3.5.1）EOT Table 14.3.5.38、EOT Figure 14.3.5.48、14.3.5.52 及び 14.3.5.56〕。総コレステロール、HDL コレステロール及び LDL コレステロールについて、faster aspart の各群とノボラピッド®注群の間の変化率に統計的な有意差はみられなかった〔Trial 4131（M 5.3.5.1）EOT Table 14.3.5.46〕。

個々の被験者における HDL コレステロール、LDL コレステロール及び総コレステロールのベースラインから無作為割り付け後 26 週までの変化に投与群間で違いは認められなかった。3 つの投与群ともに、ベースラインと無作為割り付け後 26 週の値は、大部分の被験者において正常値であった〔Trial 4131（M 5.3.5.1）EOT Table 14.3.5.42〕。

ベースラインと 26 週時に、脂質が基準範囲外の値を示した被験者の割合〔Trial 4131（M 5.3.5.1）EOT Table 14.3.5.42〕 や、ベースラインの正常値から 26 週の高値又は低値への変化がみられた被験者の割合に、投与群間で臨床的に意味のある違いは認められなかった〔脂質のベースラインから投与終了時までのシフトテーブルは、Trial 4131（M 5.3.5.1）EOT Table 14.3.5.44 を参照〕。

2.7.4.3.4.2.2　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

ベースラインの総コレステロール、HDL コレステロール及び LDL コレステロールの平均値に、3 つの投与群間で臨床的に意味のある違いは認められなかった。全体として、無作為割り付け後 26 週の総コレステロール、HDL コレステロール及び LDL コレステロールの幾何平均（実測値）には、いずれの投与群においても、ベースラインからの顕著な変化は認められなかった。

変化率の比の検討に基づくと、総コレステロール及び LDL コレステロールは、ノボラピッド®注群と比較して faster aspart（食前投与）群で低下し、統計的な有意差が認められたものの、臨床的に意味のある違いではないと考えられた〔総コレステロールの変化率の比の推定値：0.97（95%信頼区間：0.95; 0.99）、LDL コレステロールの変化率の比の推定値：0.97（95%信頼区間：0.94;1.00）〕。HDL コレステロールについては、faster aspart（食前投与）群とノボラピッド®注群の間の変化率に統計的な有意差は認められなかった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.5.44〕。

Faster aspart（食後投与）群とノボラピッド®注群の間の変化率の比に基づくと、総コレステロール、LDL コレステロール及び HDL コレステロールのいずれにおいても統計的な有意差は認められなかった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.5.44〕。

個々の被験者における HDL コレステロール、LDL コレステロール及び総コレステロールのベースラインから無作為割り付け後 26 週の変化に投与群間で違いは認められなかった。3 つの投与群ともに、大部分の被験者において、ベースライン及び無作為割り付け後 26 週の値は正常値であった〔Trial 4101（M 5.3.5.1）EOT Table14.3.5.40〕。

2.7.4.3.4.3　結論

4131 及び 4101 試験において、ベースライン及び無作為割り付け後 26 週時の総コレステロール、HDL コレステロール及び LDL コレステロールに、3 つの投与群間で臨床的に意味のある違いは認められなかった。

2.7.4.3.5　尿検査

2.7.4.3.5.1　評価方法

4131 試験では、スクリーニング、ベースライン、投与期間の概ね中間時点の来院（12 週）及び投与終了来院（26 週）で採尿を実施し、以下の項目を測定した。

- アルブミン／クレアチニン比
- 潜血
- タンパク
- ケトン

4101 試験では、高血糖の疑いがあり、血糖自己測定値が 250 mg/dL 超で、体調不良の被験者のみを対象に、尿中ケトンを測定した（2.7.4.2.3.8 項参照）。

2.7.4.3.5.2　検証的試験

2.7.4.3.5.2.1　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

尿検査項目の平均値は試験期間を通して安定しており、試験期間中の平均値や平均変化量に投与群間で明らかな違いは認められなかった〔Trial 4131（M 5.3.5.1）EOT Table 14.3.5.97～14.3.5.100 ならびに EOT Figure 14.3.5.101 及び 14.3.5.102（尿中アルブミン／クレアチニン比）、ならびに EOT Table 14.3.5.103～14.3.5.106（尿試験紙法による検査項目）〕。

大部分の被験者において、尿検査の値は試験期間を通して正常値であった。正常値から高値又は低値への変化がみられた被験者はわずかであり、投与群間で違いは認められなかった。

2.7.4.3.6 妊娠検査

2.7.4.3.6.1 評価方法

Faster aspart 開発プログラムでは「妊婦（妊娠した場合）又は妊娠を希望する場合」を除外基準として規定しており、妊娠する可能性のある女性に対しては避妊を行うよう求めた。試験中に妊娠した又は妊娠を希望した女性被験者は、直ちに治験薬の投与を中止することとした。4131 及び 4101 試験では、妊娠した又は妊娠を希望した女性被験者は、run-in 期間であれば試験を中止することとしたが、その他の試験ではいずれの期間においても試験を中止することと規定した。

すべての試験において、妊娠する可能性のある女性被験者に対し、スクリーニング来院時と投与終了時に血液妊娠検査を実施した。4131 及び 4101 試験では、無作為割り付け時にも妊娠検査を実施した。中央測定機関で血清中ヒト絨毛性ゴナドトロピン（hCG）を測定した。また、試験期間中に月経が停止した場合、治験実施医療機関において尿妊娠検査を実施することとした。

妊娠に関する詳細は 2.7.4.5.7 項を参照。

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、身体所見及び安全性に関連する他の観察項目の概観

本臨床概要では、4131 及び 4101 試験におけるバイタルサイン、身体所見及びその他の安全性観察項目について要約する。3918 試験の結果については、Module 2.7.6.1 及び総括報告書〔Trial 3918（M 5.3.4.2）〕を参照。

表 2.7.4.4-1 に示すとおり、バイタルサイン、身体所見、心電図及び眼底検査の評価を実施した。

スクリーニング時に「異常、臨床的に問題あり」と判定された所見はすべて、既往歴／併発疾患として記録した。バイタルサイン、眼底検査及び他の安全性評価項目について、臨床的に問題のある変化は有害事象として報告されたため、2.7.4.2 項で提示した有害事象の一部にも含まれている。

表 2.7.4.4-1 バイタルサイン、身体所見及び安全性に関連する他の観察項目の評価のタイミングの概観（4131 及び 4101 試験）

Trial		Screening	Baseline	Week 12	End of trial
4131	Vital signs and physical examination	x	x	x	x
	Body weight	x	x	x	x
	ECG	x	x		x
	Fundoscopy/fundus photography	x	x		x
4101	Vital signs and physical examination	x	x	x	x
	Body weight[a]	x	x	x	x
	Height	x	x	x	x
	Pubertal status (Tanner staging)		x	x	x

[a] SD scores were derived.

全体的に、バイタルサイン、身体所見、体重、体重 SD スコア（4101 試験のみ）、心電図（4131 試験のみ）、眼底検査（4131 試験のみ）、思春期発来の有無（4101 試験のみ）及びテクニカルな苦情について、投与群間で臨床的に意味のある違いは認められなかった。

2.7.4.4.2 バイタルサイン

2.7.4.4.2.1 評価方法

バイタルサインとして、拡張期血圧、収縮期血圧及び脈拍を 5 分間安静後に座位で測定した。

両試験における血圧及び脈拍の測定時期を表 2.7.4.4-1 に示す。

2.7.4.4.2.2　検証的試験

2.7.4.4.2.2.1　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

血圧（収縮期及び拡張期）及び脈拍の平均値は、試験期間中、各投与群内で安定していた。ベースラインと投与後 26 週の血圧（収縮期及び拡張期）及び脈拍について 3 つの投与群間に明らかな違いは認められなかった（表 2.7.4.4-2）。

表 2.7.4.4-2　バイタルサインの平均値－要約（4131 試験）

	Faster aspart (meal)		**Faster aspart (post)**		**NovoRapid® (meal)**	
	BP (S/D) (mmHg)	**Pulse (beats/min)**	**BP (S/D) (mmHg)**	**Pulse (beats/min)**	**BP (S/D) (mmHg)**	**Pulse (beats/min)**
Mean value at baseline	120.9/73.7	75.0	121.1/75.0	74.9	121.1/74.6	74.7
Mean value at end of trial	121.5/74.2	74.9	122.5/75.2	74.2	122.0/75.3	75.4
Mean change from baseline to end of trial	0.6/0.5	0.0	1.4/0.2	-0.7	0.8/0.8	0.7

Note: Safety analysis set. End of trial value is last on-treatment value
Abbreviations: BP: blood pressure; S: systolic; D: diastolic

2.7.4.4.2.2.2　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

血圧（収縮期及び拡張期）及び脈拍の平均値は、試験期間中、各投与群内で安定していた。ベースラインと投与後 26 週の血圧（収縮期及び拡張期）及び脈拍について 3 つの投与群間に明らかな違いは認められなかった（表 2.7.4.4-3）。

表 2.7.4.4-3　バイタルサインの平均値－要約（4101 試験）

	Faster aspart (meal)		**Faster aspart (post)**		**NovoRapid® (meal)**	
	BP (S/D) (mmHg)	**Pulse (beats/min)**	**BP (S/D) (mmHg)**	**Pulse (beats/min)**	**BP (S/D) (mmHg)**	**Pulse (beats/min)**
Mean value at baseline	106.4/65.4	80.6	107.0/65.7	80.5	106.8/65.4	79.4
Mean value at end of trial	107.1/66.6	80.1	108.5/67.1	80.9	107.9/66.8	80.1
Mean change from baseline to end of trial	0.8/1.2	-0.6	1.5/1.4	0.3	1.1/1.4	0.7

Note: Safety analysis set. End of trial value is last on-treatment value
Abbreviations: BP: blood pressure; S: systolic; D: diastolic

2.7.4.4.2.3　　結論

全体として、4131 及び 4101 試験において、ベースラインから投与終了時までのバイタルサインに、投与群間で臨床的に意味のある違いは認められなかった。

2.7.4.4.3　　身体所見

2.7.4.4.3.1　　評価方法

各試験における身体所見の観察時期については、表 2.7.4.4-1 を参照のこと。

身体所見には以下の項目を含めた。

- 呼吸器系
- 心血管系
- 中枢及び末梢神経系
- 口腔を含む消化器系
- 筋骨格系
- 皮膚
- 頭部、耳、眼、鼻、咽頭部、頚部

各項目における評価は以下の分類に従って行われた。

- 正常
- 異常、臨床的に問題なし
- 異常、臨床的に問題あり

2.7.4.4.3.2　　検証的試験

2.7.4.4.3.2.1　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

試験期間を通じて臨床的に意味のある変化は認められず、投与後 26 週時点の投与群間で臨床的に意味のある違いは認められなかった。

身体所見がベースラインの「正常」又は「異常、臨床的に問題なし」から投与後 26 週に「異常、臨床的に問題あり」に変化した被験者の数は、いずれの投与群においても少なく〔Trial 4131（M 5.3.5.1）EOT Table 14.3.6.2〕、逆方向への変動（改善）が認められた被験者の数と同程度であった。

2.7.4.4.3.2.2　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

試験期間を通じて臨床的に意味のある変化は認められず、投与後 26 週時点の投与群間で臨床的に意味のある違いは認められなかった。

身体所見がベースラインの「正常」又は「異常、臨床的に問題なし」から投与後 26 週に「異常、臨床的に問題あり」に変化した被験者の数は、いずれの投与群においても少なく〔Trial 4101（M 5.3.5.1）EOT Table 14.3.6.2〕、逆方向への変動（改善）が認められた被験者の数と同程度であった。

2.7.4.4.3.3　結論

4131 及び 4101 試験の身体所見において、試験期間を通じて臨床的に意味のある変化は認められず、投与後 26 週時点の投与群間で臨床的に意味のある違いは認められなかった。

2.7.4.4.4　体重

2.7.4.4.4.1　評価方法

体重は、上着や靴を脱いだ軽装の状態で測定した。可能な限り、試験を通して同一の体重計を使用した。

各試験における体重の測定時期については表 2.7.4.4-1 を参照のこと。

4101 試験での体重及び BMI については、国、年齢及び性別による体重及び BMI の違いを標準化するため、SD スコアを求めた〔Trial 4101（M 5.3.5.1）Table 9-9〕。

2.7.4.4.4.2　検証的試験

2.7.4.4.4.2.1　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

平均体重（実測値）は、faster aspart（食前投与）群ではベースラインから 26 週にかけて 72.59 kg から 73.98 kg へ、faster aspart（食後投与）群では 71.90 kg から 73.08 kg へ、ノボラピッド®注群では 71.79 kg から 73.14 kg へと変化した〔Trial 4131（M 5.3.5.1）EOT Table 14.3.6.18〕。

ベースラインから 26 週までの体重の変化量の推定値は、faster aspart（食前投与）群で+1.43 kg、faster aspart（食後投与）群で+1.16 kg、ノボラピッド®注群で+1.24 kg であった〔Trial 4131（M 5.3.5.1）EOT Table 14.3.6.20〕。

ベースラインから 26 週までの体重の変化量のノボラピッド®注群との群差の推定値は、faster aspart（食前投与）群で+0.19 kg（95%信頼区間：-0.22; +0.60）、faster aspart（食後投与）群で-0.08 kg（95%信頼区間：-0.49; +0.33）であり、いずれも統計的に有意ではなかった。

2.7.4.4.4.2.2　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

平均体重（実測値）は、faster aspart（食前投与）群ではベースラインから 26 週にかけて 46.69 kg から 48.77 kg へ、faster aspart（食後投与）群では 46.48 kg から 48.37 kg へ、ノボラピッド®注群では 46.28 kg から 48.51 kg へと変化した〔Trial 4101（M 5.3.5.1）EOT Table 14.3.6.16〕。

ベースラインから 26 週までの体重の変化量のノボラピッド®注群との群差の推定値は、faster aspart（食前投与）群で+0.06 kg（95%信頼区間：-0.39; +0.51）、faster aspart（食後投与）群で-0.24 kg（95%信頼区間：-0.68; +0.21）であり、いずれも統計的に有意ではなかった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.6.18〕。

ベースラインから 26 週までの体重 SD スコアの変化量の推定値は、faster aspart（食前投与）群で+0.03、faster aspart（食後投与）群で+0.01、ノボラピッド®注群で+0.03 であった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.6.36〕。

ベースラインから 26 週までの体重 SD スコアの変化量のノボラピッド®注群との群差の推定値は、faster aspart（食前投与）群で+0.00（95%信頼区間：-0.04; +0.05）、faster aspart（食後投与）群で-0.02（95%信頼区間：-0.06; +0.02）であり、いずれも統計的に有意な差ではなかった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.6.36〕。

2.7.4.4.4.3　結論

4131 及び 4101 試験において、ベースラインから投与後 26 週までの体重及び体重 SD スコア（4101 試験のみ）の変化量に、faster aspart 各群とノボラピッド®注群との間で統計的に有意な差は認められなかった。

2.7.4.4.5　心電図

2.7.4.4.5.1　評価方法（4131 試験のみ）

標準的 12 誘導心電図（リズムストリップ）を用いて評価した。

記録された心電図は治験責任医師が全体的な判読を行い、以下の分類に従って評価した。

- 正常
- 異常、臨床的に問題なし
- 異常、臨床的に問題あり

心電図評価の実施時期については、表 2.7.4.4-1 を参照のこと。

2.7.4.4.5.2　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

ベースライン及び投与後 26 週の心電図に、投与群間で臨床的に意味のある違いは認められなかった〔Trial 4131（M 5.3.5.1）EOT Table 14.3.6.14〕。3 つの投与群のいずれにおいても、ベースライン及び投与後 26 週の心電図の大部分は「正常」又は「異常、臨床的に問題なし」であった。

3 例〔faster aspart（食後投与）群：1 例、ノボラピッド®注群：2 例〕において、心電図の結果がベースラインの「正常」又は「異常、臨床的に問題なし」から投与後 26 週に「異常、臨床的に問題あり」に変化した〔Trial 4131（M 5.3.5.1）EOT Table 14.3.6.15 及び EOT Listing 14.3.7.2〕。

2.7.4.4.6　眼底検査／眼底写真

2.7.4.4.6.1　評価方法（4131 試験のみ）

4131 試験では、治験責任医師、治験実施施設の眼科医又は検眼医が、各国の慣例に従って眼底検査／眼底写真を実施した。眼科検査の結果は、治験責任医師が全体的な判読を行い、以下の分類に従って評価した。

- 正常
- 異常、臨床的に問題なし
- 異常、臨床的に問題あり

4131 試験での眼底検査／眼底写真の実施時期については、表 2.7.4.4-1 を参照のこと。

2.7.4.4.6.2　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

3 つの投与群のいずれにおいても、ベースライン及び投与後 26 週の眼底検査／眼底写真の大部分は「正常」又は「異常、臨床的に問題なし」であった。眼底検査／眼底写真がベースラインの「正常」又は「異常、臨床的に問題なし」から投与後 26 週に「異常、臨床的に問題あり」に変化した被験者の数は 3 つの投与群のいずれにおいても少なく、逆方向への変動（改善）が認められた被験者の数と同程度であった〔Trial 4131（M 5.3.5.1）EOT Table 14.3.6.16 及び EOT Table 14.3.6.17〕。投与群間で臨床的に意味のある違いは認められなかった。

ベースラインの「正常」又は「異常、臨床的に問題なし」から投与後 26 週での「異常、臨床的に問題あり」への変化は、faster aspart（食前投与）群の 4 例（両眼）及び 3 例（片眼）、faster aspart（食後投与）群の 6 例（両眼）及び 4 例（片眼）、ノボラピッド®注群の 6 例（両眼）及び 4 例（片眼）で認められた〔2.7.4.2.3.6 項及び Trial 4131（M 5.3.5.1）EOT Listing 14.3.7.4 参照〕。

2.7.4.4.7　　思春期発来の有無（Tanner 分類）

2.7.4.4.7.1　　評価方法（4101 試験のみ）

思春期発来の有無を、Tanner 分類（I～V[21]）により、ベースライン、投与後 12 週及び 26 週に評価した。

2.7.4.4.7.2　　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

3 つの投与群のいずれにおいても、男児被験者の最も多くが、Tanner スコア（「陰毛の発育」及び「陰茎の発育」）に従ってベースライン及び投与後 26 週では分類 I と判定された。なお試験期間中、分類 I と判定された男児被験者の割合は減少し、分類 I 以降に分類された男児被験者の割合が増加した〔Trial 4101（M 5.3.5.1）EOT Table 14.3.6.3〕。

3 つの投与群のいずれにおいても、女児被験者の最も多くが、Tanner スコア（「陰毛の発育」及び「乳房の発育」）に従ってベースライン及び投与後 26 週では分類 I 又は分類 V と判定された。なお試験期間中、分類 I と判定された女児被験者の割合は減少し、分類 I 以降に分類された女児被験者の割合が増加した〔Trial 4101（M 5.3.5.1）EOT Table 14.3.6.4〕。

2.7.4.4.8　　テクニカルな苦情

2.7.4.4.8.1　　評価方法

テクニカルな苦情とは、試験での提供品のうち、治験実施計画書で規定された医薬品又は医療機器の不具合に関する連絡とした。テクニカルな苦情は有害事象を伴うことがあるが、有害事象自体に関わるものではない。

テクニカルな苦情の例：

- 治験薬の物理的又は化学的な外観（変色、粒子、異物混入等）
- 包装資材（漏出、亀裂、カートリッジのゴム栓の問題、表示文章のミス等）
- 医療機器に関連する問題（投与機構、用量設定、注入ボタン、ペンと針の連結の不具合等）

提供品の初回使用時から最終使用時までに発生した治験薬、ペン型注入器、フレックスペン及びノボ ノルディスク社製注射針に関するテクニカルな苦情はすべて収集され、ノボ ノルディスク社に報告された。治験責任医師がテクニカルな苦情と有害事象、重篤な有害事象、特に注目すべき医学的事象（MESI）との関連性を評価した。重篤な有害事象と関連する場合は 24 時間以内に電子 CRF にて報告した。その他のテクニカルな苦情はすべて、5 暦日以内に報告した。

2.7.4.4.8.2　検証的試験

2.7.4.4.8.2.1　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

本試験では、有害事象と関連のあるテクニカルな苦情が 3 件報告された〔Trial 4131（M 5.3.5.1）Section 12.7.6〕。

1 件は、偶発的過少量投与（MESI）と関連のあるものであった〔faster aspart（食後投与）群〕。この有害事象は、非重篤、軽度で、治験責任医師により治験薬との因果関係は「なし」と判定された。この有害事象は操作ミスによるものであると結論付けられた。

2 件は、1 例〔faster aspart（食前投与）群〕において非重篤な有害事象の発現後に報告された。この有害事象は、非重篤、中等度の高血糖で、治験責任医師により治験薬との因果関係が「可能性あり」と判定された。Bolus 及び Basal インスリン両方のペン型注入器を交換した。

返却された注入器についてはノボ ノルディスク社にて外観及び動作の確認を行ったが、異常は認められなかった。

上記の有害事象の転帰は 2 件とも回復であった。

重篤な有害事象と関連のあるテクニカルな苦情は報告されなかった。

2.7.4.4.8.2.2　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

本試験では、有害事象と関連のあるテクニカルな苦情が計 3 件報告された〔Trial 4101（M 5.3.5.1）Section 12.1.2.4 及び 14.4〕。

2 件の有害事象（注射部位疼痛及び誤用量投与）が faster aspart（食前投与）群の 2 例において報告された。いずれの有害事象も非重篤で軽度であった。注射部位疼痛は治験責任医師により治験薬との因果関係は「なし」と判定されたが、誤用量投与は治験薬との因果関係が「可能性あり」と判定された〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.29 及び Appendix 16.2.7、Listing 16.2.7.1〕。

1 件の有害事象（注射部位疼痛）はノボラピッド®注群において報告された。この有害事象は、非重篤、軽度で、治験責任医師により治験薬との因果関係は「なし」と判定された〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.29 及び Appendix 16.2.7、Listing 16.2.7.1〕。

返却された注入器についてはノボ ノルディスク社にて外観及び動作の確認を行ったが、異常は認められなかった。

上記の有害事象の転帰は 3 件とも回復であった。

重篤な有害事象と関連のあるテクニカルな苦情は報告されなかった。

2.7.4.4.8.3　結論

4131 及び 4101 試験で、有害事象と関連のあるテクニカルな苦情が各 3 件報告された。返却された注入器についてはノボ ノルディスク社にて外観及び動作の確認を行ったが、異常は認められなかった。

2.7.4.5 特別な患者集団及び状況下における安全性

2.7.4.5.1 概観

Faster aspart の忍容性は、日本人 1 型糖尿病患者を対象とした臨床薬理試験である 3918 試験、及びその他の臨床薬理試験のいずれにおいても高く、安全性上の問題は認められなかった。4131 試験の成人被験者ならびに 4101 試験の小児及び青年期被験者を通じ、日本人集団と全集団の間で、有害事象及び重大な又は血糖値確定低血糖に臨床的に意味のある違いは認められなかった。

4131 試験において、内因性及び外因性民族的要因別の有害事象の種類及び単位時間あたりの発現件数は、いずれの投与群においても同程度であった。ごく少数例で過量投与の報告があったが、いずれも治験薬投与の中止又は試験の中止には至らなかった。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に関連して報告された有害事象は、faster aspart 各群及びノボラピッド®注群において同様の種類の事象であった。

インスリンポンプを用いた CSII 療法時の faster aspart の安全性及び適合性について、3854 及び 3931 の両試験で検討した。3854 試験では、ノボラピッド®注群と比較して faster aspart 群で注入部位反応の単位時間あたりの発現件数が数値的に多かった。また、予定されていない早期のインスリンポンプ注入セット交換を報告した被験者の割合は、ノボラピッド®注群と比較して faster aspart 群で高かった。3931 試験では、注入セットの顕微鏡検査を実施したが、faster aspart 群でもノボラピッド®注群でも注入セットの閉塞は確認されなかった。インスリンポンプ使用時のその他のの検討において、ノボラピッド®注との比較で faster aspart の安全性に問題は認められなかった。

3852 試験の結果から、1 型糖尿病患者における長期（52 週）投与時の安全性プロファイルは全体として faster aspart とノボラピッド®注で同様であり、インスリン アスパルトの特性から予測されるとおりであった。また、3853 試験の結果から、2 型糖尿病患者における安全性プロファイルは全体として faster aspart とノボラピッド®注で同様であり、インスリン アスパルトの特性から予測されるとおりであった。

2.7.4.5.2 日本人 1 型糖尿病患者を対象とした臨床薬理試験における安全性

2.7.4.5.2.1 評価方法

3918 試験（臨床薬理試験）では、日本人 1 型糖尿病患者における faster aspart の薬物動態及び薬力学的作用特性を、対照薬であるノボラピッド®注と比較検討した。本試験では日本人被験者が faster aspart の投与を受け、faster aspart の薬物動態及び薬力学的作用特性について価値のある情報が得られたことから、評価資料として本臨床概要に含めた。試験の詳細は、総括報告書〔Trial 4131（Module 5.3.4.2）〕参照。

2.7.4.5.2.2　曝露状況

3918 試験では、計 43 例の被験者が faster aspart の投与を受け、うち 42 例がノボラピッド®注の投与も受けた。

2.7.4.5.2.3　投与量

各被験者は、無作為割り付けにより割り当てられた投与順序に従い、所定の投与量（0.2 単位/kg）における faster aspart 又はノボラピッド®注の単回投与を受けた。

2.7.4.5.2.4　被験者の内訳、ベースラインの人口統計学的特性、併発疾患及び併用薬剤

3918 試験では、無作為割り付けされ治験薬の投与を受けた被験者はすべて日本人 1 型糖尿病患者であり、男女比はおおよそ均等であった（男性 24 例及び女性 19 例）。ベースラインにおいて、被験者の平均年齢は 39.4 歳、BMI の平均値は 22.6 kg/m^2、平均糖尿罹病期間は 16.6 年、また HbA1c の平均値は 7.4%であった。ベースラインの人口統計学的特性及び糖尿病特性の詳細は総括報告書〔Trial 3918（M 5.3.4.2）Section 10〕参照。また既往症／併発疾患、併用薬剤及びベースラインの糖尿病治療についても総括報告書〔Trial 3918（M 5.3.4.2）Appendix 16.2.4〕参照。

2.7.4.5.2.5　有害事象

2.7.4.5.2.5.1　比較的よく見られる有害事象

3918 試験で報告された有害事象は 3 例 3 件であり、うち 1 件（口腔咽頭痛）は faster aspart 投与後に、2 件（発熱、皮下出血）はノボラピッド®注投与後に報告された。いずれの有害事象も軽度であった〔Trial 3918（M 5.3.4.2）Appendix 16.2.7、Listing 16.2.7.1〕。治験責任医師により治験薬との因果関係が「可能性あり」又は「あり」と判定された有害事象はなく、試験の中止に至った有害事象もなかった。

2.7.4.5.2.5.2　死亡及びその他の重篤な有害事象

3918 試験で死亡又は重篤な有害事象の報告はなかった。

2.7.4.5.2.5.3　その他の重要な有害事象

3918 試験で、試験の中止に至った有害事象はなかった。

2.7.4.5.2.6　　結論

3918 試験においても、その他の臨床薬理試験のいずれにおいても、faster aspart の忍容性は高く、安全性上の問題は認められなかった（試験の概観は図 2.7.4.1-1、各試験の総括報告書は Module 5 参照）。

2.7.4.5.3　　検証的試験における日本人集団と全集団の安全性の結果の一貫性の検討

2.7.4.5.3.1　　評価方法

日本人集団及び全集団の比較は、2 つの検証的試験である 4131 及び 4101 試験に基づく。4131 及び 4101 試験は、「国際共同治験に関する基本的考え方（平成 19 年 9 月 28 日付、薬食審査発第 0928010 号厚生労働省医薬食品局審査管理課長通知）」に従い、国際共同試験として実施した[2]（詳細は 2.7.4.1.1.2.5 項）ことから、両試験の結果に基づき、日本人集団と全集団間の一貫性を検討した。2.7.4.5.3 項では、4131 及び 4101 試験における、日本人集団の一部の有害事象の結果及び重大な又は血糖値確定低血糖の事象を提示する。日本人集団に関するすべての図表は、M 5.3.5.1 参照。

2.7.4.5.3.2　　4131 試験（成人 1 型糖尿病患者）における日本人集団と全集団の結果の一貫性の検討

2.7.4.5.3.2.1　被験者の内訳

Module 2.7.3.3.3.5.1 参照。

2.7.4.5.3.2.2　ベースラインの人口統計学的特性及び糖尿病特性

日本人集団と全集団間でベースラインの人口統計学的特性に特記すべき違いはみられなかったが、日本人集団では全集団と比較して、BMI が低く、年齢が高く、また糖尿病罹患期間が短かった（Module 2.7.3.3.3.5.1）。

両集団間の年齢、BMI 及び糖尿病罹患期間の違いによる安全性（有害事象及び重篤な有害事象）への影響についての結果及び評価を以下に提示する。年齢、BMI 及び糖尿病罹患期間による有効性（HbA1c）への影響については、Module 2.7.3.3.3.5.1 参照。

年齢、BMI 及び糖尿病罹患期間に、日本人集団と全集団間でわずかな違いが認められたものの、その違いによる安全性の結果への顕著な影響は認められなかった。

ベースラインの年齢

日本人集団及び全集団のいずれにおいても、faster aspart（食前投与）群及びノボラピッド®注群では、若年の年齢グループと比較して高齢の年齢グループで有害事象の単位時間あたりの発現件数が多かった。Faster aspart（食後投与）群では、日本人集団及び全集団のいずれにおいても、年齢グループ間で

同程度の結果であった。日本人集団及び全集団のいずれにおいても、若年の年齢グループでは、投与群間で有害事象の単位時間あたりの発現件数は同程度であった（表 2.7.4.5-1）。

ベースラインの BMI

全集団では、いずれの投与群においても、BMI が高くなると有害事象の単位時間あたりの発現件数が増加した。日本人集団では、BMI が高いグループの被験者数が非常に少なかったことから、BMI が高いグループの評価を行うことは困難であった。日本人集団及び全集団とも、faster aspart（食後投与）群を除くいずれの投与群においても、BMI が低いグループと BMI が中程度のグループで有害事象の単位時間あたりの発現件数は同程度であった（表 2.7.4.5-2）。日本人集団及び全集団ともに faster aspart（食後投与）群では、BMI が低いグループと比較して、BMI が中程度のグループで有害事象の単位時間あたりの発現件数が多かった。

ベースラインの糖尿病罹患期間

日本人集団及び全集団のいずれにもおいても、すべての投与群で、糖尿病罹患期間が短いグループに対して罹患期間が長いグループで有害事象の単位時間あたりの発現件数が多かった（表 2.7.4.5-3）。

両集団間のベースライン特性の一貫性の詳細は、Module 2.7.3.3.3.2 及び Module 2.7.3.3.3.3 参照。

表 2.7.4.5-1　有害事象及び重篤な有害事象－治験薬投与下で発現－要約－ベースラインの年齢別－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Japanese Subgroup												
Number of subjects												
18 - <65 years	69				71				75			
>= 65 years	4				18				8			
Total exposure (yrs)												
18 - <65 years	34.6				35.4				36.3			
>= 65 years	2.0				8.6				4.0			
Adverse events												
18 - <65 years	50	(72.5)	128	369.9	55	(77.5)	142	401.3	61	(81.3)	146	402.2
>= 65 years	4	(100)	11	545.9	12	(66.7)	32	372.5	7	(87.5)	21	523.9
Serious adverse events												
18 - <65 years	4	(5.8)	7	20.2	2	(2.8)	2	5.7	4	(5.3)	4	11.0
>= 65 years	1	(25.0)	3	148.9	0				1	(12.5)	1	24.9
Entire Trial Population												
Number of subjects												
18 - <65 years	322				319				323			
>= 65 years	20				22				19			
Total exposure (yrs)												
18 - <65 years	161.4				159.5				160.6			
>= 65 years	9.8				10.7				9.6			
Adverse events												
18 - <65 years	222	(68.9)	595	368.6	223	(69.9)	616	386.1	235	(72.8)	587	365.5
>= 65 years	18	(90.0)	54	548.9	14	(63.6)	40	374.8	13	(68.4)	40	418.3
Serious adverse events												
18 - <65 years	18	(5.6)	22	13.6	17	(5.3)	23	14.4	16	(5.0)	18	11.2
>= 65 years	2	(10.0)	5	50.8	0				1	(5.3)	1	10.5

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.

表 2.7.4.5-2　有害事象及び重篤な有害事象－治験薬投与下で発現－要約－ベースラインの BMI 別－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Japanese Subgroup												
Number of subjects												
< 25 kg/m^2	52				64				63			
>= 25 - < 30 kg/m^2	18				21				18			
>= 30 kg/m^2	3				4				2			
Total exposure (yrs)												
< 25 kg/m^2	26.0				31.7				30.3			
>= 25 - < 30 kg/m^2	9.1				10.2				9.0			
>= 30 kg/m^2	1.5				2.0				1.0			
Adverse events												
< 25 kg/m^2	37	(71.2)	97	372.4	44	(68.8)	113	356.2	52	(82.5)	126	416.0
>= 25 - < 30 kg/m^2	14	(77.8)	34	375.2	20	(95.2)	54	528.2	14	(77.8)	37	410.4
>= 30 kg/m^2	3	(100)	8	531.3	3	(75.0)	7	344.1	2	(100)	4	397.0
Serious adverse events												
< 25 kg/m^2	3	(5.8)	6	23.0	1	(1.6)	1	3.2	4	(6.3)	4	13.2
>= 25 - < 30 kg/m^2	2	(11.1)	4	44.1	1	(4.8)	1	9.8	1	(5.6)	1	11.1
>= 30 kg/m^2	0				0				0			
Entire Trial Population												
Number of subjects												
< 25 kg/m^2	190				185				194			
>= 25 - < 30 kg/m^2	105				104				99			
>= 30 kg/m^2	47				52				49			
Total exposure (yrs)												
< 25 kg/m^2	95.1				92.7				95.6			
>= 25 - < 30 kg/m^2	52.7				51.3				50.2			
>= 30 kg/m^2	23.4				26.3				24.4			
Adverse events												
< 25 kg/m^2	123	(64.7)	328	344.8	123	(66.5)	307	331.3	135	(69.6)	333	348.2
>= 25 - < 30 kg/m^2	81	(77.1)	217	411.5	75	(72.1)	224	437.1	73	(73.7)	182	362.7
>= 30 kg/m^2	36	(76.6)	104	444.2	39	(75.0)	125	475.2	40	(81.6)	112	459.6
Serious adverse events												
< 25 kg/m^2	8	(4.2)	12	12.6	9	(4.9)	10	10.8	10	(5.2)	11	11.5
>= 25 - < 30 kg/m^2	10	(9.5)	13	24.7	7	(6.7)	12	23.4	4	(4.0)	5	10.0
>= 30 kg/m^2	2	(4.3)	2	8.5	1	(1.9)	1	3.8	3	(6.1)	3	12.3

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.

表 2.7.4.5-3　有害事象及び重篤な有害事象－治験薬投与下で発現－要約－ベースラインの糖尿病罹病期間別－on-treatment 観察期間－安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Japanese Subgroup												
Number of subjects												
< 15	46				61				45			
>= 15	27				28				38			
Total exposure (yrs)												
< 15	23.0				29.6				21.8			
>= 15	13.6				14.3				18.5			
Adverse events												
< 15	31	(67.4)	66	286.8	47	(77.0)	110	371.0	36	(80.0)	88	403.7
>= 15	23	(85.2)	73	536.6	20	(71.4)	64	446.6	32	(84.2)	79	426.7
Serious adverse events												
< 15	3	(6.5)	6	26.1	2	(3.3)	2	6.7	1	(2.2)	1	4.6
>= 15	2	(7.4)	4	29.4	0				4	(10.5)	4	21.6
Entire Trial Population												
Number of subjects												
< 15	177				190				175			
>= 15	165				151				167			
Total exposure (yrs)												
< 15	88.6				93.9				86.8			
>= 15	82.7				76.3				83.4			
Adverse events												
< 15	121	(68.4)	301	339.7	129	(67.9)	318	338.8	119	(68.0)	291	335.3
>= 15	119	(72.1)	348	421.0	108	(71.5)	338	442.7	129	(77.2)	336	402.9
Serious adverse events												
< 15	7	(4.0)	10	11.3	10	(5.3)	12	12.8	8	(4.6)	9	10.4
>= 15	13	(7.9)	17	20.6	7	(4.6)	11	14.4	9	(5.4)	10	12.0

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events
occurring in the run-in period.

2.7.4.5.3.2.3　有害事象

日本人集団では全集団と同様、有害事象の単位時間あたりの発現件数及び事象を報告した被験者の割合について、投与群間で臨床的に意味のある違いは認められなかった（表 2.7.4.5-4）。

日本人集団及び全集団の間でも、有害事象の種類（重症度、重篤性、及び治験薬との因果関係）及び発現頻度に顕著な違いはみられなかった。

全体的に、最も高頻度で報告された有害事象は、日本人集団及び全集団の間で同様であった〔Trial 4131（M 5.3.5.1）EOT Table 14.3.1.5（Japanese subgroup）及び EOT Table 14.3.1.7〕。

2.7.4.5.3.2.4　有害事象と治験薬との因果関係

日本人集団及び全集団のいずれにおいても、有害事象の治験薬との因果関係の分布は各投与群とも同様であり、また事象の大部分は治験責任医師により無作為割り付けされた治験薬との因果関係は「なし」と判定された。

2.7.4.5.3.2.5　重篤な有害事象及び治験薬投与の中止に至った有害事象

本試験で報告された重篤な有害事象の件数は、非常に少数であった。3 つの投与群間及び両集団間のいずれにおいても、重篤な有害事象を報告した被験者の数に顕著な違いはみられなかった（表 2.7.4.5-4）。重篤な有害事象の単位時間あたりの発現件数は、faster aspart（食前投与）群で 27.3（日本人集団）及び 15.8 件/100 人・年（全集団）、faster aspart（食後投与）群で 4.5（日本人集団）及び 13.5 件/100 人・年（全集団）、ならびにノボラピッド®注群で 12.4（日本人集団）及び 11.2 件/100 人・年（全集団）であった（表 2.7.4.5-4）。

試験を通じて、投与の中止に至った有害事象は 1 件のみ（ノボラピッド®注群の日本人被験者 1 例で報告）であった。

表 2.7.4.5-4 有害事象の概観－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団－日本人集団及び全集団（4131 試験）

	Japanese subgroup												Entire trial population											
	Faster aspart (meal)				Faster aspart (post)				NovoRapid (meal)				Faster aspart (meal)				Faster aspart (post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	73				89				83				342				341				342			
Total exposure (yrs)	36.6				44.0				40.3				171.3				170.2				170.2			
Total events	54	(74.0)	139	379.6	67	(75.3)	174	395.7	68	(81.9)	167	414.3	240	(70.2)	649	378.9	237	(69.5)	656	385.4	248	(72.5)	627	368.5
Serious																								
Yes	5	(6.8)	10	27.3	2	(2.2)	2	4.5	5	(6.0)	5	12.4	20	(5.8)	27	15.8	17	(5.0)	23	13.5	17	(5.0)	19	11.2
No	52	(71.2)	129	352.3	67	(75.3)	172	391.1	66	(79.5)	162	401.9	237	(69.3)	622	363.2	232	(68.0)	633	371.9	243	(71.1)	608	357.3
Severity																								
Severe	1	(1.4)	3	8.2	2	(2.2)	2	4.5	3	(3.6)	3	7.4	13	(3.8)	17	9.9	13	(3.8)	21	12.3	15	(4.4)	17	10.0
Moderate	5	(6.8)	6	16.4	5	(5.6)	5	11.4	6	(7.2)	7	17.4	70	(20.5)	111	64.8	61	(17.9)	103	60.5	59	(17.3)	81	47.6
Mild	52	(71.2)	130	355.0	65	(73.0)	167	379.7	65	(78.3)	157	389.5	224	(65.5)	521	304.2	213	(62.5)	532	312.6	223	(65.2)	529	310.9
Related to randomised trial product																								
Probable	11	(15.1)	18	49.2	16	(18.0)	23	52.3	11	(13.3)	15	37.2	40	(11.7)	50	29.2	31	(9.1)	44	25.9	24	(7.0)	29	17.0
Possible	12	(16.4)	14	38.2	9	(10.1)	11	25.0	12	(14.5)	16	39.7	32	(9.4)	35	20.4	24	(7.0)	30	17.6	24	(7.0)	28	16.5
Unlikely	50	(68.5)	102	278.6	57	(64.0)	132	300.1	59	(71.1)	127	315.0	215	(62.9)	519	303.0	206	(60.4)	532	312.6	218	(63.7)	520	305.6
Missing	5	(6.8)	5	13.7	8	(9.0)	8	18.2	7	(8.4)	9	22.3	38	(11.1)	45	26.3	41	(12.0)	50	29.4	43	(12.6)	50	29.4
Related to basal component																								
Probable	7	(9.6)	10	27.3	10	(11.2)	14	31.8	9	(10.8)	11	27.3	38	(11.1)	47	27.4	32	(9.4)	42	24.7	26	(7.6)	34	20.0
Possible	13	(17.8)	19	51.9	10	(11.2)	14	31.8	14	(16.9)	15	37.2	43	(12.6)	54	31.5	32	(9.4)	42	24.7	35	(10.2)	37	21.7
Unlikely	51	(69.9)	109	297.7	60	(67.4)	146	332.0	61	(73.5)	137	339.8	202	(59.1)	501	292.5	201	(58.9)	512	300.8	214	(62.6)	510	299.7
Missing	1	(1.4)	1	2.7	0				3	(3.6)	4	9.9	26	(7.6)	47	27.4	21	(6.2)	60	35.3	25	(7.3)	46	27.0

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Technical complaint is related to randomised trial product.

Overview of adverse events - treatment emergent - summary - on-treatment - safety analysis set in Japanese subgroup and entire trial population in trial 4131

	Japanese subgroup												Entire trial population									
	Faster aspart (meal)				Faster aspart (post)				NovoRapid (meal)				Faster aspart (meal)				Faster aspart (post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Related to a technical complaint																								
Yes	0				0				0				0				1	(0.3)	1	0.6	0			
No	54	(74.0)	134	366.0	66	(74.2)	166	377.5	65	(78.3)	158	391.9	235	(68.7)	604	352.6	222	(65.1)	605	355.4	231	(67.5)	577	339.1
Missing	5	(6.8)	5	13.7	8	(9.0)	8	18.2	7	(8.4)	9	22.3	38	(11.1)	45	26.3	41	(12.0)	50	29.4	43	(12.6)	50	29.4
Outcome																								
Recovered /resolved	51	(69.9)	115	314.1	63	(70.8)	136	309.2	65	(78.3)	143	354.7	230	(67.3)	571	333.4	224	(65.7)	550	323.1	240	(70.2)	547	321.5
Recovering /resolving	2	(2.7)	2	5.5	5	(5.6)	7	15.9	4	(4.8)	4	9.9	15	(4.4)	19	11.1	17	(5.0)	22	12.9	14	(4.1)	15	8.8
Recovered /resolved with sequelae	0				0				1	(1.2)	1	2.5	1	(0.3)	1	0.6	0				1	(0.3)	1	0.6
Not recovered /not resolved	16	(21.9)	22	60.1	16	(18.0)	31	70.5	14	(16.9)	19	47.1	42	(12.3)	58	33.9	54	(15.8)	84	49.4	45	(13.2)	63	37.0
Fatal	0				0				0				0				0				0			
Unknown	0				0				0				0				0				1	(0.3)	1	0.6
Leading to premature discontinuation of randomised treatment																								
Yes	0				0				1	(1.2)	1	2.5	0				0				1	(0.3)	1	0.6
Leading to withdrawal from trial																								
Yes	0				0				1	(1.2)	1	2.5	0				0				1	(0.3)	1	0.6

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Technical complaint is related to randomised trial product.

2.7.4.5.3.2.6　低血糖

評価方法

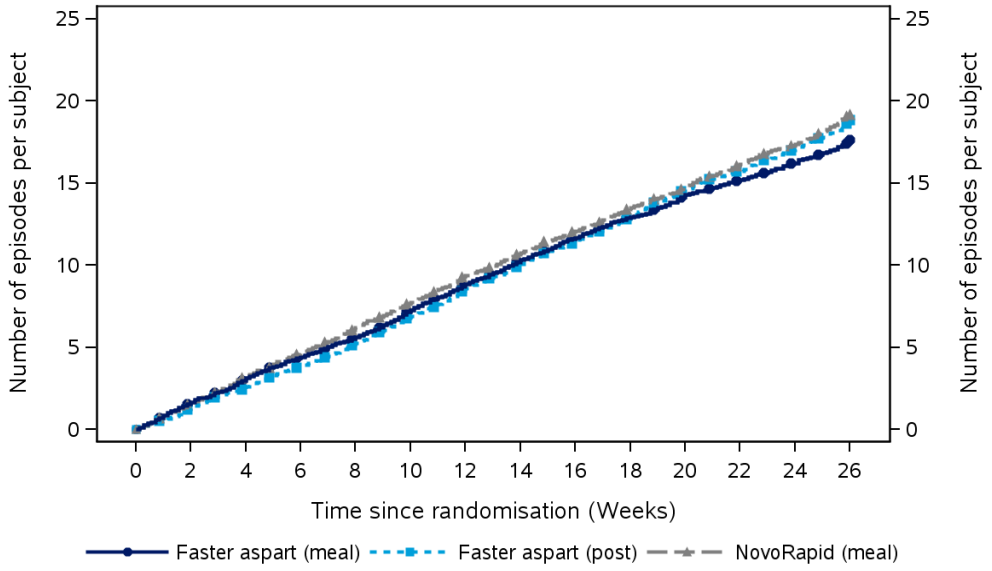
4131 試験の日本人集団及び全集団における重大な又は血糖値確定低血糖の要約を、表 2.7.4.5-5 に提示する。Faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群のいずれにおいても、日本人集団及び全集団の間で、重大な又は血糖値確定低血糖の単位時間あたりの発現件数に明らかな違いはみられなかった。

日本人集団及び全集団のいずれにおいても、重大な又は血糖値確定低血糖は、それぞれの投与群において、26 週の投与期間を通じて一定の頻度で報告された（図 2.7.4.5-1）。また、日本人集団及び全集団のいずれにおいても、重大な又は血糖値確定低血糖は、いずれの投与群においても同程度の頻度で報告された。日本人集団及び全集団のいずれにおいても、重大な又は血糖値確定低血糖の単位時間あたりの発現件数に、ノボラピッド®注群と比較して、faster aspart（食前投与）群及び faster aspart（食後投与）群とも統計的な有意差はみられなかった（表 2.7.4.5-6）。まとめると、日本人集団及び全集団のいずれにもおいても、faster aspart（食前投与）群及び faster aspart（食後投与）群の両投与群で、ノボラピッド®注群と比較した時、重大な又は血糖値確定低血糖の発現リスクの増加は認められなかった。

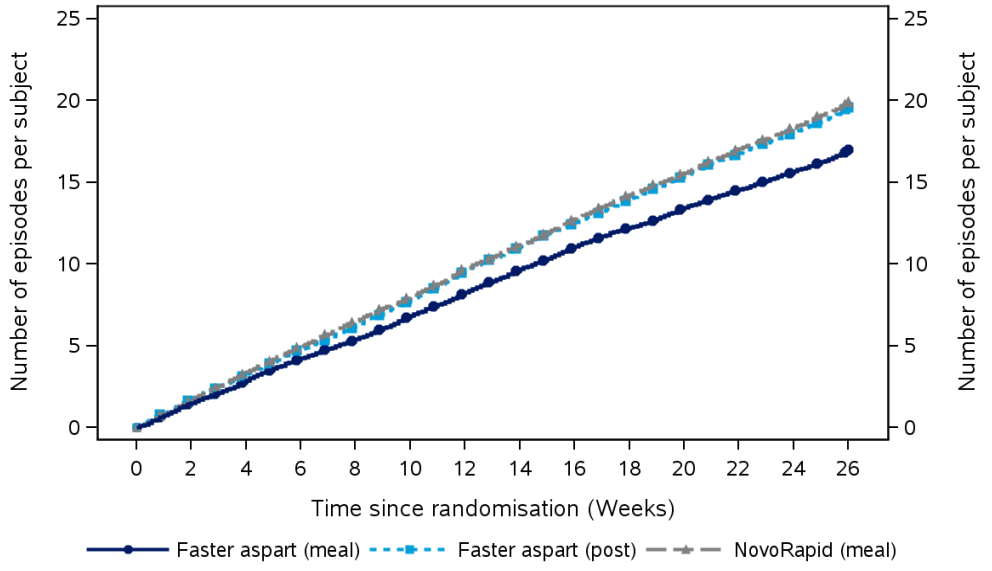
表 2.7.4.5-5 重大な又は血糖値確定低血糖－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団－日本人集団及び全集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Japanese subgroup									
Number of subjects	73			89			83		
Total exposure (yrs)	36.6			44.0			40.3		
Severe or BG confirmed	68 (93.2)	1302	3556	81 (91.0)	1659	3772	75 (90.4)	1562	3875
Entire trial population									
Number of subjects	342			341			342		
Total exposure (yrs)	171.3			170.2			170.2		
Severe or BG confirmed	304 (88.9)	5839	3409	295 (86.5)	6707	3940	302 (88.3)	6820	4008

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <56 mg/dL.



BG: Blood glucose
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.



BG: Blood glucose
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.

図 2.7.4.5-1　重大な又は血糖値確定低血糖－治験薬投与下で発現－平均累積関数－on-treatment 観察期間－安全性解析対象集団－日本人集団（上）及び全集団（下）（4131 試験）

表 2.7.4.5-6 重大な又は血糖値確定低血糖－治験薬投与下で発現－統計解析－on-treatment 観察期間－最大の解析対象集団－日本人集団及び全集団（4131 試験）

	Full analysis set	N	Estimate	95% CI	p-value*
Japanese subgroup					
LSmeans, events per 100 PYE					
Faster aspart (meal)	73	73	3513.16		
Faster aspart (post)	89	89	3678.27		
NovoRapid (meal)	83	83	3836.97		
Treatment ratio					
Faster aspart (meal) / NovoRapid (meal)			0.92	[0.65; 1.29]	0.612
Faster aspart (post) / NovoRapid (meal)			0.96	[0.69; 1.33]	0.798
Entire trial population					
LSmeans, events per 100 PYE					
Faster aspart (meal)	342	342	3372.44		
Faster aspart (post)	341	341	3883.87		
NovoRapid (meal)	342	342	4000.48		
Treatment ratio					
Faster aspart (meal) / NovoRapid (meal)			0.84	[0.70; 1.01]	0.065
Faster aspart (post) / NovoRapid (meal)			0.97	[0.81; 1.16]	0.750

ADA: American Diabetes Association, BG: Blood glucose, CI: Confidence interval, N: Number of subjects, PYE: Patient years of exposure
*p-values are from the 2-sided test for treatment ratio evaluated at the 5% level.
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <56 mg/dL.
Number of hypoglycaemic episodes is analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model includes treatment, region (for entire trial population only) and bolus adjusting method at randomisation as factors.

2.7.4.5.3.3　4101 試験（小児及び青年期の 1 型糖尿病患者）における日本人集団と全集団の結果の一貫性の検討

2.7.4.5.3.3.1　被験者の内訳

Module 2.7.3.3.3.5.2 参照。

2.7.4.5.3.3.2　ベースラインの人口統計学的特性及び糖尿病特性

日本人集団と全集団間で、ベースラインの人口統計学的特性に特筆すべき違いはみられなかった（詳細は Module 2.7.3.3.3.5.2）。

2.7.4.5.3.3.3　有害事象

全集団での結果と同様、日本人集団における有害事象の単位時間あたりの発現件数及び事象を報告した被験者の割合には、全体として投与群間で臨床的に意味のある違いは認められなかった（表 2.7.4.5-7）。

全体としては、有害事象の重症度及び発現頻度に関して、日本人集団及び全集団の間に顕著な違いはみられなかった。事象の重篤性、及び治験薬との因果関係については、日本人集団内の投与群間で若干の違いがみられた。

全体的に、最も高頻度で報告された有害事象は、日本人集団及び全集団で同様であった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.9（Japanese subgroup）及び Table 14.3.1.11〕。

2.7.4.5.3.3.4　有害事象と治験薬との因果関係

日本人集団及び全集団のいずれにおいても、有害事象の大部分は治験責任医師により無作為割り付けされた治験薬との因果関係は「なし」と判定された（表 2.7.4.5-7）。無作為割り付けされた治験薬との因果関係が「あり」と判定された有害事象の単位時間あたりの発現件数は、各投与群間及び両集団間を通じて faster aspart（食後投与）群の日本人集団（66.0 件/100 人・年；4 例 6 件の報告）が数値的に多く、このうち 2 件の有害事象（偶発的過量投与及び低血糖性意識消失）は同じ 1 例から同日に報告され、中等度かつ重篤な事象に分類された。しかしながら、日本人集団において無作為割り付けされた治験薬との因果関係が「あり」と判定されたその他の有害事象はすべて、軽度かつ非重篤と判定された〔Trial 4101（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.3〕。

2.7.4.5.3.3.5　重篤な有害事象及び治験薬投与の中止に至った有害事象

本試験で報告された重篤な有害事象の件数は非常に少なかった。重篤な有害事象の単位時間あたりの発現件数は、日本人集団のその他の投与群と比較して faster aspart（食後投与）群で数値的に多く

（44.0 件/100 人・年、3 例 4 件）、このうち 2 件の重篤な有害事象（偶発的過量投与及び低血糖性意識消失）は、同じ 1 例から同日に報告されたものだった（表 2.7.4.5-7）。重篤な有害事象の単位時間あたりの発現件数は、faster aspart（食前投与）群で 0（日本人集団）及び 5.5 件/100 人・年（全集団）、faster aspart（食後投与）群で 44.0（日本人集団）及び 11.8 件/100 人・年（全集団）、ならびにノボラピッド®注群で 17.8（日本人集団）及び 10.2 件/100 人・年（全集団）であった。

試験期間を通じて、治験薬投与の中止に至った有害事象はなかった。

表 2.7.4.5-7 有害事象の概観－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団－日本人集団及び全集団（4101 試験）

	Japanese subgroup						Entire trial population					
	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)		
	N	(%)	E R	N	(%)	E R	N	(%)	E R	N	(%)	E R	N	(%)	E R	N	(%)	E R
Number of subjects	24			19			23			261			258			258		
Total exposure (yrs)	11.7			9.1			11.2			128.4			127.7			127.7		
Total events	19	(79.2)	57 487.6	16	(84.2)	50 550.4	21	(91.3)	63 561.9	193	(73.9)	576 448.6	199	(77.1)	678 531.1	203	(78.7)	593 464.5
Serious																		
Yes	0			3	(15.8)	4 44.0	1	(4.3)	2 17.8	5	(1.9)	7 5.5	13	(5.0)	15 11.8	9	(3.5)	13 10.2
No	19	(79.2)	57 487.6	16	(84.2)	46 506.4	21	(91.3)	61 544.1	192	(73.6)	569 443.2	199	(77.1)	663 519.4	202	(78.3)	580 454.3
Severity																		
Severe	0			1	(5.3)	1 11.0	1	(4.3)	1 8.9	3	(1.1)	4 3.1	7	(2.7)	9 7.1	3	(1.2)	4 3.1
Moderate	3	(12.5)	6 51.3	5	(26.3)	7 77.1	4	(17.4)	5 44.6	52	(19.9)	80 62.3	58	(22.5)	100 78.3	51	(19.8)	77 60.3
Mild	19	(79.2)	51 436.2	14	(73.7)	42 462.3	20	(87.0)	57 508.4	178	(68.2)	492 383.2	185	(71.7)	569 445.7	186	(72.1)	512 401.0
Related to randomised trial product																		
Probable	1	(4.2)	1 8.6	4	(21.1)	6 66.0	1	(4.3)	1 8.9	10	(3.8)	12 9.3	13	(5.0)	16 12.5	11	(4.3)	12 9.4
Possible	0			0			1	(4.3)	1 8.9	3	(1.1)	3 2.3	6	(2.3)	7 5.5	9	(3.5)	12 9.4
Unlikely	19	(79.2)	56 479.0	16	(84.2)	44 484.4	21	(91.3)	61 544.1	192	(73.6)	547 426.0	196	(76.0)	647 506.8	200	(77.5)	559 437.9
Missing	0			0			0			14	(5.4)	14 10.9	8	(3.1)	8 6.3	10	(3.9)	10 7.8
Related to basal component																		
Probable	1	(4.2)	1 8.6	2	(10.5)	3 33.0	1	(4.3)	1 8.9	4	(1.5)	6 4.7	15	(5.8)	19 14.9	15	(5.8)	15 11.7
Possible	0			0			0			10	(3.8)	12 9.3	9	(3.5)	9 7.1	11	(4.3)	13 10.2
Unlikely	19	(79.2)	56 479.0	16	(84.2)	47 517.4	21	(91.3)	62 553.0	193	(73.9)	558 434.6	199	(77.1)	650 509.2	201	(77.9)	564 441.8
Missing	0			0			0			0			0			1	(0.4)	1 0.8

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Technical complaint is related to randomised trial product.

Overview of adverse events - treatment emergent - summary - on-treatment - safety analysis set in the Japanese subgroup and the entire trial population in trial 4101

	Japanese subgroup								Entire trial population							
	Faster aspart (meal)				Faster aspart (post)				NovoRapid (meal)				Faster aspart (meal)				Faster aspart (post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Related to a technical complaint																								
Yes	0				0				0				2	(0.8)	2	1.6	0				1	(0.4)	1	0.8
No	19	(79.2)	57	487.6	16	(84.2)	50	550.4	21	(91.3)	63	561.9	193	(73.9)	560	436.2	197	(76.4)	670	524.9	202	(78.3)	582	455.9
Missing	0				0				0				14	(5.4)	14	10.9	8	(3.1)	8	6.3	10	(3.9)	10	7.8
Outcome																								
Recovered /resolved	19	(79.2)	52	444.8	16	(84.2)	47	517.4	21	(91.3)	62	553.0	187	(71.6)	538	419.0	196	(76.0)	647	506.8	202	(78.3)	573	448.8
Recovering /resolving	2	(8.3)	2	17.1	1	(5.3)	1	11.0	1	(4.3)	1	8.9	12	(4.6)	14	10.9	8	(3.1)	8	6.3	9	(3.5)	10	7.8
Recovered /resolved with sequelae	0				0				0				0				1	(0.4)	1	0.8	3	(1.2)	3	2.3
Not recovered /not resolved	3	(12.5)	3	25.7	2	(10.5)	2	22.0	0				20	(7.7)	24	18.7	20	(7.8)	22	17.2	6	(2.3)	7	5.5
Fatal	0				0				0				0				0				0			
Unknown	0				0				0				0				0				0			
Missing	0				0				0				0				0				0			
Leading to premature discontinuation of randomised treatment																								
Yes	0				0				0				0				0				0			
Leading to withdrawal from trial																								
Yes	0				0				0				0				0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Technical complaint is related to randomised trial product.

2.7.4.5.3.3.6　低血糖

日本人集団及び全集団における、重大な又は血糖値確定低血糖の要約を、表 2.7.4.5-8 に提示する。

重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、全集団ではいずれの投与群においても同程度であった一方、日本人集団では投与群間でわずかに差がみられた。Faster aspart（食後投与）群及びノボラピッド®注群における単位時間あたりの発現件数は、全集団よりも日本人集団で多かったが、faster aspart（食前投与）群での単位時間あたりの発現件数は、両集団において同程度であった。日本人集団における単位時間あたりの発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 2429、4910 及び 3684 件/100 人・年であった。

一方、重大な又は血糖値確定低血糖を報告した被験者の割合について、日本人集団の投与群間と全集団の投与群間のバランスに明らかな違いはなかった。日本人集団の投与群間でみられた低血糖の単位時間あたりの発現件数の違いについては、数例の被験者が多数の重大な又は血糖値確定低血糖を報告したことが原因の一つとして考えられる〔Trial 4101（M 5.3.5.1）EOT Figure 14.3.1.58（Japanese subgroup）〕。投与期間に faster aspart（食後投与）群の日本人被験者のうち、17 例で報告された 446 件の重大な又は血糖値確定低血糖は、うち 139 件が 1 例で、また 58 件が別の 1 例で報告された（いずれの被験者も重大な低血糖は報告していない）〔Trial 4101（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.10〕。またノボラピッド®注群の計 23 例の日本人被験者で報告された 413 件の重大な又は血糖値確定低血糖のうち、94 件が 1 例の被験者で投与期間中に報告された（重大な低血糖 1 件を含む）。各投与群における日本人被験者は少数であったことから、日本人集団における単位時間あたりの発現件数の治療間の違いは上述のような多数の事象を報告した一部の被験者に起因する可能性がある。

日本人集団及び全集団のいずれにおいても、重大な又は血糖値確定低血糖は、それぞれの投与群において、26 週の投与期間を通じて一定の頻度で報告された（図 2.7.4.5-2）。日本人集団において、重大な又は血糖値確定低血糖は、faster aspart（食前投与）群ではノボラピッド®注群と比較して低い頻度で、faster aspart（食後投与）群ではノボラピッド®注群と比較して高い頻度で報告された。

2.7.4.1.1.2.5 項にも記載のとおり、4101 試験の日本人集団では投与群間の統計的比較を行わなかった。

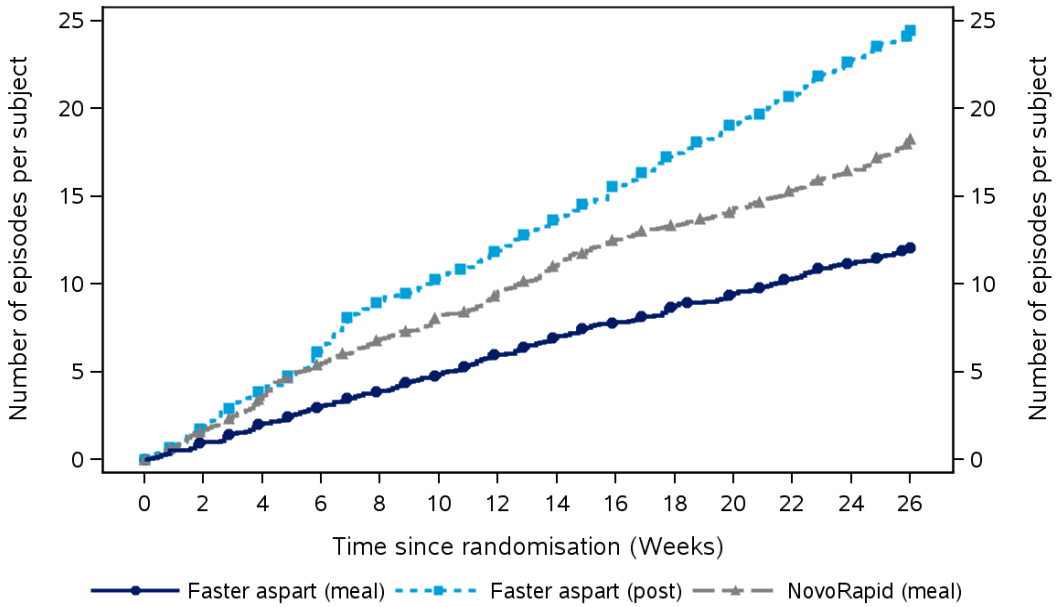
結論として、日本人集団と全集団間で重大な又は血糖値確定低血糖の単位時間あたりの発現件数にわずかに差があったが、低血糖を発現した被験者の割合に明らかな違いは認められなかった。日本人集団と全集団間で、重大な又は血糖値確定低血糖の発現について臨床的に意味のある差は認められなかった。

日本人集団における年齢グループ別の重大な又は血糖値確定低血糖の要約は、総括報告書〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.44～14.3.1.46（Japanese subgroup）〕参照。

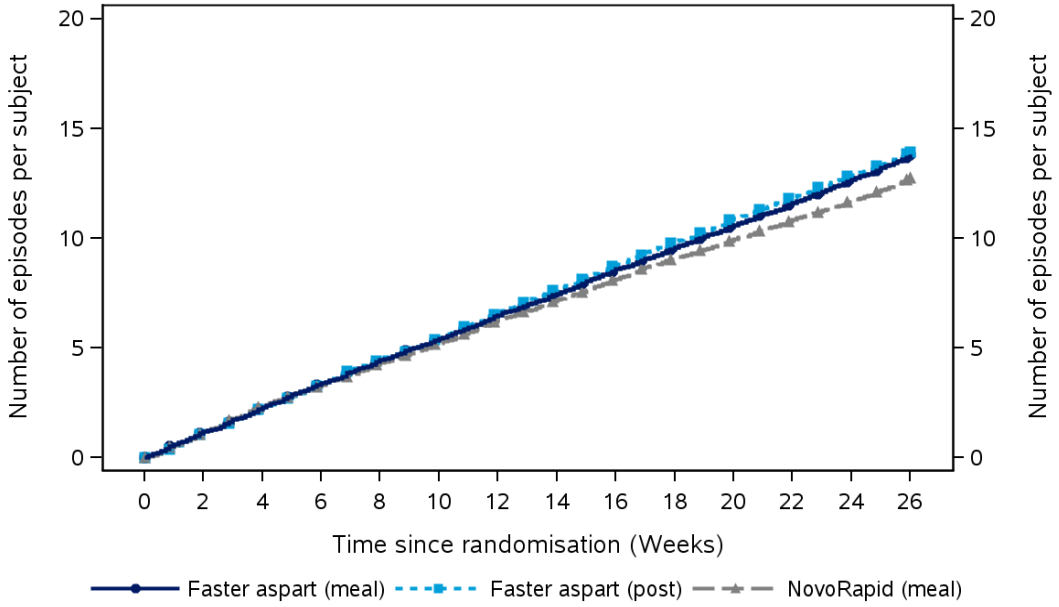
表 2.7.4.5-8　重大な又は血糖値確定低血糖－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団－日本人集団及び全集団（4101 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Japanese subgroup												
Number of subjects	24				19				23			
Total exposure (yrs)	11.7				9.1				11.2			
Severe or BG confirmed	21	(87.5)	284	2429	17	(89.5)	446	4910	23	(100.0)	413	3684
Entire trial population												
Number of subjects	261				258				258			
Total exposure (yrs)	128.4				127.7				127.7			
Severe or BG confirmed	228	(87.4)	3583	2791	227	(88.0)	3594	2815	217	(84.1)	3276	2566

%: Percentage of subjects, BG: Blood glucose, E: Number of events, ISPAD: International Society for Pediatric and Adolescent Diabetes, N: Number of subjects, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ISPAD 2014 classification and/or have a recorded PG <56 mg/dL.



BG: Blood glucose
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.



BG: Blood glucose
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.

図 2.7.4.5-2　　重大な又は血糖値確定低血糖－治験薬投与下で発現－平均累積関数－on-treatment 観察期間－安全性解析対象集団－日本人集団（上）及び全集団（下）（4101 試験）

2.7.4.5.3.4　　結論

全体として、4131 及び 4101 試験において、日本人集団及び全集団のベースライン特性について顕著な違いはみられなかった。

4131 試験の成人被験者ならびに 4101 試験の小児及び青年期被験者を通じ、日本人集団及び全集団では、有害事象、あるいは重大な又は血糖値確定低血糖について、臨床的に意味のある違いは認められなかった。4101 試験では、重大な又は血糖値確定低血糖の単位時間あたりの発現件数において日本人集団と全集団間でわずかに差があったが、事象を報告した被験者の割合に明らかな差はみられず、両集団間で重大な又は血糖値確定低血糖の発現について臨床的に意味のある差はないことが示唆された。

2.7.4.5.4　　成人 1 型糖尿病患者における内因性及び外因性民族的要因別の安全性

2.7.4.5.4.1　　評価方法

4131 試験の結果に基づき、faster aspart の安全性プロファイルに対する内因性及び外因性民族的要因による潜在的な影響を、各部分集団間で検討した。

安全性に対する内因性及び外因性民族的要因による潜在的な影響の評価は、主に faster aspart の両投与群とノボラピッド®注群間で有害事象の単位時間あたりの発現件数を比較することにより実施した。この内因性及び外因性民族的要因の評価では、投与のタイミングによる影響が予想されなかったため、これらの部分集団解析において faster aspart（食前投与）群及び faster aspart（食後投与）群のデータは併合した（以下、『faster aspart 併合群』とする）。なお、これら内因性及び外因性民族的要因による低血糖発現への潜在的影響について実施した評価は、2.7.4.2.4.3 項に提示する。

2.7.4.5.4.2　　4131 試験（成人 1 型糖尿病患者）における内因性民族的要因別の安全性

有害事象及び重篤な有害事象の、単位時間あたりの発現件数及び事象を報告した被験者の割合につき評価した結果、成人 1 型糖尿病患者において、投与群間で、内因性民族的要因に起因する臨床的に意味のある違いは認められなかった。ごく一部の部分集団間では異なる有害事象プロファイルがみられたが、これらは様々な比較を実施したこと、ならびに一部の部分集団では該当する被験者の数が比較的少なかったことを考慮すると、予測されるとおりの所見であった。内因性民族的要因に基づく各部分集団の比較結果を以下に提示する。それぞれの内因性民族的要因における有害事象及び重篤な有害事象の一覧は付録 2.7.4.7.3.2 に提示する。

人口統計学的特性に関連する内因性民族的要因

- 年齢：いずれの年齢グループにおいても、有害事象を報告した被験者の割合、及び全体的な有害事象の単位時間あたりの発現件数は、いずれの投与群においても同程度であった（表 2.7.4.5-9）。高齢の年齢グループ（65 歳以上）の faster aspart 群で報告された重篤な有害事象の単位時間あたりの発

現件数は、高齢の年齢グループのノボラピッド®注群、ならびに若年の年齢グループの faster aspart 併合群及びノボラピッド®注群のいずれと比較しても多かった。ただし、この結果は非常に少数の被験者の報告に基づいたものである（表 2.7.4.5-9）。いずれの年齢グループにおいても、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であった（付録 2.7.4.7.3.2、表 2.7.4.7.3.2-1 及び 2.7.4.7.3.2-2）。

- 性別：女性被験者及び男性被験者のいずれにおいても、有害事象及び重篤な有害事象の単位時間あたりの発現件数はいずれの投与群においても同程度であった（表 2.7.4.5-9）。
- ベースラインの BMI：BMI に基づく部分集団間の比較を行った場合、事象を報告した被験者の割合及び全体的な有害事象の単位時間あたりの発現件数は、ベースラインの BMI が高いグループ（30 kg/m^2 以上）でいずれの投与群においても最も多かった。しかしながら、BMI が高いグループにおける重篤な有害事象の単位時間あたりの発現件数は、faster aspart 併合群では他の BMI 別のグループと比較して最も低く、ノボラピッド®注群では他の BMI 別のグループと同程度であった（表 2.7.4.5-9）。BMI が中程度のグループ（25kg/m^2 以上 30 kg/m^2 未満）では、faster aspart 併合群における重篤な有害事象の単位時間あたりの発現件数が、ノボラピッド®注群ならびに他の BMI 別の部分集団の両投与群のいずれと比較しても多かった。BMI が低いグループ（25 kg/m^2 未満）では、有害事象及び重篤な有害事象を報告した被験者の割合及び単位時間あたりの発現件数は、両投与群とも同程度だった。BMI 別の部分集団のいずれにおいても、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であった（付録 2.7.4.7.3.2、表 2.7.4.7.3.2-5～2.7.4.7.3.2-7）。

糖尿病特性に関連する内因性民族的要因

- ベースラインの HbA1c：有害事象を報告した被験者の割合、ならびに有害事象及び重篤な有害事象の単位時間あたりの発現件数はいずれの投与群においても同程度であり、部分集団間で明らかな違いはみられなかった（表 2.7.4.5-10）。いずれの HbA1c 別の部分集団においても、最も高頻度で報告された事象は、ウイルス性上気道感染であった（付録 2.7.4.7.3.2、表 2.7.4.7.3.2-8 及び 2.7.4.7.3.2-9）。
- ベースラインの糖尿病罹患期間：糖尿病罹患期間の異なる 2 つの部分集団間で比較を行った場合、ベースラインの糖尿病罹患期間が長いグループでは、有害事象を報告した被験者の割合がノボラピッド®注群でわずかに高かった。また、有害事象の単位時間あたりの発現件数は、ベースラインの糖尿病罹患期間が長いグループの方が、いずれの投与群においてもわずかに多かった（表 2.7.4.5-10）。いずれの部分集団においても、最も高頻度で報告された事象は、ウイルス性上気道感染及び血中ブドウ糖減少であった（付録 2.7.4.7.3.2、表 2.7.4.7.3.2-10 及び 2.7.4.7.3.2-11）。

併発疾患に関連する内因性民族的要因

- 肝機能障害：肝機能障害を有する被験者と正常な肝機能を有する被験者の比較では、肝機能障害を有する被験者の部分集団で、いずれの投与群においても重篤な有害事象を報告した被験者の割合が

高かった。しかしながらベースラインで肝機能障害を有していた被験者は各投与群で約 6%のみであり、さらにこのうち重篤な有害事象を報告した被験者はごく少数であった（表 2.7.4.5-11）。肝機能障害を有する被験者の部分集団では、ノボラピッド®注群で、faster aspart 併合群ならびに正常な肝機能を有する被験者の部分集団の両投与群のいずれと比較しても、有害事象の単位時間あたりの発現件数が多かった。しかしながら、重篤な有害事象に関しては、報告した被験者の割合及び単位時間あたりの発現件数ともに、肝機能障害を有する被験者の部分集団の faster aspart 併合群で、ノボラピッド®注群ならびに正常な肝機能を有する被験者の部分集団の両投与群のいずれと比較しても多かった。いずれの部分集団においても、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及び血中ブドウ糖減少であった（付録 2.7.4.7.3.2、表 2.7.4.7.3.2-12 及び 2.7.4.7.3.2-13）。

- 腎機能障害：被験者の大部分は、正常な腎機能を有していた。腎機能障害を有する被験者の大部分は軽度の腎機能障害であり、中等度の腎機能障害を有する被験者は数例みられたが、重度の腎機能障害を有する被験者はいなかった。有害事象の単位時間あたりの発現件数はいずれの投与群においても、正常な腎機能を有する被験者の部分集団と比較して、軽度の腎機能障害を有する被験者の部分集団でわずかに多かった（表 2.7.4.5-11）。正常な腎機能を有する被験者の部分集団及び軽度の腎機能障害を有する被験者の部分集団いずれにおいても、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であった（付録 2.7.4.7.3.2、表 2.7.4.7.3.2-14 及び 2.7.4.7.3.2-15）。

表 2.7.4.5-9　人口統計学的特性に関連した内因性民族的要因別の有害事象及び重篤な有害事象の概観（4131 試験）

	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Age at baseline ≥18-< 65 years								
Number of subject	641				323			
Total exposure (yrs)	321.0				160.6			
SAEs	35	(5.5)	45	14.0	16	(5.0)	18	11.2
AEs	445	(69.4)	1211	377.3	235	(72.8)	587	365.5
Age at baseline >=65 years								
Number of subject	42				19			
Total exposure (yrs)	20.5				9.6			
SAEs	2	(4.8)	5	24.4	1	(5.3)	1	10.5
AEs	32	(76.2)	94	458.3	13	(68.4)	40	418.3
Females								
Number of subject	313				163			
Total exposure (yrs)	156.3				80.1			
SAEs	14	(4.5)	17	10.9	9	(5.5)	10	12.5
AEs	220	(70.3)	643	411.5	117	(71.8)	333	415.8
Males								
Number of subject	370				179			
Total exposure (yrs)	185.2				90.1			
SAEs	23	(6.2)	33	17.8	8	(4.5)	9	10.0
AEs	257	(69.5)	662	357.4	131	(73.2)	294	326.4
BMI at baseline <25 kg/m^2								
Number of subject	375				194			
Total exposure (yrs)	187.8				95.6			
SAEs	17	(4.5)	22	11.7	10	(5.2)	11	11.5
AEs	246	(65.6)	635	338.2	135	(69.6)	333	348.2
BMI at baseline ≥25-<30 kg/m^2								
Number of subject	209				99			
Total exposure (yrs)	104.0				50.2			
SAEs	17	(8.1)	25	24.0	4	(4.0)	5	10.0
AEs	156	(74.6)	441	424.1	73	(73.7)	182	362.7
BMI at baseline >= 30 kg/m^2								
Number of subject	99				49			
Total exposure (yrs)	49.7				24.4			
SAEs	3	(3.0)	3	6.0	3	(6.1)	3	12.3
AEs	75	(75.8)	229	460.6	40	(81.6)	112	459.6

%: Percentage of subjects within subgroup, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms. MedDRA version 20.0.

表 2.7.4.5-10　糖尿病特性に関連した内因性民族的要因別の有害事象及び重篤な有害事象の概観（4131 試験）

	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
HbA_{1c} at baseline < 8%								
Number of subject	545				276			
Total exposure (yrs)	272.4				137.1			
SAEs	27	(5.0)	40	14.7	13	(4.7)	15	10.9
AEs	375	(68.8)	1024	376.0	200	(72.5)	515	375.7
HbA_{1c} at baseline >= 8%								
Number of subject	138				66			
Total exposure (yrs)	69.1				33.1			
SAEs	10	(7.2)	10	14.5	4	(6.1)	4	12.1
AEs	102	(73.9)	281	406.6	48	(72.7)	112	338.4
Duration of diabetes at baseline <15 yrs								
Number of subject	367				175			
Total exposure (yrs)	182.5				86.8			
SAEs	17	(4.6)	22	12.1	8	(4.6)	9	10.4
AEs	250	(68.1)	619	339.2	119	(68.0)	291	335.3
Duration of diabetes at baseline ≥15 yrs								
Number of subject	316				167			
Total exposure (yrs)	159.0				83.4			
SAEs	20	(6.3)	28	17.6	9	(5.4)	10	12.0
AEs	227	(71.8)	686	431.4	129	(77.2)	336	402.9

%: Percentage of subjects within subgroup, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms. MedDRA version 20.0.

表 2.7.4.5-11　併発疾患に関連した内因性民族的要因別の有害事象及び重篤な有害事象の概観（4131 試験）

	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Hepatic impairment at baseline: no								
Number of subject	638				318			
Total exposure (yrs)	318.6				158.1			
SAEs	32	(5.0)	44	13.8	15	(4.7)	17	10.8
AEs	448	(70.2)	1217	382.0	230	(72.3)	562	355.5
Hepatic impairment at baseline: yes								
Number of subject	45				24			
Total exposure (yrs)	22.9				12.1			
SAEs	5	(11.1)	6	26.2	2	(8.3)	2	16.6
AEs	29	(64.4)	88	384.0	18	(75.0)	65	538.0
Renal impairment at baseline: normal								
Number of subject	535				277			
Total exposure (yrs)	267.7				138.1			
SAEs	25	(4.7)	32	12.0	14	(5.1)	15	10.9
AEs	366	(68.4)	993	370.9	199	(71.8)	495	358.3
Renal impairment at baseline: mild								
Number of subject	137				58			
Total exposure (yrs)	68.7				28.5			
SAEs	12	(8.8)	18	26.2	3	(5.2)	4	14.0
AEs	104	(75.9)	292	425.0	44	(75.9)	117	410.5
Renal impairment at baseline: moderate								
Number of subject	11				7			
Total exposure (yrs)	5.1				3.5			
SAEs	0				0			
AEs	7	(63.6)	20	393.2	5	(71.4)	15	425.7
Renal impairment at baseline: severe								
Number of subject	0				0			
Total exposure (yrs)	0				0			
SAEs	0				0			
AEs	0				0			

%: Percentage of subjects within subgroup, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms. MedDRA version 20.0.

2.7.4.5.4.3　4131 試験（成人 1 型糖尿病患者）における外因性民族的要因別の安全性

外因性民族的要因（Bolus インスリン投与量の調節方法）別の部分集団及び投与群ごとの概要を、以下に提示する。外因性民族的要因別の有害事象及び重篤な有害事象の一覧表は、付録 2.7.4.7.3.2 を参照のこと。

有害事象及び重篤な有害事象の概括評価（事象の件数、単位時間あたりの発現件数及び事象を報告した被験者の割合）に基づき、成人 1 型糖尿病患者において、外因性民族的要因による部分集団間で臨床的に意味のある違いは認められなかった。

Bolus インスリン投与量の調節方法別に、投与群ごとの有害事象及び重篤な有害事象の概要を表 2.7.4.5-12 に提示する。有害事象及び重篤な有害事象を報告した被験者の割合及び単位時間あたりの発現件数は、いずれの Bolus インスリン投与量の調節方法においても、faster aspart 併合群及びノボラピッド®注群で同程度であった。フレキシブルな Bolus インスリンの用量調節法（カーボカウント）を用いてインスリン投与量の調節を行った被験者は、事前に規定した Bolus インスリン投与量調節アルゴリズムを使用した被験者と比較してわずかに少なかった。両部分集団の比較では、いずれの投与群においても、Bolus インスリン投与量調節アルゴリズムを使用した被験者と比較して、カーボカウントを使用した部分集団では有害事象を報告した被験者の割合がわずかに高く、単位時間あたりの発現件数も多かった。一方、faster aspart 併合群の重篤な有害事象については、Bolus インスリン投与量調節アルゴリズムを使用した被験者と比較して、カーボカウントを使用した部分集団で重篤な有害事象を報告した被験者の割合が低く、単位時間あたりの発現件数も少なかった（表 2.7.4.5-12）。なお、本試験において、2 つの Bolus インスリン投与量の調節方法に対する被験者の無作為割り付けは実施していない（スクリーニング以前にフレキシブルな Bolus インスリンの用量調節法を使用していた被験者、ならびに同法について適切な指導を受けたと治験責任医師が判断した被験者は、投与期間中も本調節法を継続した。その他の被験者は、Bolus インスリン投与量調節アルゴリズムにより調節した）。

最も高頻度で報告された有害事象は、いずれの部分集団においても、ウイルス性上気道感染及び血中ブドウ糖減少に関するものであった（付録 2.7.4.7.3.2、表 2.7.4.7.3.2-18 及び 2.7.4.7.3.2-19）。血中ブドウ糖減少の単位時間あたりの発現件数は、いずれの投与群においても、カーボカウントを使用した被験者の部分集団でわずかに少なかった。重篤な有害事象として最も高頻度で報告された事象は、低血糖であった（付録 2.7.4.7.3.2、表 2.7.4.7.3.2-37 及び 2.7.4.7.3.2-38）。

表 2.7.4.5-12　Bolus インスリン投与量の調節に関連した外因性民族的要因別の有害事象及び重篤な有害事象の概観（4131 試験）

	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Bolus dosing algorithm								
Number of subject	391				206			
Total exposure (yrs)	195.7				102.4			
SAEs	27	(6.9)	38	19.4	10	(4.9)	11	10.7
AEs	253	(64.7)	621	317.3	142	(68.9)	329	321.4
Carbohydrate counting								
Number of subject	292				136			
Total exposure (yrs)	145.8				67.8			
SAEs	10	(3.4)	12	8.2	7	(5.1)	8	11.8
AEs	224	(76.7)	684	469.2	106	(77.9)	298	439.5

%: Percentage of subjects within subgroup, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years.Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms. MedDRA version 20.0.

2.7.4.5.4.4　結論

4131 試験において、内因性及び外因性民族的要因別の有害事象の種類は投与群間で同様であり、単位時間あたりの発現件数はいずれの投与群においても同程度であった。一部の部分集団内では投与群間で単位時間あたりの発現件数にわずかな違いがみられたものの、臨床的に意味のあるものではないと評価された。

2.7.4.5.5　小児及び青年期被験者の 1 型糖尿病患者における年齢別の安全性

2.7.4.5.5.1　4101 試験（小児及び青年期の 1 型糖尿病患者）における年齢別の安全性

2.7.4.5.5.1 項では、一部の安全性の結果（すべての有害事象、治験薬との因果関係が否定できない有害事象、重篤な有害事象、治験薬投与の中止に至った有害事象）について年齢グループ別（1 歳以上 6 歳未満、6 歳以上 12 歳未満及び 12 歳以上 18 歳未満）に提示する。年齢グループ別の有効性については、Module 2.7.3.3.3.6 を参照のこと。

有害事象

年齢グループ別のすべての有害事象、重篤な有害事象及び重度の有害事象を、表 2.7.4.5-13 に提示する。

表 2.7.4.5-13　年齢別の有害事象－要約－on-treatment 観察期間－安全性解析対象集団（4101 試験）

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Total events			
1 to < 6 years	9 (56.3) 33 411.7	10 (62.5) 46 575.6	8 (57.1) 22 314.6
6 to < 12 years	77 (76.2) 234 462.3	75 (75.8) 283 573.2	81 (80.2) 262 523.7
12 to < 18 years	107 (74.3) 309 443.0	114 (79.7) 349 496.5	114 (79.7) 309 437.4
Serious events			
1 to < 6 years	0	1 (6.3) 1 12.5	0
6 to < 12 years	4 (4.0) 5 9.9	5 (5.1) 7 14.2	4 (4.0) 6 12.0
12 to < 18 years	1 (0.7) 2 2.9	7 (4.9) 7 10.0	5 (3.5) 7 9.9
Severe events			
1 to < 6 years	0	1 (6.3) 1 12.5	0
6 to < 12 years	2 (2.0) 3 5.9	3 (3.0) 5 10.1	3 (3.0) 4 8.0
12 to < 18 years	1 (0.7) 1 1.4	3 (2.1) 3 4.3	0

Abbreviations: % = percentage of subjects; E = number of events; N = number of subjects; R: event rate per 100 patient years of exposure

3 つの年齢グループいずれにおいても、報告された有害事象の大部分は、器官別大分類の「感染症および寄生虫症」及び「胃腸障害」に分類される事象であった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.17～14.3.1.19〕。全体として、年齢グループ間で、有害事象の発現頻度及び種類に顕著な違いはみられなかった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.17～14.3.1.19〕。

器官別大分類「感染症および寄生虫症」に分類された事象のうち、3 つの年齢グループすべてで最も高頻度で報告された有害事象（基本語）は、ウイルス性上気道感染及び上気道感染であり、全集団でみられたものと一致した〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.11〕。器官別大分類「胃腸障害」に分類された事象のうち、最も高頻度で報告された有害事象（基本語）は、年齢グループ間で同様であり、1 歳以上 6 歳未満の年齢グループでは便秘、下痢及び嘔吐、6 歳以上 12 歳未満の年齢グループでは、嘔吐、腹痛及び下痢、ならびに 12 歳以上 18 歳未満の年齢グループでは腹痛、嘔吐及び悪心であった。さらに、器官別大分類「神経系障害」に分類される頭痛は、6 歳以上 12 歳未満の年齢グループ及び 12 歳以上 18 歳未満の年齢グループで高頻度に報告された〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.17～14.3.1.19〕。

有害事象と治験薬との因果関係

1 歳以上 6 歳未満の年齢グループで報告された有害事象のうち、無作為割り付けされた治験薬との因果関係が「あり」又は「可能性あり」と判定された事象はなかった。6 歳以上 12 歳未満の年齢グループで 30 件、12 歳以上 18 歳未満の年齢グループで 32 件の事象が、無作為割り付けされた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〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.2～14.3.1.4〕。無作為割り付けされた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は、3 つの投与群いずれにおいても報告頻度が低く、有害事象の発現頻度及び種類に、治療又は年齢グループ間で顕著な違いはみられなかった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.27 及び 14.3.1.28〕。

重篤な有害事象及び治験薬投与の中止に至った有害事象

年齢グループ別の重篤な有害事象の要約を表 2.7.4.5-13 に提示する。1 歳以上 6 歳未満の年齢グループでは、faster aspart（食後投与）群で 1 件の重篤な有害事象（インフルエンザ）が報告されたが、同年齢グループでは、faster aspart（食前投与）群及びノボラピッド®注群では重篤な有害事象は報告されなかった（表 2.7.4.5-13）〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.21〕。

重篤な有害事象は、6 歳以上 12 歳未満の年齢グループ全体で 18 件、12 歳以上 18 歳未満の年齢グループで 16 件報告された。いずれの年齢グループにおいても、報告された重篤な有害事象は一部の器官別大分類に限られており、また事象の種類と投与群に特有の発現パターンは認められなかった。各年齢グループのいずれかの投与群において、複数の被験者で報告された重篤な有害事象は、偶発的過量投与及び低血糖性意識消失〔いずれも 6 歳以上 12 歳未満の年齢グループの faster aspart（食後投与）群の 2 例で報告〕ならびに胃腸炎（12 歳以上 18 歳未満の年齢グループのノボラピッド®注群の 2 例で報告）のみであり、他は 1 例ずつの報告であった〔Trial 4101（M 5.3.5.1）EOT Table 14.3.1.22 及び 14.3.1.23〕。

2.7.4.5.6　　薬物相互作用

4131 及び 4101 試験において薬物相互作用の検討は行っていない。

一般的に用いられる薬剤には、糖代謝に影響を及ぼし、血糖値に影響を与える可能性があることが知られている。高血糖を引き起こすおそれのある薬剤（血糖値を上げる薬剤）としては、利尿剤、ジアゾキシド、糖質ステロイド、甲状腺ホルモン、グルカゴン、交感神経 β 受容体作動薬、成長ホルモン、ホルモン避妊薬などが挙げられる。低血糖を引き起こすおそれのある薬剤（血糖値を下げる薬剤）としては、モノアミン酸化酵素阻害剤、β-遮断剤、アンジオテンシン変換酵素阻害薬、サリチル酸誘導体などが挙げられる。なお、β-遮断剤との併用では、低血糖症状が現れにくくなる可能性がある。

2.7.4.5.7　　妊娠及び授乳期の使用

Faster aspart については妊婦及び授乳女性を対象とした検討は実施しておらず、本剤のヒト母乳への移行や授乳児への影響に関する情報は得られていない。そのため、妊娠中及び授乳期の潜在的リスクは現時点で不明である。

Faster aspart 開発プログラムでは「妊婦（妊娠した場合）又は妊娠を希望する場合」を除外基準として規定しており、妊娠する可能性のある女性に対しては避妊を行うよう求めた。試験中に妊娠した又は妊娠を希望した女性被験者は、直ちに治験薬の投与を中止することとした。4131 及び 4101 試験では、妊娠した又は妊娠を希望した女性被験者は、run-in 期間であれば試験を中止することとしたが、その他の試験ではいずれの期間においても試験を中止することと規定した。詳細については 2.7.4.3.6.1 項を参照のこと。

4131 試験では 4 例が妊娠により治験薬投与を中止し、内訳は 1 例が faster aspart（食前投与）群、1 例が faster aspart（食後投与）群、2 例がノボラピッド®注群であった〔Trial 4131（M 5.3.5.1）Appendix 16.2.1、Listing 16.2.1.3〕。さらに別の 1 例が投与終了来院の翌日に妊娠陽性と判定された〔Trial 4131（M 5.3.5.1）Section 12.7.5〕。

4101 試験では妊娠は報告されなかった。

3854 試験ではノボラピッド®注群の 1 例が妊娠により治験薬の投与を中止した〔Trial 3854（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.1〕。さらに別の 1 例の妊娠が事後調査期間中に報告された〔Trial 3854（M 5.3.5.1）Section 12.11.4〕。

3852 試験（52 週）では妊娠が 6 件報告され、6 例とも試験を中止した〔Trial 3852 (M 5.3.5.1), Appendix 16.2.1, Listing 2 and 3〕。さらに別の 1 例の妊娠が事後調査期間中に報告された〔Trial 3852（M 5.3.5.1）Section 12.8.4〕。

本データパッケージに含めた他の臨床試験（図 2.7.4.1-1）及び進行中の試験では、妊娠は報告されなかった。

完了した試験における妊娠症例の簡潔な叙述を表 2.7.4.5-14 に示す。完了済み試験の詳細な叙述は Module 5.3.5.1 の個々の総括報告書に含まれている。

表 2.7.4.5-14 完了した faster aspart 試験で報告された妊娠

Trial	Subject ID/Case	Age (years)	Treatment	Dates of treatment	Pregnancy outcome	Short narrative
3852	704020 399372	26	Faster aspart	16 Dec 2013 – 24 Jan 2014	Healthy child	The subject had a positive pregnancy test on 24 Jan 2014. Trial product was discontinued the same day. On 04 Sep 2014, the subject had an elective caesarean section and gave birth to a baby girl at GW 38. No health problems or congenital anomalies were reported at delivery.
3852	768007 398406	34	NovoRapid®	27 Nov 2013 – 15 Jan 2014	Healthy child	The subject was confirmed pregnant on 16 Jan 2014. Last treatment with trial product was 15 Jan 2014; treatment with insulins lispro and glargine commenced on 16 Jan 2014. Date of first day of last menstruation was 14 Dec 2013. The subject had an induced delivery on 16 Sep 2014 and gave birth to a healthy baby at GW 39. There were no complications or congenital anomalies reported at the 1 month follow up.
3852	771007 402887 435223 (linked child case)	27	NovoRapid®	24 Jan 2014 – 09 Mar 2014	Healthy child	The subject was confirmed pregnant 09 Mar 2014 and trial product was stopped the same day. Date of first day of last menstruation was 05 Feb 2014. The subject had an emergency caesarean section on 02 Oct 2014 at GW 34 due premature membrane rupture and gave birth to a baby boy. No congenital anomalies were reported and no health problems were reported at the 1 month follow up.
3852	790029 422336	21	NovoRapid®	02 May 2014 – 05 Sep 2014	Healthy child	The subject was confirmed pregnant on an unknown date. Date of the first day of the last menstruation was 30 Jul 2013. The subject informed the investigator on 05 Sep 2014, whereupon trial product was discontinued. The subject delivered a healthy baby boy at GW 38 and 5 days, without complications. There were no complications or congenital anomalies at the 1 month follow-up.
3852	216001 415423	23	NovoRapid®	20 Dec 2013 – 27 Jun 2014	Induced abortion	The subject reported delayed menstruation of 2 weeks on 26 Jun 2014. Pregnancy was confirmed on 27 Jun 2014 and trial product was stopped the same day. The subject was withdrawn from the study on 03 Jul 2014 and had an elective abortion on 29 Jul 2014. This was not due to foetal death or congenital anomalies.
3852	713005 415424	18	Faster aspart	15 Nov 2013 – 07 Jul 2014	Healthy child	The subject reported pregnancy on 30 Jun 2014. Date of first day of last menstruation was 05 May 2014. Trial product was discontinued on 07 Jul 2014 and the subject withdrawn for the trial on 08 Jul 2014. The subject gave birth to a healthy baby boy on 15 Jan 2015, GW 35, without complications. There were no complications or congenital anomalies at the 1 month follow-up.

Trial	Subject ID/Case	Age (years)	Treatment	Dates of treatment	Pregnancy outcome	Short narrative
3852	304004 445453	24	NovoRapid®	13 Feb 2014 – 13 Feb 2015	Healthy child	The subject informed the investigator about her pregnancy 11 days after the last follow-up visit, she was then approximately 4 weeks into her pregnancy (time of conception approximately in the middle of the follow-up period). Information in the safety database (03 March 2016) documented that the subject had delivered without complications. The subject gave birth to a healthy baby boy on 14 Nov 2015, GW 37. The subject had an elective caesarean section performed without any complications. At the age of one month, there had been no health problems and no congenital anomalies.
4131	753005 538230	29	Faster aspart	01 Nov 2016 – 23 Mar 2017	Healthy child	On 22 Mar 2017, the subject was discovered to be pregnant. On 23 Mar 2017, the gestational age was estimated at 7 weeks and one day. Due in part to the baby's growth being >99th percentile (foetal macrosomia), induced premature delivery was initiated and then, due to the baby's atypical and progressively abnormal heart rate, an emergency caesarean section was performed (week 36, day 6). These issues were judged by the investigator as unlikely related to trial products. The baby was healthy at birth and at one month.
4131	111001[a] 520646	20	Faster aspart	27 Jul 2016 – 21 Nov 2016	Healthy child	The subject did not report to the site that her monthly period was absent until scheduled visit 14 Nov 2016 where a b-hCG was obtained. Pregnancy was confirmed 16 Nov 2016 and the subject was advised to stop trial product. The subject delivered a baby boy on GW 37, day 2. The newborn was diagnosed with health problems (transient apnea and transient tachypnea which were assessed to be unlikely related to trial drugs) at delivery but had no health problems in the period from birth and one month of age.
4131	857008 554107	29	NovoRapid®	17 Jan 2017 – 10 Jul 2017	Healthy child	A positive pregnancy test the day after her end of trial visit. The patient and foetus did not experience any adverse events during the pregnancy. In gestational week 38, the patient gave birth to an infant girl. The infant's weight was 4252 grams. No complications occurred during pregnancy or labor.
4131	101011 [a] 514992	33	NovoRapid®	12 Sep 2016 – 11 Oct 2016	Healthy child	The subject was confirmed pregnant on 13 Oct 2016. Date of first day of last menstruation was 30 Aug 2016. On 13 Oct 2016, the patient was hospitalised for adopting CSII for tighter glycaemic control (not an SAE as per Investigator). The subject had an emergency caesarean section at GW 38, day 3 due to that the cervical opening did not proceed and there were disturbances due to abnormal rotations. The baby was healthy at birth and at one month.

Trial	Subject ID/Case	Age (years)	Treatment	Dates of treatment	Pregnancy outcome	Short narrative
4131	117011[a] 531086	31	NovoRapid®	15 Dec 2016 – 09 Feb 2017	Healthy child	On 09 Feb 2017 the site discovered that the patient was pregnant, investigational therapy was discontinued and replacement therapy started. Date of first day of last menstruation was 24 Dec 2014. On 07 Sep 2017, the subject was examined and it was discovered that one umbilical cord artery was occluded and a diagnosis of fetal dysfunction was made. The subject had an emergency caesarean delivery on the same day (GW 36, day 5) and gave birth to a baby girl. At delivery the newborn baby was diagnosed with health problems but no congenital anomalities. The baby was hospitalised for 8 days to recover. On 03 Oct 2017, the baby was brought back to the hospital for health check one month after birth and no health complication was found.
3854	903007 534770	24	NovoRapid®	31 Jan 2017 – 23 Feb 2017	Healthy child	When the pregnancy was discovered trial product was discontinued. Date of first day of last menstruation was 19 Jan 2017. In gestational week 37+3 the patient gave birth which was vaginal and spontaneous. It was a live birth without any congenital anomalies. During delivery no complications were observed. Infant was a female. The baby was healthy at birth and at one month.
3854	700021 550335	25	Faster aspart	25 Jan 2017 – 17 May 2017	Healthy child	On 2 Jun 2017 the subject was confirmed pregnant. Date of first day of last menstruation was 29 Apr 2017. On 15 Jun 2017 at follow-up visit 2, patient informed the investigator of her pregnancy. In gestational week 38+4, the patient gave birth by elective Caesarean section to a female. During delivery, no complications were observed. The baby was healthy at birth and at one month.

Abbreviations: GW: Gestational week.

2.7.4.5.8 過量投与

2.7.4.5.8.1 評価方法

付録 2.7.4.7.8 に示す一覧の基本語を用いた基本語検索に基づき、4131 及び 4101 試験における過量投与の事象と関連している可能性のある有害事象を特定した。

過量投与に関連する有害事象は投薬過誤でもあり、その詳細は 2.7.4.2.3.2 項に記載する。

2.7.4.5.8.2 4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

偶発的過量投与（規定を上回る用量での投与）の事象が faster aspart（食後投与）群で 1 例 1 件報告された（付録 2.7.4.7.4、表 2.7.4.7.4-2）。治験責任医師は、この過量投与の主な理由として被験者の注意散漫を挙げた〔Trial 4131（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.6〕。本事象により治験薬の投与中止や試験の中止に至ることはなかった〔Trial 4131（M 5.3.5.1）Section 14.3.3 ならびに Appendix 16.2.1、Listing 16.2.1.4 及び 16.2.1.6〕。

2.7.4.5.8.3 4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

偶発的過量投与が 5 例（faster aspart 群でそれぞれ 2 例ずつ及びノボラピッド®注群で 1 例）において 5 件報告された（付録 2.7.4.7.4、表 2.7.4.7.4-4）。Faster aspart（食前投与）群では、偶発的過量投与の理由として、新たなスライディングスケールによる混乱と注意散漫が挙げられた。Faster aspart（食後投与）群では、偶発的過量投与の理由として、インスリン／カーボ比（1 単位：20g）の間違い、あるいはインスリン投与量の計算の間違い及び注意散漫が挙げられた。ノボラピッド®注群では、偶発的過量投与の理由として、投与量の計算の間違いが挙げられた〔Trial 4101（M 5.3.5.1）Section 14.3.3 及び Appendix 16.2.7、Listing 16.2.7.6〕。

いずれの事象も治験薬の投与中止や試験の中止には至らなかった〔Trial 4101（M 5.3.5.1）EOT Tables 14.3.1.40 及び 14.3.1.41〕。

3 件の偶発的過量投与〔faster aspart（食後投与）群：2 件、faster aspart（食前投与）群：1 件〕が重篤な投薬過誤であった。詳細については 2.7.4.2.3.2.3 項を参照のこと。

2.7.4.5.8.4 結論

過量投与に関連する有害事象は、4131 試験で 1 例、4101 試験で 5 例において報告された。いずれの事象も治験薬の投与中止や試験の中止には至らなかった。

2.7.4.5.9 薬物乱用

該当なし。

2.7.4.5.10　離脱症状及び反跳現象

インスリン製剤において反跳作用は認められていない。

2.7.4.5.11　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

2.7.4.5.11.1　評価方法

Faster aspart の自動車運転／機械操作や精神機能に対する影響を検討する特定の臨床試験は実施していない。インスリン治療では低血糖により自動車運転／機械操作能力に影響を及ぼし得る症状が現れることがわかっている。他の血糖コントロールを目的とした薬剤と同様に、低血糖によって患者の集中力や対応力が損なわれることがある。患者には運転中に低血糖を起こさないように注意を与えるべきである。このことは、低血糖の前兆に対する自覚が低下している患者や低血糖を頻繁に起こしている患者において特に重要である。

付録 2.7.4.7.8 に示す一覧の基本語を用いた基本語検索に基づき、検証的試験（4131 及び 4101 試験）において報告された、自動車運転／機械操作能力や精神機能に影響を及ぼす可能性のある有害事象を特定した。

2.7.4.5.11.2　4131 試験（成人 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

自動車運転／機械操作能力や精神機能に影響を及ぼす可能性のある有害事象の件数及び単位時間あたりの発現件数は、faster aspart（食前投与）群及びノボラピッド®注群で同様であったが、faster aspart（食後投与）群で多かった（表 2.7.4.5-15）。いずれの群においても、最も多く報告された事象は浮動性めまいであった。Faster aspart（食後投与）群において発現がより多かった主な有害事象（基本語）は、転倒（3 件）、交通事故（2 件）、疲労（3 件）及び無力症（2 件）（付録 2.7.4.7.5、表 2.7.4.7.5-1 及び 2.7.4.7.5-2）であった。発現件数は faster aspart（食後投与）群で多かったが、同じ種類の有害事象が faster aspart（食前投与）群及びノボラピッド®注群でも報告された。Faster aspart（食前投与）群で報告された嗜眠 1 件について、治験薬との因果関係が「可能性あり」と判定された〔Trial 4131（M 5.3.5.1〕Memo Appendix 16.2.7, Listing 16.2.7.1〕。

表 2.7.4.5-15　自動車運転及び機械操作の能力又は精神機能の障害に関連する可能性のある有害事象の概観（4131 試験）

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects	342	341	342
Total exposure (yrs)	171.3	170.2	170.2
Total events	7 (2.0) 7 4.1	17 (5.0) 19 11.2	7 (2.0) 8 4.7

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.

2.7.4.5.11.3　4101 試験（小児及び青年期の 1 型糖尿病患者を対象とした 26 週間の Basal-Bolus 療法）

自動車運転／機械操作能力や精神機能に影響を及ぼす可能性のある有害事象を発現した被験者数及び単位時間あたりの発現件数は、いずれの投与群においても同程度であった（表 2.7.4.5-16）。最も多く報告された報告された事象は疲労〔faster aspart（食前投与）群：1 件、faster aspart（食後投与）群：4 件（4 例）〕であった。その他の報告された有害事象（基本語）は、無力症〔faster aspart（食後投与）群：1 件、ノボラピッド®注群：1 件〕、失神〔faster aspart（食前投与）群：2 件（2 例）、ノボラピッド®注群：2 件（1 例）〕、浮動性めまい〔faster aspart（食前投与）群：1 件〕、失神寸前の状態（ノボラピッド®注群：1 件）、転倒〔faster aspart（食前投与）群：2 件（2 例）〕、交通事故〔faster aspart（食前投与）群：1 件〕及び回転性めまい（ノボラピッド®注群：1 件）であった（付録 2.7.4.7.5、表 2.7.4.7.5-3 及び 2.7.4.7.5-4）。

表 2.7.4.5-16　自動車運転及び機械操作の能力又は精神機能の障害に関連する可能性のある有害事象の概観（4101 試験）

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects	261	258	258
Total exposure (yrs)	128.4	127.7	127.7
Total events	7 (2.7) 7 5.5	5 (1.9) 5 3.9	4 (1.6) 5 3.9

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.

2.7.4.5.11.4　結論

報告された自動車運転／機械操作能力や精神機能に影響を及ぼす可能性のある有害事象の種類は、faster aspart の両群及びノボラピッド®注群で同様であった。4131 試験では、ノボラピッド®注群と比較

して faster aspart（食後投与）群で報告件数が多かったが、4101 試験では報告件数に投与群間で違いは認められなかった。

2.7.4.5.12　インスリンポンプ使用時の安全性及び適合性

2.7.4.5.12.1　評価方法

成人 1 型糖尿病患者を対象とした 3 つの試験（図 2.7.4.1-1）において、インスリンポンプを用いて投与した時の faster aspart の安全性を評価した。3 つの試験は、インスリンポンプを用いた CSII 療法において faster aspart とノボラピッド®注の効果及び安全性を比較した 3854 試験（16 週、並行群、インスリンポンプ使用時の有効性及び安全性を検討した検証的試験）、インスリンポンプを用いて異なる 3 処方のインスリン アスパルト製剤を評価した 3930 試験〔3 期（14 日間）クロスオーバーによる探索的試験〕、ならびにインスリンポンプ使用時の faster aspart の適合性及び安全性を評価した 3931 試験（6 週、インスリンポンプ適合性試験）であった。2.7.4.5.12 項では、インスリンポンプ使用時の faster aspart の安全性を示す目的で 3854 試験の結果を提示するとともに、faster aspart のインスリンポンプ適合性について評価する目的で 3931 試験の結果を提示する。3930 試験は探索目的の短期試験であるため、本臨床概要では提示しない。

3854 試験の試験デザインは Module 2.7.3.1.3.12 を参照。3930 及び 3931 試験の試験デザインについては、各総括報告書〔Trial 3930（M 5.3.5.1）及び Trial 3931（M 5.3.5.1）〕を参照。

インスリンポンプ使用時の有効性評価項目（3854 試験）については Module 2.7.3.3.2.2 に提示する。

詳細については、個々の試験の総括報告書〔Trial 3854（M 5.3.5.1）、Trial 3930（M 5.3.5.1）及び Trial 3931（M 5.3.5.1）〕参照。

2.7.4.5.12.2　3854 試験（成人 1 型糖尿病患者における CSII 試験）

2.7.4.5.12.2.1 評価方法

3854 試験の主要目的は、成人 1 型糖尿病患者を対象として、インスリンポンプを用いた CSII 療法における faster aspart の効果（血糖コントロールを指標とする）を、インスリンポンプ使用時のノボラピッド®注と比較検討することであった。副次的目的として、インスリンポンプ使用時の faster aspart 及びノボラピッド®注の効果及び安全性を比較した。この試験に組み入れられた被験者は、試験期間を通じて、被験者自身のインスリンポンプ（市販品）を用いた。

3854 試験の評価方法については、本臨床概要中の関連する項に記載されている 4131 試験の評価方法、又は総括報告書〔Trial 3854（M 5.3.5.1）〕を参照のこと。

2.7.4.5.12.2.2 曝露状況

16 週間の投与期間における総曝露期間（人･年）は、faster aspart 群で 72.8 人･年、ノボラピッド®注群で 71.7 人・年であった。Faster aspart 又はノボラピッド®注の投与が少なくとも 1 回行われたすべての被験者を安全性解析対象集団に含めた（faster aspart 群 236 例、ノボラピッド®注群 236 例）〔Trial 3854（M 5.3.5.1）EOT Table 14.2.1 及び 14.2.2〕。

2.7.4.5.12.2.3 投与量

3854 試験での投与量については、Module 2.7.3.3.2.2.8 参照。

2.7.4.5.12.2.4 被験者の内訳

472 例が faster aspart 群（236 例）又はノボラピッド®注群（236 例）に 1：1 の比率で無作為割り付けされた。17 例（3.6%）〔faster aspart 群 7 例（3.0%）及びノボラピッド®注群 10 例（4.2%）〕が治験薬の投与を中止した。治験薬の投与を中止した 17 例のうち、9 例（1.9%）〔faster aspart 群 3 例（1.3%）及びノボラピッド®注群 6 例（2.5%）〕が、無作為割り付け以降に試験を中止した〔Trial 3854（M 5.3.5.1）EOT Table 14.1.1〕。

2.7.4.5.12.2.5 ベースラインの人口統計学的特性及び糖尿病特性

本試験には 1 型糖尿病患者の男女を組み入れた。全体として、2 つの投与群の人口統計学的特性及びベースライン特性は類似していた。

被験者の平均年齢は 43.5 歳であった〔Trial 3854（M 5.3.5.1）EOT Table 14.1.10〕。被験者の大部分（91.5%）が 18～64 歳で、残りの 8.5%が 65 歳以上であった。被験者の大部分が白人（88.8%）で非ヒスパニック系／非ラテン系（90.0%）であった。また、24.8%の被験者は、自身の持続血糖測定（CGM）機器を使用した〔Trial 3854（M 5.3.5.1）EOT Table 14.1.9〕。

ベースラインにおいて、被験者の BMI の平均値は 26.33 kg/m^2 であった。来院 1 の HbA1c の平均値は 7.80%〔Trial 3854（M 5.3.5.1）EOT Table 14.2.38〕、ベースラインの HbA1c の平均値は 7.49%であった〔Trial 3854（M 5.3.5.1）EOT Table 14.1.10〕。ベースラインの平均空腹時血糖値は 135.09 mg/dL、平均糖尿病罹病期間は 24.2 年であった〔Trial 3854（M 5.3.5.1）EOT Table 14.1.10〕。

2.7.4.5.12.2.6 併発疾患及び併用薬剤

3854 試験のベースラインで報告された併用薬剤及び併発疾患は、1 型糖尿病患者集団において予期されるものであり、4131 試験において報告されたもの（2.7.4.1.3.3.2 項）と同様であった。

2.7.4.5.12.2.7 有害事象

本試験では 852 件の有害事象が報告された〔Trial 3854（M 5.3.5.1）EOT Table 14.3.1.1〕。有害事象の単位時間あたりの発現件数は、faster aspart 群（604.7 件/100 人・年）とノボラピッド®注群（574.7 件/100 人・年）で同様であった。有害事象を報告した被験者の割合も、faster aspart 群（69.9%）とノボラピッド®注群（65.7%）で同様であった。有害事象の大部分が非重篤で、軽度又は中等度であり、治験責任医師により治験薬との因果関係は「なし」と判定された。ほとんどの有害事象において、試験終了時の転帰は回復であった（表 2.7.4.5-17）。重度の有害事象及び治験責任医師により治験薬との因果関係が「可能性あり」又は「あり」と判定された有害事象の単位時間あたりの発現件数に、投与群間で臨床的に意味のある違いは認められなかった。

表 2.7.4.5-17　有害事象－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（3854 試験）

	Faster aspart N	(%)	E	R	NovoRapid N	(%)	E	R
Number of subjects	236				236			
Total exposure (yrs)	72.8				71.7			
Total events	165	(69.9)	440	604.7	155	(65.7)	412	574.7
Serious								
Yes	5	(2.1)	5	6.9	8	(3.4)	11	15.3
No	164	(69.5)	435	597.8	154	(65.3)	401	559.4
Severity								
Severe	4	(1.7)	5	6.9	4	(1.7)	8	11.2
Moderate	56	(23.7)	95	130.6	49	(20.8)	81	113.0
Mild	149	(63.1)	340	467.3	137	(58.1)	323	450.6
Related to randomised trial product								
Probable	7	(3.0)	10	13.7	5	(2.1)	8	11.2
Possible	21	(8.9)	32	44.0	17	(7.2)	26	36.3
Unlikely	151	(64.0)	381	523.6	151	(64.0)	368	513.3
Missing	14	(5.9)	17	23.4	7	(3.0)	10	13.9
Related to a technical complaint								
Yes	0				0			
No	158	(66.9)	423	581.4	154	(65.3)	402	560.8
Missing	14	(5.9)	17	23.4	7	(3.0)	10	13.9
Outcome								
Recovered/resolved	157	(66.5)	388	533.3	145	(61.4)	347	484.0
Recovering/resolving	4	(1.7)	4	5.5	2	(0.8)	3	4.2
Recovered/resolved with sequelae	1	(0.4)	1	1.4	0			
Not recovered/not resolved	36	(15.3)	47	64.6	39	(16.5)	62	86.5
Fatal	0				0			
Unknown	0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
MedDRA version 20.0.

最も高頻度で報告された有害事象（基本語）は、ウイルス性上気道感染（単位時間あたりの発現件数は faster aspart 群で 82.5 件/100 人・年、ノボラピッド®注群で 89.3 件/100 人・年）、注入部位反応（2.7.4.5.12.2.11 項）及び上気道感染（単位時間あたりの発現件数は faster aspart 群で 24.7 件/100 人・年、ノボラピッド®注群で 16.7 件/100 人・年）であった（Module 2.7.6.19.2、表 2.7.6.19.2-1）。

2.7.4.5.12.2.8 死亡

本試験で死亡は報告されなかった。

2.7.4.5.12.2.9 その他の重篤な有害事象

本試験では重篤な有害事象が 16 件報告された。重篤な有害事象の単位時間あたりの発現件数は、faster aspart 群で 6.9 件/100 人･年、ノボラピッド®注群で 15.3 件/100 人・年であった。3 件の重篤な有害事象（faster aspart 群で報告された低血糖性意識消失及び薬疹と、ノボラピッド®注群で報告された低血糖性痙攣）が治験責任医師により治験薬との因果関係が「可能性あり」と判定された〔Trial 3854（M 5.3.5.1）EOT Table 14.3.1.17〕。重篤な有害事象の転帰はすべて、試験終了時点で回復であった。

重篤な有害事象の叙述は総括報告書〔Trial 3854（M 5.3.5.1）Section 14.3.3〕を参照。

2.7.4.5.12.2.10 試験の中止、投与の中止又は投与量の減量に至った有害事象

2 件の重篤な有害事象（faster aspart 群：薬疹、ノボラピッド®注群：低血糖性痙攣）及び 1 件の有害事象（faster aspart 群：発疹）が治験薬の投与中止に至った〔Trial 3854（M 5.3.5.1）EOT Listing 14.3.2.4〕。重篤な有害事象である低血糖性痙攣は試験の中止にも至った〔Trial 3854（M 5.3.5.1）EOT Listing 14.3.2.5〕。

投与量の減量に至った有害事象が 13 件報告された〔faster aspart 群：6 件、ノボラピッド®注群：7 件〕。このうち、6 件（faster aspart 群：2 件及びノボラピッド®注群：4 件）が重篤な有害事象であった〔Trial 3854（M 5.3.5.1）EOT Table 14.3.1.24〕。

有害事象の各表については総括報告書〔Trial 3854（M 5.3.5.1）〕を参照。

2.7.4.5.12.2.11 器官別又は症候群別有害事象の解析

3854 試験については、付録 2.7.4.7.8 又は総括報告書〔Trial 3854（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.14〕に示す一覧の基本語を用いた基本語検索に基づき、特に注目すべき安全性領域の有害事象を特定した。

心血管系事象

心血管系事象は報告されなかった（付録 2.7.4.7.2.1、表 2.7.4.7.2.1-5 及び 2.7.4.7.2.1-6）。

投薬過誤

基本語検索により、3 例 4 件の投薬過誤が特定された。このうち 3 件（faster aspart 群：1 件及びノボラピッド®注群：2 件）が偶発的過量投与に分類される事象であり（2.7.4.5.12.2.16 項）、残り 1 件（ノボラピッド®注群）はその他の投薬過誤に分類された〔Trial 3854（M 5.3.5.1）Appendix 16.2.7, Listing 16.2.7.6〕。

免疫原性に関連する有害事象（アレルギー反応）

アレルギー反応に関連する有害事象が 17 例 17 件報告された〔faster aspart 群：10 例 10 件、ノボラピッド®注群：7 例 7 件〕〔Safety Appendix 5（M 5.3.5.1）、Table 9〕。単位時間あたりの発現件数は、faster aspart 群で 13.7 件/100 人・年、ノボラピッド®注群で 9.8 件/100 人・年であった〔Trial 3854（M 5.3.5.1）EOT Table 14.3.1.33〕。

基本語検索により特定されたアレルギー反応に関連する有害事象のうち、重篤な有害事象は faster aspart 群の 1 件（薬疹）であった〔Trial 3854（M 5.3.5.1）EOT Table 14.3.1.35〕。

基本語検索により特定されたアレルギー反応に関連する有害事象のうち、3 件の有害事象が治験責任医師により faster aspart との因果関係が「可能性あり」又は「あり」と判定された〔発疹 2 件（2 例）、重篤な有害事象の薬疹 1 件〕〔Trial 3854（M 5.3.5.1）EOT Table 14.3.1.36〕。

基本語検索により特定されたアレルギー反応に関連する有害事象のうち、faster aspart 群の 2 件の有害事象（薬疹及び発疹）が治験薬の投与中止に至った〔Trial 3854（M 5.3.5.1）EOT Listing 14.3.2.4〕。

注入部位反応及びリポジストロフィー

基本語検索により、注入部位反応に関連する有害事象が 45 例 76 件特定された。注入部位反応に関連する有害事象の単位時間あたりの発現件数は、ノボラピッド®注群（44.6 件/100 人・年）と比較して faster aspart 群（60.5 件/100 人・年）で数値的に多かった〔Trial 3854（M 5.3.5.1）EOT LTable 14.3.1.28〕。22 例 34 件が、治験責任医師により治験薬との因果関係が「可能性あり」又は「あり」と判定された〔faster aspart 群：21 件（13 例）及びノボラピッド®注群：13 件（9 例）〕〔Trial 3854（M 5.3.5.1）EOT Listing 14.3.1.30〕。

本試験において、リポジストロフィーに関連する有害事象は報告されなかった〔Safety Appendix 5（M 5.3.5.1）Table 6〕。

末梢性浮腫

末梢性浮腫に関連する有害事象は報告されなかった（付録 2.7.4.7.2.1、表 2.7.4.7.2.1-29）。

眼障害（糖尿病網膜症及び屈折障害）

本試験において、糖尿病網膜症に関連する有害事象は 14 件（faster aspart 群：6 例 6 件、ノボラピッド®注群：6 例 8 件）報告され、屈折障害に関連する有害事象は報告されなかった（付録 2.7.4.7.2.1、表 2.7.4.7.2.1-11、2.7.4.7.2.1-12 及び 2.7.4.7.2.1-17）。

末梢性ニューロパチー

末梢性ニューロパチーに関連する有害事象は、faster aspart 群で 6 例 7 件、ノボラピッド®注群で 4 例 4 件報告された（付録 2.7.4.7.2.1、表 2.7.4.7.2.1-23 及び 2.7.4.7.2.1-24）。

原因が特定できない高血糖

原因が特定できない高血糖は、血糖値が 300 mg/dL 以上で、原因が不明であるもの（すなわち、医学的な理由、食事、インスリン投与量、インスリンポンプの不具合などの明らかな理由が存在しない）と定義した。原因が特定できない高血糖が報告された被験者の割合は両投与群で同程度で、faster aspart 群で 68.2%、ノボラピッド®注群で 65.3%であった。原因が特定できない高血糖の単位時間あたりの発現件数は、ノボラピッド®注群（1476 件/100 人・年）と比較して faster aspart 群（1629 件/100 人・年）で多かった〔Trial 3854（M 5.3.5.1）EOT Table 14.3.1.88〕。

稀な事象

本試験では、稀な事象がノボラピッド®注群で 3 例 4 件〔洞性徐脈 1 件及び上室性期外収縮 1 件（同一被験者において報告）、失神 1 件、顔面腫脹 1 件〕報告された。いずれの事象も治験薬の投与中止や試験の中止には至らなかった〔Trial 3854（M 5.3.5.1）Appendix 16.2.1、Listing 16.2.1.4 及び 16.2.1.6〕。これらの 4 件のうち、1 件が治験責任医師により中等度と判定され、残りの事象は軽度と判定された。いずれの事象も治験薬との因果関係は「なし」と判定された〔付録 2.7.4.7.2.1、表 2.7.4.7.2.1-35 及び 2.7.4.7.2.1-36、ならびに Trial 3854（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.1〕。

治験薬による病原体感染の疑い

本試験において、治験薬による病原体感染の疑いに関連する有害事象は報告されなかった（付録 2.7.4.7.2.1、表 2.7.4.7.2.1-41 及び 2.7.4.7.2.1-42）。

2.7.4.5.12.2.12　低血糖

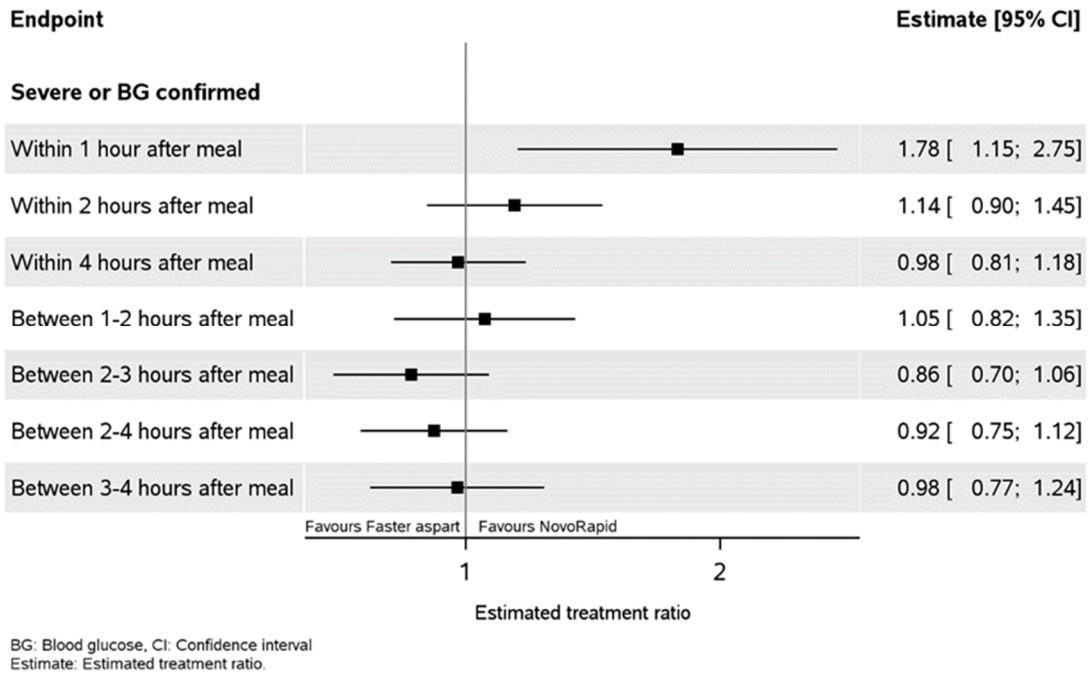
治験薬投与下で発現した低血糖（分類別）の要約を表 2.7.4.5-18 に示す。重大な又は血糖値確定低血糖の単位時間あたりの発現件数に投与群間で統計的に有意な違いは認められなかった〔単位時間あたりの発現件数の比の推定値は、faster aspart 群／ノボラピッド®注群で 1.00（95%信頼区間：0.85; 1.16）、Trial 3854（M 5.3.5.1）EOT Table 14.3.1.48〕。重大な又は血糖値確定低血糖の大部分（86%、6526 件中 5585 件）が日中に発現した。日中及び夜間の重大な又は血糖値確定低血糖を報告した被験者の割合は、両投与群で同程度であった〔Trial 3854（M 5.3.5.1）EOT Table 14.3.1.39、14.3.1.41 及び 14.3.1.42〕。

表 2.7.4.5-18　分類別の低血糖－治験薬投与下で発現－要約－on-treatment 観察期間－安全性解析対象集団（3854 試験）

	Faster aspart N	(%)	E	R	NovoRapid N	(%)	E	R
Number of subjects	236				236			
Total exposure (yrs)	72.8				71.7			
Total events	236	(100.0)	11068	15211	234	(99.2)	11375	15867
BG confirmed	231	(97.9)	3258	4478	227	(96.2)	3240	4520
Severe or BG confirmed symptomatic	223	(94.5)	2751	3781	220	(93.2)	2779	3877
Severe or BG confirmed	231	(97.9)	3279	4507	228	(96.6)	3247	4529
NN unclassifiable	236	(100.0)	7789	10705	232	(98.3)	8128	11338
ADA								
Severe	11	(4.7)	21	29	5	(2.1)	7	10
Documented symptomatic	233	(98.7)	8372	11506	226	(95.8)	8904	12421
Asymptomatic	192	(81.4)	2530	3477	202	(85.6)	2273	3171
Probable symptomatic	20	(8.5)	88	121	15	(6.4)	32	45
Pseudo-hypoglycaemia	13	(5.5)	56	77	22	(9.3)	159	222
ADA unclassifiable	1	(0.4)	1	1	0			

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years. Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period. Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <56 mg/dL. NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <56 mg/dL) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data. Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

食事開始後 1 時間以内における重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、ノボラピッド®注群と比較して faster aspart 群で統計的に有意に多かった（図 2.7.4.5-3）。なお、食後 1 時間の間に報告された重大な又は血糖値確定低血糖の件数が総件数に占める割合は、いずれの群においても低かった〔Trial 3854（M 5.3.5.1）EOT Figure 14.3.1.71〕。



BG: Blood glucose, CI: Confidence interval
Estimate: Estimated treatment ratio.

図 2.7.4.5-3　　食事に関連した重大な又は血糖値確定低血糖

重大な低血糖の単位時間あたりの発現件数は、ノボラピッド®注群（10 件/100 人･年）と比較して faster aspart 群（29 件/100 人･年）で数値的に多かった〔Trial 3854（M 5.3.5.1）EOT Table 14.3.1.39〕。単位時間あたりの発現件数の比の推定値は、faster aspart 群／ノボラピッド®注群で 2.78（95%信頼区間：0.78; 9.94）で、統計的に有意ではなかった〔Trial 3854（M 5.3.5.1）EOT Table 14.3.1.48〕。

Faster aspart 群に割り付けられた被験者のうち 3 例が、run-in 期間中に重大な低血糖を発現した。投与期間中は、faster aspart 投与後に報告された重大な低血糖 21 件中 10 件が、この 3 例の被験者で発現した。ノボラピッド®注群に無作為割り付けされた被験者では、run-in 期間中に重大な低血糖は認められなかった〔Trial 3854（M 5.3.5.1）Appendix 16.2.7, Listing 16.2.7.11〕。本試験の選択基準及び除外基準において、重大な低血糖や無自覚性低血糖の既往を有する被験者は除外しなかった。

2.7.4.5.12.2.13　臨床検査値

血液生化学的検査項目、血液学的検査項目及び尿検査項目の平均値は試験期間中安定していた。試験期間中の平均値や平均変化量に、投与群間で明らかな違いは認められなかった〔Trial 3854（M 5.3.5.1）EOT Table 14.3.5.1～14.3.5.4、14.3.5.23～14.3.5.26、14.3.5.71～14.3.5.74 及び EOT Figure 14.3.5.5～14.3.5.22、14.3.5.27～14.3.5.36 及び 14.3.5.75～14.3.5.76〕。

ベースライン及び無作為割り付け後 16 週の脂質の平均値は基準範囲内であった。ノボラピッド®注群と比較して faster aspart 群で LDL コレステロール〔製剤間の比：1.05（95%信頼区間：1.02; 1.08）〕及び総コレステロール〔製剤間の比：1.02（95%信頼区間：1.00; 1.05）〕に統計的に有意な増加が認められたが、その差はわずかであった〔Trial 3854（M 5.3.5.1）EOT Table 14.3.5.37～14.3.5.46 及び EOT Figure 14.3.5.47～14.3.5.70〕。

2.7.4.5.12.2.14 バイタルサイン及び身体所見

バイタルサイン及び身体所見について、試験期間を通じて臨床的に意味のある変化は認められず、投与群間でも臨床的に意味のある違いは認められなかった〔Trial 3854（M 5.3.5.1）EOT Table 14.3.6.1～14.3.6.4〕。

2.7.4.5.12.2.15 テクニカルな苦情

3854 試験では、テクニカルな苦情に関連する有害事象は報告されなかった〔Trial 3854（M 5.3.5.1）EOT Table 14.3.1.1〕。

2.7.4.5.12.2.16 特別な患者集団及び状況下における安全性

過量投与

ノボラピッド®注群の 1 例において、偶発的過量投与が 2 件（いずれも重篤な有害事象）報告された（付録 2.7.4.7.4、表 2.7.4.7.4-5 及び 2.7.4.7.4-6、ならびに Trial 3854（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.2）。

基本語検索で特定した事象に加え、faster aspart 群の 1 例で非重篤な用量算出過誤 1 件が報告された。治験責任医師は、本事象に関する追加情報を提供した際、当該事象を「偶発的過量投与」に分類した〔Trial 3854（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.1 及び 16.2.7.6〕。

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／機械操作能力に影響を及ぼす可能性のある有害事象を発現した被験者の割合及び単位時間あたりの発現件数は、ノボラピッド®注群と比較して faster aspart 群で少なかった〔faster aspart 群：5 例 5 件（6.9 件/100 人・年）及びノボラピッド®注群：11 例 11 件（15.3 件/100 人・年）〕。両群ともに最も多く報告された事象は、疲労及び浮動性めまいであった（付録 2.7.4.7.5、表 2.7.4.7.5-5 及び 2.7.4.7.5-6）。

妊娠及び授乳期の使用

2.7.4.5.7 項参照。

2.7.4.5.12.2.17 予定されていない早期のインスリンポンプ注入セット交換

週あたりの注入セットの平均交換回数は両群で同様で、faster aspart 群で 2.55 回、ノボラピッド®注群で 2.49 回であった〔Trial 3854（M 5.3.5.1）EOT Table 14.3.1.93〕。予定されていない早期の注入セットの交換は、両群とも、報告された注入セットの交換の総件数の約 5%であった。予定されていない早期の注入セットの交換の単位時間あたりの回数は、faster aspart 群（697 件/100 人・年）及びノボラピッド®注群（668 件/100 人・年）で同様であった。予定されていない早期の注入セットの交換が報告された被験者の割合は、ノボラピッド®注群（57.2%）と比較して faster aspart 群（71.2%）で高かった。予定されていない早期の注入セットの交換の理由で最も多く報告されたものは、「注入セットに関する問題」、「他に原因が特定できない高血糖」及び「被験者が確認した閉塞」であった（表 2.7.4.5-19）。

表 2.7.4.5-19　インスリンポンプ注入セット交換－要約－on-treatment 観察期間－安全性解析対象集団（3854 試験）

	Faster aspart N	(%)	E	R	NovoRapid N	(%)	E	R
Number of subjects	236				236			
Total exposure (yrs)	72.8				71.7			
All changes	236	(100.0)	9653	13267	236	(100.0)	9360	13057
Routine change	236	(100.0)	9113	12525	236	(100.0)	8868	12370
Non-routine change	168	(71.2)	507	697	135	(57.2)	479	668
A perceived occlusion by the subject	50	(21.2)	120	165	50	(21.2)	112	156
Any problems related to the infusion set	108	(45.8)	201	276	75	(31.8)	206	287
Any technical issues with the pump	23	(9.7)	31	43	17	(7.2)	22	31
Changes in the insulin solution in the infusion set or reservoir	3	(1.3)	3	4	8	(3.4)	8	11
High BG with no other explanation which made the subject change the infusion set	66	(28.0)	121	166	60	(25.4)	119	166
Infusion site reaction	16	(6.8)	28	38	8	(3.4)	11	15
Missing	3	(1.3)	3	4	1	(0.4)	1	1
Missing	11	(4.7)	33	45	10	(4.2)	13	18

%: Percentage of subjects, BG: Blood glucose, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years

2.7.4.5.12.3　3931 試験（成人 1 型糖尿病患者における CSII 試験）

2.7.4.5.12.3.1 評価方法

3931 試験の主要目的は、6 週間の CSII 療法における faster aspart とノボラピッド®注のインスリンポンプ適合性を評価することであった。

注入セット（Quick-Set®及び Silhouette®）とリザーバーは、治験実施計画書に従って、ノボ ノルディスク社より提供された。被験者は Quick-Set®又は Silhouette®のいずれかの注入セットを過去 6 ヵ月以内

に 1 ヵ月間以上使用しており、治験開始前に使用していたものと同じ注入セットを提供することとした。被験者は試験期間を通して同じ注入セットを使用することとした。被験者には、注入セットとリザーバーを 72 時間（±4 時間）ごとに交換し、閉塞、漏出、原因が特定できない（すなわち、医学的な理由、食事、インスリン投与量、インスリンポンプの不具合などの明らかな理由が存在しない）高血糖、注入部位反応、テクニカルな理由又はその他の理由が疑われた場合にのみ 72 時間（±4 時間）を待たずに交換するように指示した。

注入セットとリザーバーは、自宅で定期的又は予定外に交換を行った後に被験者自身により目視で評価し、かつ規定来院時に定期的な交換を行った後に治験実施施設にて目視かつ顕微鏡により評価した（表 2.7.4.5-20）。詳細については Trial 3931（M 5.3.5.1）Section 9.5.1.2 を参照のこと。

表 2.7.4.5-20　　インスリンポンプ注入セット及びリザーバーの評価要件（3931 試験）

Assessments of infusion set and reservoir		
	Inspection at site	*Inspection at home*
Macroscopic evaluation	Insulin solution in the infusion set and reservoir appeared clear and colourless (yes/no) Particles/crystal formation of the insulin solution in the infusion set or reservoir (yes/no)	Insulin solution appeared clear and colourless (yes/no) Any noticeable particles or crystal formation in the insulin solution (yes/no)
Microscopic evaluation	Particles/crystal formation of the insulin solution in the infusion set or reservoir In case of particles/crystal formation of the insulin solution of the infusion set or reservoir: Particles/crystal formation of the insulin appeared: • Close to the cannula (Yes/No) • In the proximal half of the infusion set (closest to the reservoir) (Yes/No) • In the distal half of the infusion set (farthest away from the reservoir) (scale: 0 = none, 1 = minimal, 2 = moderate, 3 = many) • In reservoir (scale: 0 = none, 1 = minimal, 2 = moderate, 3 = many)	NA

NA: Not applicable

2.7.4.5.12.3.2 適合性の結果

6 週間のインスリンポンプ適合性試験では、顕微鏡により確定された注入セットの閉塞や、被験者によって閉塞の疑いや予定されていない早期の注入セット交換に至るような詰まりが認められた事例は、faster aspart 又はノボラピッド®注のいずれの投与群においてもなかった。特記すべき点として、本試験は小規模な試験であり、faster aspart 群（25 例）又はノボラピッド®注群（12 例）に 2：1 の比率で無作為割り付けが行われた〔Trial 3931（M 5.3.5.1）EOT Table 14.1.1〕。

注入セット閉塞の可能性に起因する早期の注入セットの交換が、faster aspart 群で 5 例 7 件報告された（表 2.7.4.5-21）。これらの事例のうち、1 件を除く全件が、原因が特定できない高血糖によるものと報告された。残りの 1 件は、注入セットの漏出によるものと報告された。これらの注入セットのうち、3 セットは、治験実施施設での目視検査及び顕微鏡検査で粒子、結晶及びインスリン溶液の変色は認められなかった。残りの 4 セットは、治験実施施設に提出されなかったため、閉塞、粒子、結晶又は変色の有無は確認できなかった。しかしながら、これら 4 つの注入セットを被験者が自宅において目視で調べた際には、変色や粒子は認められなかった。早期の注入セットの交換のうち、原因が特定できない高血糖が理由と報告されたものの大部分（6 件中 5 件）で、治験実施計画書に規定されている「原因が特定できない高血糖」の基準は満たしていなかった。

このように、早期に交換された注入セットのうち 4 セットは治験実施施設での顕微鏡検査が実施できなかった（被験者による目視での評価のみ行われた）ものの、3931 試験における予定されていない早期の注入セットの交換が注入セットの閉塞に起因するという証拠は示されなかった。

表 2.7.4.5-21　インスリンポンプ注入セットの閉塞の可能性（3931 試験）

Subject ID	Treatment	Reason for premature change	Date/time of premature change	Days inserted	Macroscopy subject/site	Microscopy (site)	Descriptions from CRF and additional information
505002	Faster aspart	Leakage	12 Dec 2013 15:50	2.3	Neg/Neg	Neg	At the injection site/Microscopy post-DBL[a]. The reason for the leakage was that the cannula was kinked.
606001	Faster aspart	Unexplained hyperglycaemia	08 Feb 2014 18:08	2.2	Neg/ND	ND	Infusion set not shipped. The site reported that the 'unexplained hyperglycaemic episode' that had prompted the change of infusion set did not meet the criteria for unexplained hyperglycaemia, as per protocol
606006	Faster aspart	Unexplained hyperglycaemia	19 Jan 2014 22:50	0.5	Neg/Neg	Neg	The site reported that the 'unexplained hyperglycaemic episode' that had prompted the change of infusion set did not meet the criteria for unexplained hyperglycaemia, as per protocol
606009	Faster aspart	Unexplained hyperglycaemia	07 Mar 2014 23:15	0.2	Neg/ND	ND	Infusion sets not shipped. The site reported that the 'unexplained hyperglycaemic episodes' that had prompted the changes of infusion set did not meet the criteria for unexplained hyperglycaemia, as per protocol. The site confirmed that the 3 premature changes of infusion sets and reservoirs were not due to possible occlusions and were attributed to infusion site issues, which were not unusual for this subject as he had a history of bad infusion sites.
		Unexplained hyperglycaemia	08 Mar 2014 03:18	0.2	Neg/ND	ND	
		Unexplained hyperglycaemia	17 Mar 2014 01:31	1.4	Neg/ND	ND	
606011	Faster aspart	Unexplained hyperglycaemia	12 Mar 2014 08:25	1.7	Neg/Neg	Neg	Premature site change due to hyperglycaemic episode attributed to bad site (blood vessel). Nothing remarkable after micro- and macroscopy.

Abbreviations: CRF: Case report form; DBL: Database lock; Neg: no particles or colour change of insulin solution observed; ND: not done – infusion set not shipped to site

[a] Microscopy was performed per protocol but the results of the microscopy were received post-DBL.

2.7.4.5.12.4　結論

3854 試験の有害事象プロファイルに、faster aspart 群とノボラピッド®注群間で臨床的に意味のある違いは認められなかった。

重大な又は血糖値確定低血糖の単位時間あたりの発現件数に、投与群間で統計的に有意な違いは認められなかった。重大な低血糖の単位時間あたりの発現件数は、ノボラピッド®注群と比較して faster aspart 群で数値的に多かったものの、いずれの投与群でも単位時間あたりの発現件数は少なく、統計的な有意差は認められなかった。食事開始後 1 時間以内における重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、faster aspart 群で統計的に有意に多かった。

注入部位反応に関連する有害事象の単位時間あたりの発現件数は、ノボラピッド®注群と比較して faster aspart 群で数値的に多かった。予定されていない早期の注入セットの交換を報告した被験者の割合は、ノボラピッド®注群と比較して faster aspart 群で高かった。

ノボラピッド®注と比較して faster aspart で、その他の安全性上の問題は認められなかった。

3931 試験では、faster aspart 群及びノボラピッド®注群のいずれにおいても、顕微鏡検査で確定された注入セットの閉塞は認められなかった。本試験で、新たな安全性に関する所見は認められなかった。

2.7.4.5.13　1 型糖尿病患者を対象とした長期安全性の結果（3852 試験）

2.7.4.5.13.1　評価方法

日本人被験者を組み入れたいずれの検証的試験においても、faster aspart の長期安全性は検討しなかった。Faster aspart の長期安全性に関する情報は、日本人被験者を組み入れなかった 1 つの試験（1 型糖尿病患者を対象とした 3852 試験）から得られた。1 型糖尿病患者を対象とした長期安全性評価の補足として、2.7.4.5.13 項に 3852 試験の安全性の要約を提示する。試験デザインは Module 2.7.3.1.3.13.1 参照。

3852 試験は、Basal-Bolus 療法におけるインスリン デグルデクの 1 日 1 回又は 1 日 2 回投与の併用下での faster aspart（食前投与）とノボラピッド®注（食前投与）の有効性及び安全性を二重盲検下で比較する 26＋26 週間の試験であった。また、本試験ではインスリン デテミルの 1 日 1 回又は 1 日 2 回投与の併用下で faster aspart（食後投与）を投与する 26 週間の非盲検投与群を設定した。この投与群には追加の 26 週間の投与期間は含まれなかった。2.7.4.5.13 項では、最初の 26 週間〔faster aspart（食前投与）、faster aspart（食後投与）及びノボラピッド®注〕の投与期間の結果と、52 週間のすべての投与期間の結果〔faster aspart（食前投与）及びノボラピッド®注〕を別々に示す。

関連する評価方法については、総括報告書〔Trial 3852（M 5.3.5.1）〕を参照。

2.7.4.5.13.2　有害事象

26 週間

全体的な有害事象の単位時間あたりの発現件数は、いずれの投与群においても同程度であり、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 478.6、441.0 及び 458.5 件/100 人・年であった。有害事象を報告した被験者の割合は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 73.6%、70.0%及び 75.0%であった。全体として、有害事象の大部分が非重篤（97%）で、軽度又は中等度（97%）であり、治験責任医師により治験薬との因果関係は「なし」と判定された（95%）。また、有害事象の大部分が 26 週間の投与期間終了時には回復していた〔Trial 3852（M.5.3.5.1）EOT Table 14.3.1.1〕。3 つのいずれの投与群においても、有害事象により試験を中止した被験者は数例ずつであった〔faster aspart（食前投与）群で 5 例、faster aspart（食後投与）群で 4 例、ノボラピッド®注群で 2 例〕〔Trial 3852（M 5.3.5.1）EOT Table 14.1.1〕。

52 週間

長期投与に関連する特定の有害事象は認められなかった。全体的な有害事象の単位時間あたりの発現件数は、faster aspart（食前投与）群（445.8 件/100 人・年）とノボラピッド®注群（411.0 件/100 人・年）で同程度であり、両投与群ともに 26 週間投与後と比較して少なかった。有害事象を報告した被験者の割合は、26 週間投与後と比較して 52 週間投与後で高かったが〔faster aspart（食前投与）群で 83.9%、ノボラピッド®注群で 84.2%〕、これは同一被験者の投与期間を延長したことで予測されるとおりであった〔Trial 3852-52w（M 5.3.5.1）EOT Table 14.3.1.1〕。有害事象の大部分が試験終了時（52 週投与後）には回復していた。試験の中止に至った有害事象は、両投与群で計 9 例の被験者より報告され、内訳は faster aspart（食前投与）群で 5 例、ノボラピッド®注群で 4 例であった〔Trial 3852-52w（M 5.3.5.1）EOT Table 14.3.1.23〕。

2.7.4.5.13.3　死亡、重篤な有害事象及びその他の重要な有害事象

26 週間

Faster aspart（食後投与）群で 1 例の死亡が報告された。この死亡はイベント判定委員会により心血管死と確定され、治験責任医師により治験薬との因果関係は「なし」と判定された〔Trial 3852（M 5.3.5.1）EOT Table 14.3.2.1〕。計 69 例（6%）85 件の重篤な有害事象が報告された。単位時間あたりの重篤な有害事象の発現件数は、faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 13.4、19.7 及び 12.7 件/100 人・年であった〔Trial 3852（M 5.3.5.1）EOT Table 14.3.1.3〕。イベント判定委員会により確定された心血管系事象は計 6 件であった。このうち 3 件が主要な心血管系イベント（MACE）と確定された。1 件が心血管死〔faster aspart（食後投与）群〕、1 件

が非 ST 上昇型心筋梗塞〔faster aspart（食後投与）群〕、1 件が脳卒中（ノボラピッド®注群）であった〔Trial 3852（M 5.3.5.1）EOT Table 14.3.1.27〕。

52 週間

最初の 26 週間の投与期間に報告された死亡に加え、ノボラピッド®注群で 1 例の死亡が報告された〔Trial 3852-52w（M 5.3.5.1）EOT Table 14.3.2.1〕。本事象は、イベント判定委員会により心血管死と確定され、治験責任医師により治験薬との因果関係は「なし」と判定された。Faster aspart（食前投与）群及びノボラピッド®注群で計 68 例（9%）89 件の重篤な有害事象が報告された。単位時間あたりの重篤な有害事象の発現件数は、faster aspart（食前投与）群で 14.0 件/100 人・年、ノボラピッド®注群で 10.8 件/100 人・年であった。最初の 26 週間の投与期間に発現した 3 件の MACE に加え、1 件の有害事象（ノボラピッド®注群における心血管死）がイベント判定委員会により MACE と確定された〔Trial 3852-52w（M 5.3.5.1）EOT Table 14.3.1.27〕。

2.7.4.5.13.4　低血糖

26 週間

重大な又は血糖値確定低血糖について、単位時間あたりの発現件数（全体、日中又は夜間）に、投与群間で統計的な有意差はみられなかった（表 2.7.4.5-22）。重大な又は血糖値確定低血糖の大部分は、いずれの投与群においても日中に発現した事象であった。食事開始後 1 時間以内に発現した低血糖の単位時間あたりの発現件数は、ノボラピッド®注群と比較して faster aspart（食前投与）群で多かった。26 週間の投与期間中に、1 件以上の重大な低血糖（ADA 分類）を発現した被験者の割合は、いずれの投与群においても同程度であった。Faster aspart（食前投与）群、faster aspart（食後投与）群及びノボラピッド®注群でそれぞれ 6.7%、8.0%及び 8.4%であった〔Trial 3852（M 5.3.5.1）EOT Table14.3.1.30〕。

52 週間

26 週間の投与期間でみられたように、単位時間あたりの低血糖の発現件数は、faster aspart（食前投与）群とノボラピッド®注群間で同程度であり、重大な又は血糖値確定低血糖、ならびに重大な低血糖（ADA 分類）の単位時間あたりの発現件数について、faster aspart（食前投与）群とノボラピッド®注群間に統計的な有意差はみられなかった（表 2.7.4.5-22）。52 週間の投与期間中に、1 件以上の重大な低血糖を発現した被験者の割合は、faster aspart（食前投与）群で 9.6%、ノボラピッド®注群で 12.1%であり、いずれの投与群も 26 週間の投与期間と比較してわずかに高かった。単位時間あたりの重大な低血糖の発現件数は、faster aspart（食前投与）群で 18 件/100 人・年、ノボラピッド®注群で 23 件/100 人・年であり、26 週の投与期間と比較してわずかに少なかった〔Trial 3852-52w（M 5.3.5.1）EOT Table14.3.1.30〕。

表 2.7.4.5-22　低血糖の統計解析（3852 試験）

Hypoglycaemic episodes	Episodes per 100 PYE			Estimated treatment ratio, [95% CI]	
	Faster aspart (meal)	Faster aspart (post)	NovoRapid®	Faster aspart (meal)/ NovoRapid®	Faster aspart (post)/ NovoRapid®
26 weeks					
Severe or BG confirmed					
Overall	5899	5443	5865	1.01 [0.88; 1.15]	0.92 [0.81; 1.06]
Daytime	5203	4730	5065	1.03 [0.90; 1.18]	0.93 [0.81; 1.07]
Nocturnal	695	713	800	0.87 [0.71; 1.05]	0.88 [0.73; 1.07]
1 hr after a meal start	147.6	71.6	96.4	1.48 [1.11; 1.96]	0.75 [0.55; 1.02]
Severe (ADA criteria)	25	26	27	0.87 [0.47; 1.62]	0.93 [0.50; 1.73]
52 weeks					
Severe or BG confirmed					
Overall	5329	NA	5319	1.01 [0.88; 1.15]	NA
Daytime	4692	NA	4571	1.03 [0.90; 1.19]	NA
Nocturnal	637	NA	748	0.84 [0.69; 1.01]	NA
1 hr after a meal start	123.5	NA	86.2	1.37 [1.06; 1.76]	NA
Severe (ADA criteria)	18	NA	23	0.79 [0.46; 1.36]	NA

Abbreviations: PYE: patient years of exposure. CI: confidence interval; ADA: American Diabetes Association; BG: Blood glucose; NA: not applicable

2.7.4.5.13.5　バイタルサイン、身体所見及び臨床検査値

26 週間

全体的に、抗体産生に投与群間で違いはみられなかった。総インスリン アスパルト抗体価の平均値はベースラインで低く、試験中にわずかに増加した。ベースラインからの変化量はいずれの投与群においても同程度であった。投与後 26 週のバイタルサイン、身体所見、心電図又は安全性に関する臨床検査値（血液生化学的検査、血液学的検査及び脂質）に、投与群間で臨床的に問題となる違いはみられなかった〔Trial 3852（M 5.3.5.1）Section 12.7 及び 12.8〕。

52 週間

総インスリン アスパルト抗体価の平均値は、52 週間の投与期間中にわずかに増加し、これは投与後 26 週の結果と一致していた。抗体産生に投与群間で違いはみられなかった。投与後 52 週のバイタルサイン、身体所見、心電図又は安全性に関する臨床検査値（血液生化学的検査、血液学的検査及び脂質）

に、投与群間で臨床的に問題となる違いはみられなかった〔Trial 3852-52w（M 5.3.5.1）Section 12.7 及び 12.8〕。

2.7.4.5.13.6　結論

1 型糖尿病患者における faster aspart（食前投与）及びノボラピッド®注の長期間投与（52 週間）後の全体的な安全性プロファイルは同様であり、インスリン アスパルトの製剤として予測されるとおりであった。

2.7.4.5.14　2 型糖尿病患者を対象とした安全性の結果（3853 試験）

2.7.4.5.14.1　評価方法

日本人被験者を組み入れたいずれの検証的試験においても、2 型糖尿病患者における faster aspart の使用経験は検討しなかった。2 型糖尿病患者における faster aspart の使用経験は、日本人被験者を組み入れなかった 1 つの試験（3853 試験）から得られた。2 型糖尿病患者を対象とした安全性評価の補足として、2.7.4.5.14 項に 3853 試験の結果を提示する。試験デザインは Module 2.7.3.1.3.13.2 に示す。

2.7.4.5.14.2　有害事象

有害事象を報告した被験者の割合及び単位時間あたりの発現件数は、2 つの投与群とも同程度であった（faster aspart 群で 302.9 件/100 人・年及び 51.0%、ノボラピッド®注群で 292.1 件/100 人・年及び 54.5%）。有害事象の大部分は非重篤、軽度で、治験責任医師により治験薬との因果関係は「なし」と判定された。治験薬投与下で報告された有害事象のうち、試験の中止に至った事象は 5 例 5 件であった。内訳は、faster aspart 群で 1 件の非重篤な有害事象及び 1 件の重篤な有害事象、ノボラピッド®注群で 3 件の重篤な有害事象であった〔Trial 3853（M 5.3.5.1）EOT Table 14.3.1.1 及び 14.3.2.5〕。

2.7.4.5.14.3　死亡、重篤な有害事象及びその他の重要な有害事象

本試験では 3 例の死亡が報告された。投与期間中に報告された死亡は faster aspart 群で 1 例（肺塞栓症）及びノボラピッド®注群で 1 例（急性心筋梗塞）であった〔Trial 3853（M 5.3.5.1）EOT Table 14.3.2.1〕。また、30 日間の事後調査期間中にノボラピッド®注群で治験薬投与下でない死亡が 1 例（心停止）報告された〔Trial 3853（M 5.3.5.1）Appendix 16.2.7、Listing 16.2.7.6 及び Section 14.3.3〕。死亡に至った肺塞栓症は、治験責任医師により、faster aspart 及び Basal インスリンとの因果関係は「可能性あり」と判定された。死亡に至ったその他の 2 件の事象は、ノボラピッド®注及び Basal インスリンとの因果関係は「なし」と判定された。3 例の死亡とも、イベント判定委員会により心血管死に分類された〔Trial 3853（M 5.3.5.1）Section 12.4.1〕。

イベント判定委員会により確定された心血管系事象は計 27 件であった。このうち、6 件が MACE と確定された（faster aspart 群で 2 件及びノボラピッド®注群で 4 件）。重篤な有害事象の単位時間あたりの発現件数は、faster aspart 群で 12.5 件/100 人・年、ノボラピッド®注群で 19.1 件/100 人・年であった〔Trial 3853（M 5.3.5.1）EOT Table 14.3.1.12 及び 14.3.1.27〕。

2.7.4.5.14.4　低血糖

重大な低血糖、もしくは重大な又は血糖値確定低血糖の単位時間あたりの発現件数について、投与群間に統計的な有意差はみられなかった（表 2.7.4.5-23）。また、日中又は夜間（00 時 01 分～05 時 59 分）の重大な又は血糖値確定低血糖の単位時間あたりの発現件数について、投与群間に統計的な有意差はみられなかった。食事開始後 2 時間以内に発現した重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、ノボラピッド®注群と比較して、faster aspart 群で統計的に有意に多かった。この低血糖が、全体の低血糖の総発現件数に占める割合は低かった。

低血糖に関する詳細は、総括報告書〔Trial 3853（M 5.3.5.1）Section 12.6〕参照。

表 2.7.4.5-23　低血糖の統計解析（3853 試験）

Hypoglycaemic episodes	**Episodes per 100 PYE**		**Estimated treatment ratio, [95% CI]**
	Faster aspart	**NovoRapid®**	**Faster aspart/ NovoRapid®**
Severe or BG confirmed			
Overall	1787.8	1659.1	1.09 [0.88; 1.36]
Daytime	1609.5	1525.3	1.07 [0.86; 1.33]
Nocturnal	178.3	133.7	1.38 [0.96; 2.00]
Up to 2 hours after a meal	226.5	148.5	1.60 [1.13; 2.27]
Severe (ADA criteria)	16.9	10.5	1.25 [0.44; 3.55]

Abbreviations: ADA: American Diabetes Association, BG: Blood glucose, CI: confidence interval, PYE: patient years of exposure.

2.7.4.5.14.5　バイタルサイン、身体所見及び臨床検査値

ベースラインから投与終了時まで、身体所見、バイタルサイン、眼底検査、心電図又は臨床検査値について、いずれの投与群においても臨床的に意味のある変化は認められず、投与群間でも臨床的に意味のある違いは認められなかった〔Trial 3853（M 5.3.5.1）Section 12.7 及び 12.8〕。

2.7.4.5.14.6　結論

2 型糖尿病患者における faster aspart 及びノボラピッド®注の全体的な安全性プロファイルは同様であり、インスリン アスパルトの薬剤として予測されるとおりであった。

2.7.4.6 市販後データ

2.7.4.6.1 評価方法

2.7.4.6 項には、faster aspart と同一の有効成分（インスリン アスパルト）を含有するノボラピッド®注、ノボラピッド®30 ミックス注、ノボラピッド®50 ミックス注、ノボラピッド®70 ミックス注及び本剤（海外の販売名：Fiasp®）の 2016 年 10 月 1 日から 2017 年 9 月 30 日までの期間を対象とした PSUR/PBRER のグローバル最新版に基づき、市販後の安全性情報を提示する。当該 PSUR/PBRER は、faster aspart のベネフィット・リスクのバランスに関する資料として、Module 5 に含めた。

Faster aspart は、当該 PSUR/PBRER の報告期間中に海外で製造販売承認を取得している〔カナダ、EU 及び米国で、それぞれ 2017 年 1 月 6 日、2017 年 1 月 9 日及び 2017 年 9 月 29 日に承認（Module 1.6）〕。

2.7.4.6.2 市販後の情報

平均 1 日用量を 40 単位（世界保健機関による超速効型インスリンアナログの Defined Daily Dose）とする仮定に基づくと、前出の PSUR/PBRER 報告期間中におけるインスリン アスパルトを含有する製剤の総曝露期間は 9,985,190 人・年であり、うち約 0.25%が Fiasp®の曝露期間であると推定された。

報告期間中における Fiasp®の市販後曝露期間の推定値は全世界で 24,914 人・年であり、地域別分布は、欧州が 21,652 人・年、日本、中国及び米国がいずれも 0 人・年、その他の国々が 3,262 人・年であった。

PSUR の報告期間中に、市販後に得られたデータから 2 つの安全性シグナルが検出された。

- Fiasp®とトレシーバ®注の取り違え
- インスリンポンプ使用時に起こり得る効果欠如

Fiasp®とトレシーバ®注の取り違えに関するシグナル

Fiasp®の既存の重要な潜在的リスクである「投薬過誤（主に誤薬投与）」に関して、PSUR の報告期間中に新たな重要な情報が得られた。製剤の外観の色が類似していることによる Fiasp®とトレシーバ®注の取り違えは、安全性シグナルとして検出された。Fiasp®の市販後、計 40 例 42 件の投薬過誤に関連する有害事象が報告された。このうち 19 例 20 件の事象は、患者が製剤を使用する際に起こり得る Fiasp®とトレシーバ®注の取り違えに関するものであり、実際に誤薬投与に至った事例も、未然に防がれた事例も含まれていた。そのため、重要な潜在的リスクである「投薬過誤（主に誤薬投与）」を、グローバルでは Fiasp®の重要な特定されたリスクに変更した。取り違えに関するシグナルへの対応として、製剤の外観の色を他剤と取り違えにくいように変更しており、日本においては新しい色のラベルや包装箱を使用した製剤を販売する予定である。以上により、製剤の取り違えに関する安全性上の懸念は、日本においては軽減されると考えられる。

インスリンポンプ使用時に起こり得るFiasp®の効果欠如に関するシグナル

Fiasp®で、計20例の効果欠如が報告された。このうち、6例で報告された事象はインスリンポンプ使用者から、7例の事象はペン型注入器使用者において報告されたものであった。残りの7例においては、投与方法は不明と報告された。報告された症例の評価に基づき、本件についてはさらなる調査が必要であると考えられたため、安全性シグナルとした。このシグナルが検出された時点では、Fiasp®の使用とこれらの報告症例との因果関係は確認されていなかった。報告されたロット番号及び参照見本の調査により、得られたデータからは、Fiasp®の品質に関する問題は示唆されなかった。この安全性シグナルについては、PSURのデータ固定時点で精査中であった。

2.7.4.6.3 ベネフィットとリスクのバランス

得られているデータ（臨床試験データ、市販後データ及び非自発的な情報源からのデータを含む）に基づき、faster aspartのベネフィット・リスクのバランスは良好に維持されていると考えられる。

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フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.4.7. 付録
1. 曝露状況

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2.7.4.7.1.1. 曝露 - 投与期間別 - 安全性解析対象集団（4131 試験）

	Any exposure N	>= 3 - <6 months N	>= 6 months N
Faster aspart (meal)	342	4	335
Faster aspart (post)	341	6	332
Faster aspart (meal+post)	683	10	667
NovoRapid (meal)	342	6	332

N: Number of subjects
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
A month is set to 30 days. A treatment completer is considered to have exposure >= 6 months. Exposure during run-in is excluded.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:09:42 - t_exp.sas/t_exp_4131_sas.txt

2.7.4.7.1.2. 曝露 - 投与期間別 - 安全性解析対象集団（4101 試験）

	Any exposure N	>= 3 - <6 months N	>= 6 months N
Faster aspart (meal)	261	0	255
Faster aspart (post)	258	5	249
Faster aspart (meal+post)	519	5	504
NovoRapid (meal)	258	3	252

N: Number of subjects
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
A month is set to 30 days. A treatment completer is considered to have exposure >= 6 months. Exposure during run-in is excluded.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:09:44 - t_exp.sas/t_exp_4101_sas.txt

2.7.4.7.1.3. 曝露 - 投与期間別 - 日本人集団 - 安全性解析対象集団（4131 試験）

	Any exposure N	>= 3 - <6 months N	>= 6 months N
Faster aspart (meal)	73	1	72
Faster aspart (post)	89	4	84
Faster aspart (meal+post)	162	5	156
NovoRapid (meal)	83	1	79

N: Number of subjects
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
A month is set to 30 days. A treatment completer is considered to have exposure >= 6 months. Exposure during run-in is excluded.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:09:43 - t_exp.sas/t_exp_4131_jp_sas.txt

2.7.4.7.1.4. 曝露 - 投与期間別 - 日本人集団 - 安全性解析対象集団（4101 試験）

	Any exposure N	>= 3 - <6 months N	>= 6 months N
Faster aspart (meal)	24	0	23
Faster aspart (post)	19	0	18
Faster aspart (meal+post)	43	0	41
NovoRapid (meal)	23	0	22

N: Number of subjects
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
A month is set to 30 days. A treatment completer is considered to have exposure >= 6 months. Exposure during run-in is excluded.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:09:45 - t_exp.sas/t_exp_4101_jp_sas.txt

フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.4.7. 付録
2. 有害事象
1. 特に注目すべき安全性領域

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	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	342			341			683			342		
Total exposure (yrs)	171.3			170.2			341.5			170.2		
Total events	4 (1.2)	4	2.3	1 (0.3)	1	0.6	5 (0.7)	5	1.5	0		
Cardiac disorders	2 (0.6)	2	1.2	0			2 (0.3)	2	0.6	0		
Coronary artery disease	1 (0.3)	1	0.6	0			1 (0.1)	1	0.3	0		
Myocardial ischaemia	1 (0.3)	1	0.6	0			1 (0.1)	1	0.3	0		
Nervous system disorders	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Carotid arteriosclerosis	1 (0.3)	1	0.6	0			1 (0.1)	1	0.3	0		
Cerebrovascular accident	0			1 (0.3)	1	0.6	1 (0.1)	1	0.3	0		
Injury, poisoning and procedural complications	1 (0.3)	1	0.6	0			1 (0.1)	1	0.3	0		
Extradural haematoma	1 (0.3)	1	0.6	0			1 (0.1)	1	0.3	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.2.1.2. 治験薬投与下で発現した心血管系事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4131 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 113006/ Faster aspart (meal)/ 39/M/24.0	3	Injury, poisoning and procedural complications/ Extradural haematoma/ Left Acute Extradural Haematoma	04JAN2017	Y/ Y	Japan
NN1218-4131/ 113009/ Faster aspart (meal)/ 66/F/23.5	8	Nervous system disorders/ Carotid arteriosclerosis/ Right Internal Carotid Artery Plaque	07DEC2016	Y/ Y	Japan
NN1218-4131/ 204001/ Faster aspart (post)/ 44/F/26.3	2	Nervous system disorders/ Cerebrovascular accident/ Cerebro Vascular Accident Right Hemiparesis	03APR2017	Y/ Y	Asia (Excluding Japan)
NN1218-4131/ 756005/ Faster aspart (meal)/ 53/M/28.1	5	Cardiac disorders/ Myocardial ischaemia/ Mild Inferior Ischemia At Thallium Stress Test	30JAN2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Cardiovascular adverse events - treatment emergent – listing – trial 4131 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 840002/ Faster aspart (meal)/ 63/M/23.6	7	Cardiac disorders/ Coronary artery disease/ Coronary Artery Disease	12JAN2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:22 - l_ae_te.sas/l_card_ae_4131_in_sas.txt

2.7.4.7.2.1.3. 治験薬投与下で発現した心血管系事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4101 試験）

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:08:16 - t_ae_te_sum.sas/t_card_ae_sum_4101_on_sas.txt

2.7.4.7.2.1.4. 治験薬投与下で発現した心血管系事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4101 試験）

There are no data for this output.

2.7.4.7.2.1.5. 治験薬投与下で発現した心血管系事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（3854 試験）

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:08:03 - t_ae_te_3854_sum.sas/t_card_ae_sum_3854_on_sas.txt

2.7.4.7.2.1.6. 治験薬投与下で発現した心血管系事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（3854 試験）

There are no data for this output.

2.7.4.7.2.1.7. 治験薬投与下で発現した糖尿病網膜症に関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	342			341			683			342		
Total exposure (yrs)	171.3			170.2			341.5			170.2		
Total events	12 (3.5)	12	7.0	16 (4.7)	18	10.6	28 (4.1)	30	8.8	14 (4.1)	15	8.8
Eye disorders	12 (3.5)	12	7.0	16 (4.7)	18	10.6	28 (4.1)	30	8.8	14 (4.1)	15	8.8
Diabetic retinopathy	7 (2.0)	7	4.1	12 (3.5)	12	7.1	19 (2.8)	19	5.6	7 (2.0)	7	4.1
Macular oedema	0			2 (0.6)	2	1.2	2 (0.3)	2	0.6	2 (0.6)	2	1.2
Retinopathy	2 (0.6)	2	1.2	0			2 (0.3)	2	0.6	2 (0.6)	2	1.2
Retinopathy proliferative	0			1 (0.3)	1	0.6	1 (0.1)	1	0.3	1 (0.3)	1	0.6
Vitreous haemorrhage	0			2 (0.6)	2	1.2	2 (0.3)	2	0.6	0		
Cystoid macular oedema	0			0			0			1 (0.3)	1	0.6
Maculopathy	0			0			0			1 (0.3)	1	0.6
Retinal exudates	0			1 (0.3)	1	0.6	1 (0.1)	1	0.3	0		
Retinal haemorrhage	1 (0.3)	1	0.6	0			1 (0.1)	1	0.3	0		
Retinal ischaemia	0			0			0			1 (0.3)	1	0.6
Visual acuity reduced transiently	1 (0.3)	1	0.6	0			1 (0.1)	1	0.3	0		
Vitreous detachment	1 (0.3)	1	0.6	0			1 (0.1)	1	0.3	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.2.1.8. 治験薬投与下で発現した糖尿病網膜症に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4131 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 101018/ NovoRapid (meal)/ 30/F/33.5	4	Eye disorders/ Diabetic retinopathy/ Simple Retinopathy(Right)	02MAY2017	Y/ Y	Japan
NN1218-4131/ 101020/ Faster aspart (post)/ 64/F/24.2	3	Eye disorders/ Diabetic retinopathy/ Simple Retinopathy(Left)	12JUN2017	Y/ Y	Japan
NN1218-4131/ 102006/ Faster aspart (post)/ 53/F/21.6	7	Eye disorders/ Diabetic retinopathy/ Proliferative Diabetic Retinopathy(Right Eye)	12SEP2016	Y/ Y	Japan
NN1218-4131/ 102010/ Faster aspart (post)/ 48/M/27.7	2	Eye disorders/ Diabetic retinopathy/ Simple Diabetic Retinopathy	07FEB2017	Y/ Y	Japan

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Diabetic retinopathy adverse events - treatment emergent - listing - trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 103010/ Faster aspart (post)/ 37/M/19.0	4	Eye disorders/ Diabetic retinopathy/ Worsening Of Diabetic Retinopathy	07DEC2016	Y/ Y	Japan
	7	Eye disorders/ Macular oedema/ Macular Oedema	29MAR2017	Y/ Y	Japan
NN1218-4131/ 104010/ Faster aspart (meal)/ 42/F/20.9	10	Eye disorders/ Diabetic retinopathy/ Simple Retinopathy(Right)	09MAR2017	Y/ Y	Japan
NN1218-4131/ 105006/ Faster aspart (meal)/ 64/F/23.5	3	Eye disorders/ Diabetic retinopathy/ Diabetic Retinopathy	23FEB2017	Y/ Y	Japan

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Diabetic retinopathy adverse events - treatment emergent - listing - trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 106001/ NovoRapid (meal)/ 54/M/22.5	1	Eye disorders/ Diabetic retinopathy/ Sinple Diabetic Retinopathy	08AUG2016	Y/ Y	Japan
NN1218-4131/ 107002/ NovoRapid (meal)/ 32/M/22.0	4	Eye disorders/ Diabetic retinopathy/ Left Eye Simple Diabetic Retinopathy	23JAN2017	Y/ Y	Japan
NN1218-4131/ 107010/ Faster aspart (post)/ 59/F/26.7	8	Eye disorders/ Macular oedema/ Macular Edema	01DEC2016	Y/ Y	Japan
NN1218-4131/ 109009/ Faster aspart (meal)/ 41/M/32.8	3	Eye disorders/ Retinal haemorrhage/ Preretinal Hemorrhage(Left)	01MAR2017	Y/ Y	Japan

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Diabetic retinopathy adverse events - treatment emergent - listing - trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 112012/ Faster aspart (meal)/ 22/F/19.2	5	Eye disorders/ Visual acuity reduced transiently/ Visual Acuity Reduced Transiently(Left Eye)	03MAY2017	Y/ Y	Japan
NN1218-4131/ 113009/ Faster aspart (meal)/ 66/F/23.5	5	Eye disorders/ Diabetic retinopathy/ Diabetic Retinopathy Aggravated(Right)	13OCT2016	Y/ Y	Japan
NN1218-4131/ 114007/ NovoRapid (meal)/ 44/F/27.7	4	Eye disorders/ Diabetic retinopathy/ Diabetic Retinopathy	09MAY2017	Y/ Y	Japan
NN1218-4131/ 114008/ NovoRapid (meal)/ 47/F/24.7	3	Eye disorders/ Diabetic retinopathy/ Worsening Of Diabetic Retinopathy	13MAY2017	Y/ Y	Japan

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Diabetic retinopathy adverse events - treatment emergent - listing - trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 118005/ Faster aspart (meal)/ 56/F/21.5	8	Eye disorders/ Diabetic retinopathy/ Diabetic Retinopathy(Right)	23MAR2017	Y/ Y	Japan
NN1218-4131/ 124003/ Faster aspart (post)/ 58/F/26.8	2	Eye disorders/ Diabetic retinopathy/ Worsening Of Diabetic Retinopathy	10JAN2017	Y/ Y	Japan
NN1218-4131/ 124010/ NovoRapid (meal)/ 59/M/26.2	3	Eye disorders/ Diabetic retinopathy/ Diabetic Maculopathy Left Eye	20JUN2017	Y/ Y	Japan
NN1218-4131/ 202008/ Faster aspart (post)/ 25/M/24.8	4	Eye disorders/ Diabetic retinopathy/ Mild Non Proliferatic Diabetic Retinopathy In Right Eye	14JUN2017	Y/ Y	Asia (Excluding Japan)

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Diabetic retinopathy adverse events - treatment emergent - listing - trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 203004/ Faster aspart (post)/ 30/F/23.2	7	Eye disorders/ Diabetic retinopathy/ Worsening Of Retinopathy Right Eye Mild Npdr To Moderate Npdr	26OCT2016	Y/ Y	Asia (Excluding Japan)
NN1218-4131/ 401003/ Faster aspart (meal)/ 68/F/25.4	1	Eye disorders/ Diabetic retinopathy/ Very Minimal Background Diabetic Retinopathy -Left Eye	10JAN2017	Y/ Y	Europe
NN1218-4131/ 404001/ Faster aspart (meal)/ 57/M/28.0	4	Eye disorders/ Vitreous detachment/ Vitreous Floaters (Pvd - Posterior Vitreous Detachment)	30DEC2016	Y/ Y	Europe
NN1218-4131/ 556003/ NovoRapid (meal)/ 45/M/26.6	4	Eye disorders/ Macular oedema/ Worsening Macula Edema Left Eye	02FEB2017	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Diabetic retinopathy adverse events - treatment emergent - listing - trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 601002/ NovoRapid (meal)/ 40/F/20.2	2	Eye disorders/ Diabetic retinopathy/ Non-Proliferative Diabetic Retinopathy	06MAR2017	Y/ Y	Europe
NN1218-4131/ 601012/ Faster aspart (meal)/ 45/M/30.5	2	Eye disorders/ Retinopathy/ Non Prolipherant Retinopathy	31MAY2017	Y/ Y	Europe
NN1218-4131/ 603001/ NovoRapid (meal)/ 56/F/27.8	2	Eye disorders/ Retinal ischaemia/ Peripheric Iscaemic Area Right Eye	15NOV2016	Y/ Y	Europe
NN1218-4131/ 603008/ Faster aspart (post)/ 20/F/17.8	1	Eye disorders/ Diabetic retinopathy/ Initial Diabetix Retinopathy	18MAY2017	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Diabetic retinopathy adverse events - treatment emergent - listing - trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 651002/ Faster aspart (meal)/ 23/F/22.9	8	Eye disorders/ Retinopathy/ Mild Nonproliferative Retinopathy	16JAN2017	Y/ Y	Europe
NN1218-4131/ 702004/ NovoRapid (meal)/ 21/F/25.5	2	Eye disorders/ Macular oedema/ Macular Edema(Ou)	01MAY2017	Y/ Y	Asia (Excluding Japan)
NN1218-4131/ 751003/ Faster aspart (post)/ 28/M/28.4	2	Eye disorders/ Retinal exudates/ Isolated Hard Exudate Macula (Left Eye, Temporal/Inferior Quadrant)	22MAR2017	Y/ Y	North America
NN1218-4131/ 753004/ Faster aspart (post)/ 61/F/21.7	3	Eye disorders/ Diabetic retinopathy/ Non Proliferative Diabetic Retinopathy - Right Eye	27MAR2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Diabetic retinopathy adverse events - treatment emergent – listing – trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 755004/ NovoRapid (meal)/ 64/M/23.7	4	Eye disorders/ Maculopathy/ Right Eye Malculopathy	28MAR2017	Y/ Y	North America
	3	Eye disorders/ Retinopathy/ Bilateral Retinopathy	30MAR2017	Y/ Y	North America
NN1218-4131/ 801002/ NovoRapid (meal)/ 24/F/21.0	3	Eye disorders/ Retinopathy/ Worsening Of Retinopathy	11JAN2017	Y/ Y	North America
NN1218-4131/ 811001/ Faster aspart (post)/ 37/M/19.0	3	Eye disorders/ Diabetic retinopathy/ Bilateral Background Retinopathy	05JAN2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Diabetic retinopathy adverse events - treatment emergent - listing - trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 811002/ Faster aspart (meal)/ 51/M/31.1	10	Eye disorders/ Diabetic retinopathy/ Background Retinopathy Bilateral	07JAN2017	Y/ Y	North America
NN1218-4131/ 813002/ Faster aspart (post)/ 33/M/21.6	2	Eye disorders/ Vitreous haemorrhage/ Both Eye Vitreous Hemorrhage-Worsened	28SEP2016	Y/ Y	North America
NN1218-4131/ 813006/ Faster aspart (post)/ 58/F/33.8	1	Eye disorders/ Retinopathy proliferative/ Proliferative Retinopathy With Macular Edema	25JAN2017	Y/ Y	North America
	2	Eye disorders/ Vitreous haemorrhage/ Vitreous Hemorrhage In The Right Eye	28APR2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Diabetic retinopathy adverse events - treatment emergent - listing - trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 827002/ NovoRapid (meal)/ 59/F/28.1	7	Eye disorders/ Cystoid macular oedema/ Cystoid Macular Edema, Le	16SEP2016	Y/ Y	North America
NN1218-4131/ 827010/ NovoRapid (meal)/ 43/F/32.6	3	Eye disorders/ Retinopathy proliferative/ Proliferative Retinopathy Of Both Eyes, Worsening From Baseline	29DEC2016	Y/ Y	North America
NN1218-4131/ 834005/ Faster aspart (post)/ 25/M/33.7	2	Eye disorders/ Diabetic retinopathy/ Mild Nonproliferative Diabetic Retinophaty	20JUN2017	Y/ Y	North America
NN1218-4131/ 859001/ Faster aspart (meal)/ 35/M/35.6	2	Eye disorders/ Diabetic retinopathy/ Moderate To Severe Back Round Diabetic Retinopathy With Possible Early Macula Involvement Left Eye	16FEB2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Diabetic retinopathy adverse events - treatment emergent – listing – trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 859003/ Faster aspart (post)/ 35/F/23.0	3	Eye disorders/ Diabetic retinopathy/ Early Diabetic Retinopathy	28FEB2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:23 - l_ae_te.sas/l_diab_ae_4131_in_sas.txt

2.7.4.7.2.1.9. 治験薬投与下で発現した糖尿病網膜症に関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4101 試験）

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:08:18 - t_ae_te_sum.sas/t_diab_ae_sum_4101_on_sas.txt

2.7.4.7.2.1.10. 治験薬投与下で発現した糖尿病網膜症に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4101 試験）

There are no data for this output.

2.7.4.7.2.1.11. 治験薬投与下で発現した糖尿病網膜症に関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（3854 試験）

	Faster aspart N	(%)	E	R	NovoRapid N	(%)	E	R
Number of subjects	236				236			
Total exposure (yrs)	72.8				71.7			
Total events	6	(2.5)	6	8.2	6	(2.5)	8	11.2
Eye disorders	6	(2.5)	6	8.2	6	(2.5)	8	11.2
Diabetic retinopathy	4	(1.7)	4	5.5	4	(1.7)	4	5.6
Retinal haemorrhage	0				1	(0.4)	2	2.8
Retinopathy	1	(0.4)	1	1.4	1	(0.4)	1	1.4
Macular oedema	0				1	(0.4)	1	1.4
Vitreous opacities	1	(0.4)	1	1.4	0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:08:05 - t_ae_te_3854_sum.sas/t_diab_ae_sum_3854_on_sas.txt

2.7.4.7.2.1.12. 治験薬投与下で発現した糖尿病網膜症に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（3854 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-3854/ 400002/ Faster aspart/ 50/M/21.2	2	Eye disorders/ Retinopathy/ Worsening Retinopathy	28NOV2016	Y/ Y	Europe
NN1218-3854/ 402004/ Faster aspart/ 76/M/22.6	6	Eye disorders/ Vitreous opacities/ Vitreous Opacity	30JAN2017	Y/ Y	Europe
NN1218-3854/ 404002/ Faster aspart/ 42/M/30.0	5	Eye disorders/ Diabetic retinopathy/ Diabetic Retinopathy Left Eye, Not Proliferated	21DEC2016	Y/ Y	Europe
NN1218-3854/ 405010/ Faster aspart/ 62/M/28.1	1	Eye disorders/ Diabetic retinopathy/ Non-Proliferative Retinopathy Both Eyes	18MAY2017	Y/ Y	Europe
NN1218-3854/ 409004/ NovoRapid/ 21/M/29.3	3	Eye disorders/ Diabetic retinopathy/ Non-Proliferative Diabetic Retinpathy	29MAY2017	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Diabetic retinopathy adverse events - treatment emergent - listing - trial 3854 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-3854/ 609001/ NovoRapid/ 26/F/22.0	3	Eye disorders/ Diabetic retinopathy/ Worsening Of Non-Proliferative Diabetic Retinopathy (Hemorrhage In Both Eyes)	15MAR2017	Y/ Y	Europe
NN1218-3854/ 904012/ Faster aspart/ 53/M/28.3	2	Eye disorders/ Diabetic retinopathy/ New Finding Of Mild-Moderate Non Proliferative Diabetic Retinopathy On 6/2017 Not Present 11/2016	08JUN2017	Y/ Y	North America
NN1218-3854/ 906006/ NovoRapid/ 36/F/29.2	3	Eye disorders/ Diabetic retinopathy/ Mild Diabetic Retinopathy, Right Eye	09MAY2017	Y/ Y	North America
	4	Eye disorders/ Retinopathy/ Mild Non-Proliferative Retinopathy, Left Eye	31MAY2017	Y/ Y	North America
NN1218-3854/ 923008/ Faster aspart/ 51/F/35.4	3	Eye disorders/ Diabetic retinopathy/ Mild Non-Proliferative Diabetic Retinopathy	09JUN2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Diabetic retinopathy adverse events - treatment emergent – listing – trial 3854 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-3854/ 926007/ NovoRapid/ 63/F/27.1	7	Eye disorders/ Macular oedema/ New Macular Edema	03FEB2017	Y/ Y	North America
NN1218-3854/ 926009/ NovoRapid/ 58/M/30.1	5	Eye disorders/ Diabetic retinopathy/ Mild Non-Proliferative Diabetic Retinopathy Without Macular Edema	02MAR2017	Y/ Y	North America
NN1218-3854/ 927003/ NovoRapid/ 55/F/23.1	1	Eye disorders/ Retinal haemorrhage/ 2 Small Peripheral Retinal Hemorrhages Right Temporal	19JAN2017	Y/ Y	North America
	2	Eye disorders/ Retinal haemorrhage/ One Small Peripheral Retinal Hemorrhage Left Eye	19JAN2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.2.1.13. 治験薬投与下で発現した屈折障害に関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	342				341				683				342			
Total exposure (yrs)	171.3				170.2				341.5				170.2			
Total events	0				1	(0.3)	2	1.2	1	(0.1)	2	0.6	0			
Eye disorders	0				1	(0.3)	2	1.2	1	(0.1)	2	0.6	0			
Astigmatism	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	0			
Myopia	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.2.1.14. 治験薬投与下で発現した屈折障害に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4131 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 841003/ Faster aspart (post)/ 32/M/30.0	4	Eye disorders/ Myopia/ Myopia	24JAN2017	Y/ Y	North America
	5	Eye disorders/ Astigmatism/ Astigmatism	24JAN2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.2.1.15. 治験薬投与下で発現した屈折障害に関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4101 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	261			258			519			258		
Total exposure (yrs)	128.4			127.7			256.0			127.7		
Total events	2 (0.8)	3	2.3	1 (0.4)	1	0.8	3 (0.6)	4	1.6	0		
Eye disorders	2 (0.8)	3	2.3	1 (0.4)	1	0.8	3 (0.6)	4	1.6	0		
Myopia	2 (0.8)	2	1.6	1 (0.4)	1	0.8	3 (0.6)	3	1.2	0		
Astigmatism	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.2.1.16. 治験薬投与下で発現した屈折障害に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4101 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4101/ 144006/ Faster aspart (meal)/ 14/F/24.1	2	Eye disorders/ Myopia/ Slight Right Eye Myopia	18JUL2017	Y/ Y	North America
	3	Eye disorders/ Astigmatism/ Bilateral Astygmatism	18JUL2017	Y/ Y	North America
NN1218-4101/ 808013/ Faster aspart (post)/ 16/F/18.1	2	Eye disorders/ Myopia/ Myopia	14SEP2017	Y/ Y	Europe
NN1218-4101/ 810008/ Faster aspart (meal)/ 12/F/15.6	1	Eye disorders/ Myopia/ Worsening Of Myopia	23MAR2017	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.2.1.17. 治験薬投与下で発現した屈折障害に関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（3854 試験）

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:08:06 - t_ae_te_3854_sum.sas/t_ref_ae_sum_3854_on_sas.txt

2.7.4.7.2.1.18. 治験薬投与下で発現した屈折障害に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（3854 試験）

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:10 - l_ae_3854_te.sas/l_ref_ae_3854_in_sas.txt

2.7.4.7.2.1.19. 治験薬投与下で発現した末梢性ニューロパチーに関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	342			341			683			342		
Total exposure (yrs)	171.3			170.2			341.5			170.2		
Total events	4 (1.2)	4	2.3	7 (2.1)	7	4.1	11 (1.6)	11	3.2	2 (0.6)	2	1.2
Nervous system disorders	4 (1.2)	4	2.3	6 (1.8)	6	3.5	10 (1.5)	10	2.9	2 (0.6)	2	1.2
Diabetic neuropathy	3 (0.9)	3	1.8	0			3 (0.4)	3	0.9	0		
Hypoaesthesia	0			2 (0.6)	2	1.2	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Paraesthesia	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Polyneuropathy	0			2 (0.6)	2	1.2	2 (0.3)	2	0.6	0		
Hyporeflexia	0			1 (0.3)	1	0.6	1 (0.1)	1	0.3	0		
Musculoskeletal and connective tissue disorders	0			1 (0.3)	1	0.6	1 (0.1)	1	0.3	0		
Muscular weakness	0			1 (0.3)	1	0.6	1 (0.1)	1	0.3	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:08:22 - t_ae_te_sum.sas/t_per_neu_ae_sum_4131_on_sas.txt

2.7.4.7.2.1.20. 治験薬投与下で発現した末梢性ニューロパチーに関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4131 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 102012/ NovoRapid (meal)/ 67/F/20.0	3	Nervous system disorders/ Hypoaesthesia/ Numbness In Fingertips	15DEC2016	Y/ Y	Japan
NN1218-4131/ 103007/ Faster aspart (post)/ 78/F/18.8	3	Nervous system disorders/ Hypoaesthesia/ Numbness In Hand	02MAR2017	Y/ Y	Japan
NN1218-4131/ 104010/ Faster aspart (meal)/ 42/F/20.9	8	Nervous system disorders/ Diabetic neuropathy/ Diabetic Neuropathy	04MAR2017	Y/ Y	Japan
NN1218-4131/ 454001/ Faster aspart (meal)/ 41/F/21.2	2	Nervous system disorders/ Diabetic neuropathy/ Exacerbation Of Diabetic Polyneuropathic Symptoms	28SEP2016	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Peripheral neuropathy adverse events - treatment emergent - listing - trial 4131 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 454006/ Faster aspart (post)/ 38/M/27.2	3	Nervous system disorders/ Polyneuropathy/ Exacerbation Of Polyneuropathic Symptoms	14DEC2016	Y/ Y	Europe
NN1218-4131/ 454008/ Faster aspart (post)/ 52/F/18.1	1	Nervous system disorders/ Polyneuropathy/ Exacerbation Of Poluneuropatic Symptoms	07SEP2016	Y/ Y	Europe
NN1218-4131/ 756005/ Faster aspart (meal)/ 53/M/28.1	7	Nervous system disorders/ Diabetic neuropathy/ Worsening Of Diabetic Neuropathy	30NOV2016	Y/ Y	North America
NN1218-4131/ 807003/ Faster aspart (post)/ 34/F/32.9	6	Nervous system disorders/ Hypoaesthesia/ Bi-Lateral Numbness In Fingers	17DEC2016	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Peripheral neuropathy adverse events - treatment emergent - listing - trial 4131 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 811002/ Faster aspart (meal)/ 51/M/31.1	9	Nervous system disorders/ Paraesthesia/ Intermittent Episodes Of Generalized Paresthesias	01NOV2016	Y/ Y	North America
NN1218-4131/ 827005/ NovoRapid (meal)/ 53/M/28.1	3	Nervous system disorders/ Paraesthesia/ Tingling And Numbness Tip Of Left Middle Finger	15JAN2017	Y/ Y	North America
NN1218-4131/ 830001/ Faster aspart (post)/ 53/M/25.0	3	Musculoskeletal and connective tissue disorders/ Muscular weakness/ Left Knee Weakness	27OCT2016	Y/ Y	North America
NN1218-4131/ 846002/ Faster aspart (post)/ 29/F/29.0	10	Nervous system disorders/ Paraesthesia/ Recurring Bilateral Toes Tingling	24JAN2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Peripheral neuropathy adverse events - treatment emergent – listing – trial 4131 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 851003/ Faster aspart (post)/ 47/M/25.7	2	Nervous system disorders/ Hyporeflexia/ Diminished Deep Tendon Reflexes - Knees And Ankles	27OCT2016	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.2.1.21. 治験薬投与下で発現した末梢性ニューロパチーに関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4101 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	261			258			519			258		
Total exposure (yrs)	128.4			127.7			256.0			127.7		
Total events	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
General disorders and administration site conditions	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Gait disturbance	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.2.1.22. 治験薬投与下で発現した末梢性ニューロパチーに関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4101 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4101/ 352009/ Faster aspart (meal)/ 8/F/18.4	2	General disorders and administration site conditions/ Gait disturbance/ Heel Strikes	26NOV2016	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.2.1.23. 治験薬投与下で発現した末梢性ニューロパチーに関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（3854 試験）

	Faster aspart N	(%)	E	R	NovoRapid N	(%)	E	R
Number of subjects	236				236			
Total exposure (yrs)	72.8				71.7			
Total events	6	(2.5)	7	9.6	4	(1.7)	4	5.6
Nervous system disorders	6	(2.5)	7	9.6	3	(1.3)	3	4.2
Paraesthesia	4	(1.7)	4	5.5	0			
Neuropathy peripheral	1	(0.4)	2	2.7	1	(0.4)	1	1.4
Hypoaesthesia	0				1	(0.4)	1	1.4
Hyporeflexia	0				1	(0.4)	1	1.4
Polyneuropathy	1	(0.4)	1	1.4	0			
Musculoskeletal and connective tissue disorders	0				1	(0.4)	1	1.4
Muscular weakness	0				1	(0.4)	1	1.4

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:08:07 - t_ae_te_3854_sum.sas/t_per_neu_ae_sum_3854_on_sas.txt

2.7.4.7.2.1.24. 治験薬投与下で発現した末梢性ニューロパチーに関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（3854 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-3854/ 103004/ Faster aspart/ 44/M/29.2	7	Nervous system disorders/ Polyneuropathy/ Worsening Polyneuropathy	26OCT2016	Y/ Y	Europe
NN1218-3854/ 202002/ NovoRapid/ 57/F/31.5	6	Nervous system disorders/ Neuropathy peripheral/ Peripheral Neuropathy	22NOV2016	Y/ Y	North America
NN1218-3854/ 500002/ Faster aspart/ 43/F/21.4	8	Nervous system disorders/ Paraesthesia/ Feeling Of Tingling In Ri Upperarm	31JAN2017	Y/ Y	Europe
NN1218-3854/ 500003/ Faster aspart/ 55/M/25.0	2	Nervous system disorders/ Paraesthesia/ Tingling In Left Hand	27OCT2016	Y/ Y	Europe
NN1218-3854/ 509003/ NovoRapid/ 45/F/24.2	1	Nervous system disorders/ Hyporeflexia/ Reduced Knee Tension Reflex Right Leg	20MAR2017	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Peripheral neuropathy adverse events - treatment emergent - listing - trial 3854 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-3854/ 803001/ NovoRapid/ 54/F/21.8	5	Nervous system disorders/ Hypoaesthesia/ Intermittent Numbness In Hands And Occasionally Into The Arms	03NOV2016	Y/ Y	Europe
NN1218-3854/ 904004/ Faster aspart/ 50/M/29.4	2	Nervous system disorders/ Paraesthesia/ Right Hand Parasthesias Thumb And Forefinger	25JAN2017	Y/ Y	North America
NN1218-3854/ 906004/ Faster aspart/ 59/M/26.8	1	Nervous system disorders/ Paraesthesia/ Intermittent Tingling, Right Hand	27DEC2016	Y/ Y	North America
NN1218-3854/ 919002/ Faster aspart/ 56/M/30.4	2	Nervous system disorders/ Neuropathy peripheral/ Worsening Of Peripheral Neuropathy	27SEP2016	Y/ Y	North America
	5	Nervous system disorders/ Neuropathy peripheral/ Worsening Of Peripheral Neuropathy	19NOV2016	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Peripheral neuropathy adverse events - treatment emergent – listing – trial 3854 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-3854/ 926010/ NovoRapid/ 58/F/30.6	2	Musculoskeletal and connective tissue disorders/ Muscular weakness/ Extremities Weakness	26DEC2016	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.2.1.25. 治験薬投与下で発現した末梢性浮腫に関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	342			341			683			342		
Total exposure (yrs)	171.3			170.2			341.5			170.2		
Total events	1 (0.3)	1	0.6	2 (0.6)	3	1.8	3 (0.4)	4	1.2	2 (0.6)	2	1.2
General disorders and administration site conditions	1 (0.3)	1	0.6	2 (0.6)	3	1.8	3 (0.4)	4	1.2	2 (0.6)	2	1.2
Oedema peripheral	1 (0.3)	1	0.6	2 (0.6)	2	1.2	3 (0.4)	3	0.9	2 (0.6)	2	1.2
Oedema	0			1 (0.3)	1	0.6	1 (0.1)	1	0.3	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.2.1.26. 治験薬投与下で発現した末梢性浮腫に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4131 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 203007/ Faster aspart (meal)/ 41/F/23.6	2	General disorders and administration site conditions/ Oedema peripheral/ B/L Pedal Edema	05MAY2017	Y/ Y	Asia (Excluding Japan)
NN1218-4131/ 815009/ Faster aspart (post)/ 66/F/26.9	2	General disorders and administration site conditions/ Oedema/ Unilateral (Left-Sided) Edema	18DEC2016	Y/ Y	North America
	3	General disorders and administration site conditions/ Oedema peripheral/ Unilateral Left Foot Edema	05MAR2017	Y/ Y	North America
NN1218-4131/ 819008/ NovoRapid (meal)/ 74/M/29.9	1	General disorders and administration site conditions/ Oedema peripheral/ Bilateral Pedal Edema	01APR2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Peripheral oedema adverse events - treatment emergent – listing – trial 4131 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 841012/ Faster aspart (post)/ 46/F/35.7	4	General disorders and administration site conditions/ Oedema peripheral/ Bilateral Lower Extremity 1+ Edema	30MAR2017	Y/ Y	North America
NN1218-4131/ 848006/ NovoRapid (meal)/ 58/M/32.9	2	General disorders and administration site conditions/ Oedema peripheral/ Bilateral Pedal Edema	06DEC2016	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:26 - l_ae_te.sas/l_per_oed_ae_4131_in_sas.txt

2.7.4.7.2.1.27. 治験薬投与下で発現した末梢性浮腫に関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4101 試験）

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:08:26 - t_ae_te_sum.sas/t_per_oed_ae_sum_4101_on_sas.txt

2.7.4.7.2.1.28. 治験薬投与下で発現した末梢性浮腫に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4101 試験）

There are no data for this output.

2.7.4.7.2.1.29. 治験薬投与下で発現した末梢性浮腫に関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（3854 試験）

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:08:08 - t_ae_te_3854_sum.sas/t_per_oed_ae_sum_3854_on_sas.txt

2.7.4.7.2.1.30. 治験薬投与下で発現した末梢性浮腫に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（3854 試験）

There are no data for this output.

2.7.4.7.2.1.31. 治験薬投与下で発現した稀な事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	342				341				683				342			
Total exposure (yrs)	171.3				170.2				341.5				170.2			
Total events	5	(1.5)	5	2.9	6	(1.8)	6	3.5	11	(1.6)	11	3.2	4	(1.2)	5	2.9
Cardiac disorders	1	(0.3)	1	0.6	3	(0.9)	3	1.8	4	(0.6)	4	1.2	1	(0.3)	1	0.6
Palpitations	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	1	(0.3)	1	0.6
Extrasystoles	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	0			
Sinus bradycardia	1	(0.3)	1	0.6	0				1	(0.1)	1	0.3	0			
Ventricular extrasystoles	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	0			
Hepatobiliary disorders	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	1	(0.3)	1	0.6
Hepatic steatosis	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	1	(0.3)	1	0.6
Investigations	0				0				0				1	(0.3)	2	1.2
Electrocardiogram change	0				0				0				1	(0.3)	1	0.6
Heart rate increased	0				0				0				1	(0.3)	1	0.6
Nervous system disorders	1	(0.3)	1	0.6	0				1	(0.1)	1	0.3	1	(0.3)	1	0.6
Syncope	1	(0.3)	1	0.6	0				1	(0.1)	1	0.3	1	(0.3)	1	0.6
Renal and urinary disorders	1	(0.3)	1	0.6	1	(0.3)	1	0.6	2	(0.3)	2	0.6	0			
Acute kidney injury	1	(0.3)	1	0.6	0				1	(0.1)	1	0.3	0			
Renal failure	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	0			
Blood and lymphatic system disorders	1	(0.3)	1	0.6	0				1	(0.1)	1	0.3	0			
Leukopenia	1	(0.3)	1	0.6	0				1	(0.1)	1	0.3	0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Rare events adverse events by system organ class and preferred term - treatment emergent - summary - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Congenital, familial and genetic disorders	1 (0.3)	1	0.6	0			1 (0.1)	1	0.3	0		
Accessory spleen	1 (0.3)	1	0.6	0			1 (0.1)	1	0.3	0		
Eye disorders	0			1 (0.3)	1	0.6	1 (0.1)	1	0.3	0		
Eyelid oedema	0			1 (0.3)	1	0.6	1 (0.1)	1	0.3	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.2.1.32. 治験薬投与下で発現した稀な事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4131 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 101015/ NovoRapid (meal)/ 42/F/20.6	3	Cardiac disorders/ Palpitations/ Palpitations	21DEC2016	Y/ Y	Japan
NN1218-4131/ 103007/ Faster aspart (post)/ 78/F/18.8	5	Eye disorders/ Eyelid oedema/ Blepharedema	05JUN2017	Y/ Y	Japan
NN1218-4131/ 104001/ Faster aspart (post)/ 44/F/26.9	7	Hepatobiliary disorders/ Hepatic steatosis/ Hepatic Steatosis	16SEP2016	Y/ Y	Japan
NN1218-4131/ 104009/ NovoRapid (meal)/ 41/M/25.3	9	Hepatobiliary disorders/ Hepatic steatosis/ Hepatic Steatosis	28DEC2016	Y/ Y	Japan

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Rare events adverse events - treatment emergent – listing – trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 106008/ Faster aspart (meal)/ 41/M/24.6	1	Congenital, familial and genetic disorders/ Accessory spleen/ Accessory Spleen	22FEB2017	Y/ Y	Japan
NN1218-4131/ 107010/ Faster aspart (post)/ 59/F/26.7	3	Cardiac disorders/ Ventricular extrasystoles/ Premature Ventricular Contraction	10AUG2016	Y/ Y	Japan
NN1218-4131/ 401009/ Faster aspart (post)/ 27/M/22.7	1	Cardiac disorders/ Extrasystoles/ Premature Beats On Ecg	03MAY2017	Y/ Y	Europe
NN1218-4131/ 811004/ Faster aspart (meal)/ 56/M/29.2	5	Renal and urinary disorders/ Acute kidney injury/ Acute Kidney Injury Secondary To Dehydration	04JAN2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Rare events adverse events - treatment emergent – listing – trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 814006/ Faster aspart (meal)/ 49/F/24.6	2	Blood and lymphatic system disorders/ Leukopenia/ Leukopenia	13MAR2017	Y/ Y	North America
NN1218-4131/ 832001/ NovoRapid (meal)/ 43/F/34.9	2	Nervous system disorders/ Syncope/ Fainted	28AUG2016	Y/ Y	North America
NN1218-4131/ 839005/ Faster aspart (post)/ 61/F/28.5	4	Cardiac disorders/ Palpitations/ Palpitations	17MAR2017	Y/ Y	North America
NN1218-4131/ 841010/ Faster aspart (meal)/ 52/F/24.3	2	Cardiac disorders/ Sinus bradycardia/ Sinus Bradycardia	21DEC2016	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Rare events adverse events - treatment emergent – listing – trial 4131 - in-trial- safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 848006/ NovoRapid (meal)/ 58/M/32.9	15	Investigations/ Heart rate increased/ Worsening Elevated Heart Rate	06DEC2016	Y/ Y	North America
	8	Investigations/ Electrocardiogram change/ Non-Specific Ecg Changes	22MAR2017	Y/ Y	North America
NN1218-4131/ 850005/ Faster aspart (post)/ 38/M/27.7	1	Renal and urinary disorders/ Renal failure/ Mild Renal Insufficiency	03NOV2016	Y/ Y	North America
NN1218-4131/ 858013/ Faster aspart (meal)/ 40/M/26.6	3	Nervous system disorders/ Syncope/ Syncope	29JUN2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.2.1.33. 治験薬投与下で発現した稀な事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4101 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	261				258				519				258			
Total exposure (yrs)	128.4				127.7				256.0				127.7			
Total events	3	(1.1)	3	2.3	5	(1.9)	6	4.7	8	(1.5)	9	3.5	3	(1.2)	5	3.9
Nervous system disorders	2	(0.8)	2	1.6	0				2	(0.4)	2	0.8	1	(0.4)	2	1.6
Syncope	2	(0.8)	2	1.6	0				2	(0.4)	2	0.8	1	(0.4)	2	1.6
Cardiac disorders	0				2	(0.8)	2	1.6	2	(0.4)	2	0.8	0			
Palpitations	0				2	(0.8)	2	1.6	2	(0.4)	2	0.8	0			
Hepatobiliary disorders	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	1	(0.4)	1	0.8
Hepatitis	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Hyperbilirubinaemia	0				0				0				1	(0.4)	1	0.8
Renal and urinary disorders	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	1	(0.4)	1	0.8
Nephrotic syndrome	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	1	(0.4)	1	0.8
Congenital, familial and genetic disorders	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Dermoid cyst	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Gastrointestinal disorders	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Lip swelling	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Investigations	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
White blood cell count decreased	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Skin and subcutaneous tissue disorders	0				0				0				1	(0.4)	1	0.8

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Rare events adverse events by system organ class and preferred term - treatment emergent - summary - trial 4101 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N	(%)	E R	N	(%)	E R	N	(%)	E R	N	(%)	E R
Swelling face	0			0			0			1	(0.4)	1 0.8

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.2.1.34. 治験薬投与下で発現した稀な事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4101 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4101/ 124002/ Faster aspart (meal)/ 13/F/21.7	7	Nervous system disorders/ Syncope/ Syncope	07AUG2016	Y/ Y	North America
NN1218-4101/ 148001/ NovoRapid (meal)/ 13/F/18.0	3	Skin and subcutaneous tissue disorders/ Swelling face/ Swelling In Face	26NOV2017	Y/ Y	North America
NN1218-4101/ 152001/ Faster aspart (meal)/ 17/F/28.5	3	Nervous system disorders/ Syncope/ Vasovagal Response	08AUG2017	Y/ Y	North America
NN1218-4101/ 251006/ Faster aspart (meal)/ 9/M/17.4	1	Investigations/ White blood cell count decreased/ Low Leukocyte Count In Visit14 Lab	10MAY2017	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Rare events adverse events - treatment emergent – listing – trial 4101 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4101/ 402004/ Faster aspart (post)/ 15/M/28.2	1	Congenital, familial and genetic disorders/ Dermoid cyst/ Chronic Dermoid Cyst Behind Letf Ear Lobe	03OCT2017	Y/ Y	Europe
NN1218-4101/ 514001/ Faster aspart (post)/ 13/F/24.8	1	Gastrointestinal disorders/ Lip swelling/ Swelling Of The Lip	12JUL2017	Y/ Y	Japan
	3	Cardiac disorders/ Palpitations/ Palpitations	10NOV2017	Y/ Y	Japan
NN1218-4101/ 527001/ NovoRapid (meal)/ 16/M/19.3	4	Renal and urinary disorders/ Nephrotic syndrome/ Nephrotic Syndrome	04APR2017	Y/ Y	Japan
	7	Hepatobiliary disorders/ Hyperbilirubinaemia/ Hyperbilirubinemia	15JUN2017	Y/ Y	Japan

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Rare events adverse events - treatment emergent – listing – trial 4101 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4101/ 528001/ Faster aspart (post)/ 16/M/20.3	1	Renal and urinary disorders/ Nephrotic syndrome/ Nephrotic Syndrome	07MAR2017	Y/ Y	Japan
NN1218-4101/ 601004/ NovoRapid (meal)/ 14/F/27.2	10	Nervous system disorders/ Syncope/ Faint	07APR2017	Y/ Y	Europe
	12	Nervous system disorders/ Syncope/ Faint	21APR2017	Y/ Y	Europe
NN1218-4101/ 901002/ Faster aspart (post)/ 15/F/22.7	3	Cardiac disorders/ Palpitations/ Palpitations	13NOV2016	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Rare events adverse events - treatment emergent – listing – trial 4101 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4101/ 905005/ Faster aspart (post)/ 16/F/23.3	4	Hepatobiliary disorders/ Hepatitis/ Abnormal Liver Function Tests (Hepatitis Unspecified)	09JUL2017	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.2.1.35. 治験薬投与下で発現した稀な事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（3854 試験）

	Faster aspart N	(%)	E	R	NovoRapid N	(%)	E	R
Number of subjects	236				236			
Total exposure (yrs)	72.8				71.7			
Total events	0				3	(1.3)	4	5.6
Cardiac disorders	0				1	(0.4)	2	2.8
Sinus bradycardia	0				1	(0.4)	1	1.4
Supraventricular extrasystoles	0				1	(0.4)	1	1.4
Nervous system disorders	0				1	(0.4)	1	1.4
Syncope	0				1	(0.4)	1	1.4
Skin and subcutaneous tissue disorders	0				1	(0.4)	1	1.4
Swelling face	0				1	(0.4)	1	1.4

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:08:09 - t_ae_te_3854_sum.sas/t_rare_ae_sum_3854_on_sas.txt

2.7.4.7.2.1.36. 治験薬投与下で発現した稀な事象の一覧 -in-trial 観察期間 - 安全性解析対象集団（3854 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-3854/ 505004/ NovoRapid/ 26/F/26.9	4	Nervous system disorders/ Syncope/ Syncope	09JUN2017	Y/ Y	Europe
NN1218-3854/ 924007/ NovoRapid/ 66/F/23.9	2	Cardiac disorders/ Supraventricular extrasystoles/ Atrial Premature Contractions	19JUN2017	Y/ Y	North America
	3	Cardiac disorders/ Sinus bradycardia/ Worsening Of Sinus Bradycardia	19JUN2017	Y/ Y	North America
NN1218-3854/ 926010/ NovoRapid/ 58/F/30.6	3	Skin and subcutaneous tissue disorders/ Swelling face/ C/O Facial Swelling	26DEC2016	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.2.1.37. 治験薬投与下で発現した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（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:08:30 - t_ae_te_sum.sas/t_susp_ae_sum_4131_on_sas.txt

2.7.4.7.2.1.38. 治験薬投与下で発現した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 - in-trial 観察期間 - 安全性解析対象集団（4131 試験）

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:28 - l_ae_te.sas/l_susp_ae_4131_in_sas.txt

2.7.4.7.2.1.39. 治験薬投与下で発現した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（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4101 試験）

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:08:30 - t_ae_te_sum.sas/t_susp_ae_sum_4101_on_sas.txt

2.7.4.7.2.1.40. 治験薬投与下で発現した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 - in-trial 観察期間 - 安全性解析対象集団（4101 試験）

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:29 - l_ae_te.sas/l_susp_ae_4101_in_sas.txt

2.7.4.7.2.1.41. 治験薬投与下で発現した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（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（3854 試験）

There are no data for this output.

2.7.4.7.2.1.42. 治験薬投与下で発現した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 - in-trial 観察期間 - 安全性解析対象集団（3854 試験）

There are no data for this output.

2.7.4.7.2.1.43. 心血管系事象、糖尿病網膜症、屈折障害、末梢性ニューロパチー、稀な事象及び治験薬による病原体感染の疑いに関連する有害事象の検索に用いた基本語の一覧

Adverse event class	System organ class	Preferred term
Cardiovascular	Cardiac disorders	Acute coronary syndrome
		Acute myocardial infarction
		Angina pectoris
		Angina unstable
		Anginal equivalent
		Arteriosclerosis coronary artery
		Arteriospasm coronary
		Coronary artery disease
		Coronary artery dissection
		Coronary artery embolism
		Coronary artery insufficiency
		Coronary artery occlusion
		Coronary artery reocclusion
		Coronary artery restenosis
		Coronary artery stenosis
		Coronary artery thrombosis
		Coronary bypass stenosis
		Coronary bypass thrombosis
		Coronary no-reflow phenomenon
		Coronary ostial stenosis
		Coronary vascular graft occlusion
		Coronary vascular graft stenosis
		Dissecting coronary artery aneurysm
		Haemorrhage coronary artery
		Ischaemic cardiomyopathy
		Ischaemic mitral regurgitation
		Kounis syndrome
		Microvascular coronary artery disease
		Myocardial hypoxia
		Myocardial infarction
		Myocardial ischaemia
		Myocardial necrosis
		Myocardial reperfusion injury
		Myocardial stunning
		Papillary muscle infarction
		Periprocedural myocardial infarction
		Post cardiac arrest syndrome
		Post procedural myocardial infarction
		Postinfarction angina
		Prinzmetal angina
		Silent myocardial infarction
		Stress cardiomyopathy
		Subclavian coronary steal syndrome
		Subendocardial ischaemia
	Congenital, familial and genetic disorders	Cerebral arteriovenous malformation haemorrhagic
		Congenital hemiparesis
		Vein of Galen aneurysmal malformation
	Ear and labyrinth disorders	Inner ear infarction
	Endocrine disorders	Pituitary haemorrhage
	Eye disorders	Amaurosis fugax
		Balint's syndrome

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nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:36 - l_pt.sas7l_ae_soc_pt.txt

Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Cardiovascular	Eye disorders	Millard-Gubler syndrome
	General disorders and administration site conditions	Basilar artery perforation
		Carotid artery perforation
		Carotid artery restenosis
		Cerebral artery perforation
		Cerebral artery restenosis
		Coronary artery restenosis
		Post cardiac arrest syndrome
		Vertebral artery perforation
	Immune system disorders	Kounis syndrome
		Vasculitis cerebral
	Infections and infestations	Cerebral aneurysm ruptured syphilitic
		Cerebral septic infarct
	Injury, poisoning and procedural complications	Basilar artery perforation
		Carotid artery perforation
		Carotid artery restenosis
		Cerebral aneurysm perforation
		Cerebral artery perforation
		Cerebral artery restenosis
		Cerebral hypoperfusion
		Cerebral microembolism
		Cerebral reperfusion injury
		Cerebral ventricular rupture
		Coronary artery reocclusion
		Coronary artery restenosis
		Coronary bypass stenosis
		Coronary bypass thrombosis
		Coronary vascular graft occlusion
		Coronary vascular graft stenosis
		Epidural haemorrhage
		Extra-axial haemorrhage
		Extradural haematoma
		Meningorrhagia
		Myocardial reperfusion injury
		Periprocedural myocardial infarction
		Post procedural myocardial infarction
		Post procedural stroke
		Spinal cord haematoma
		Spinal cord haemorrhage
		Spinal epidural haematoma
		Spinal epidural haemorrhage
		Spinal subarachnoid haemorrhage
		Spinal subdural haematoma
		Spinal subdural haemorrhage
		Subarachnoid haematoma
		Subarachnoid haemorrhage
		Subarachnoid haemorrhage neonatal
		Subdural haematoma
		Subdural haemorrhage

MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:36 - l_pt.sas7l_ae_soc_pt.txt

Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Cardiovascular	Injury, poisoning and procedural complications	Vertebral artery perforation
	Investigations	Blood creatine phosphokinase MB abnormal
		Blood creatine phosphokinase MB increased
		CSF bilirubin positive
		ECG signs of myocardial ischaemia
		Troponin I increased
		Troponin T increased
		Troponin increased
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Intracranial tumour haemorrhage
	Nervous system disorders	Amaurosis fugax
		Balint's syndrome
		Basal ganglia haematoma
		Basal ganglia haemorrhage
		Basal ganglia infarction
		Basal ganglia stroke
		Basilar artery aneurysm
		Basilar artery occlusion
		Basilar artery perforation
		Basilar artery stenosis
		Basilar artery thrombosis
		Brain hypoxia
		Brain stem embolism
		Brain stem haematoma
		Brain stem haemorrhage
		Brain stem infarction
		Brain stem ischaemia
		Brain stem microhaemorrhage
		Brain stem stroke
		Brain stem thrombosis
		Capsular warning syndrome
		Carotid aneurysm rupture
		Carotid arterial embolus
		Carotid arteriosclerosis
		Carotid artery aneurysm
		Carotid artery calcification
		Carotid artery disease
		Carotid artery dissection
		Carotid artery insufficiency
		Carotid artery occlusion
		Carotid artery perforation
		Carotid artery restenosis
		Carotid artery stenosis
		Carotid artery thrombosis
		Central nervous system haemorrhage
		Cerebellar artery occlusion
		Cerebellar artery thrombosis
		Cerebellar embolism
		Cerebellar haematoma

MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:36 - l_pt.sas7l_ae_soc_pt.txt

Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Cardiovascular	Nervous system disorders	Cerebellar haemorrhage
		Cerebellar infarction
		Cerebellar ischaemia
		Cerebellar microhaemorrhage
		Cerebellar stroke
		Cerebral aneurysm perforation
		Cerebral aneurysm ruptured syphilitic
		Cerebral arteriosclerosis
		Cerebral arteriovenous malformation haemorrhagic
		Cerebral arteritis
		Cerebral artery embolism
		Cerebral artery occlusion
		Cerebral artery perforation
		Cerebral artery restenosis
		Cerebral artery stenosis
		Cerebral artery thrombosis
		Cerebral capillary telangiectasia
		Cerebral circulatory failure
		Cerebral congestion
		Cerebral gas embolism
		Cerebral haematoma
		Cerebral haemorrhage
		Cerebral haemorrhage foetal
		Cerebral haemorrhage neonatal
		Cerebral hypoperfusion
		Cerebral infarction
		Cerebral infarction foetal
		Cerebral ischaemia
		Cerebral microembolism
		Cerebral microhaemorrhage
		Cerebral reperfusion injury
		Cerebral septic infarct
		Cerebral small vessel ischaemic disease
		Cerebral thrombosis
		Cerebral vascular occlusion
		Cerebral vasoconstriction
		Cerebral venous thrombosis
		Cerebral ventricular rupture
		Cerebrovascular accident
		Cerebrovascular disorder
		Cerebrovascular insufficiency
		Cerebrovascular stenosis
		Charcot-Bouchard microaneurysms
		Congenital hemiparesis
		Delayed ischaemic neurological deficit
		Dural arteriovenous fistula
		Embolic cerebral infarction
		Embolic stroke
		Epidural haemorrhage
		Extra-axial haemorrhage
		Extradural haematoma
		Haemorrhage intracranial

MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:36 - l_pt.sas7l_ae_soc_pt.txt

Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Cardiovascular	Nervous system disorders	Haemorrhagic cerebral infarction
		Haemorrhagic stroke
		Haemorrhagic transformation stroke
		Hemianaesthesia
		Hemiasomatognosia
		Hemiparaesthesia
		Hemiparesis
		Hemiplegia
		Hypoxic-ischaemic encephalopathy
		Inner ear infarction
		Intracranial aneurysm
		Intracranial haematoma
		Intracranial tumour haemorrhage
		Intracranial venous sinus thrombosis
		Intraventricular haemorrhage
		Intraventricular haemorrhage neonatal
		Ischaemic cerebral infarction
		Ischaemic stroke
		Lacunar infarction
		Lacunar stroke
		Lateral medullary syndrome
		Meningorrhagia
		Migrainous infarction
		Millard-Gubler syndrome
		Moyamoya disease
		Perinatal stroke
		Periventricular haemorrhage neonatal
		Pituitary haemorrhage
		Post cardiac arrest syndrome
		Post procedural stroke
		Post stroke depression
		Precerebral arteriosclerosis
		Precerebral artery occlusion
		Putamen haemorrhage
		Reversible cerebral vasoconstriction syndrome
		Reversible ischaemic neurological deficit
		Ruptured cerebral aneurysm
		Spinal artery embolism
		Spinal artery thrombosis
		Spinal cord haematoma
		Spinal cord haemorrhage
		Spinal epidural haematoma
		Spinal epidural haemorrhage
		Spinal subarachnoid haemorrhage
		Spinal subdural haematoma
		Spinal subdural haemorrhage
		Stroke in evolution
		Subarachnoid haematoma
		Subarachnoid haemorrhage
		Subarachnoid haemorrhage neonatal
		Subclavian steal syndrome

MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:36 - l_pt.sas7l_ae_soc_pt.txt

Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Cardiovascular	Nervous system disorders	Subdural haematoma
		Subdural haemorrhage
		Subdural haemorrhage neonatal
		Superior sagittal sinus thrombosis
		Thalamic infarction
		Thalamus haemorrhage
		Thrombotic cerebral infarction
		Thrombotic stroke
		Transient ischaemic attack
		Transverse sinus thrombosis
		Vascular encephalopathy
		Vasculitis cerebral
		Vein of Galen aneurysmal malformation
		Vertebral artery aneurysm
		Vertebral artery dissection
		Vertebral artery occlusion
		Vertebral artery perforation
		Vertebral artery stenosis
		Vertebral artery thrombosis
		Vertebrobasilar insufficiency
	Pregnancy, puerperium and perinatal conditions	Cerebral haemorrhage foetal
		Cerebral haemorrhage neonatal
		Cerebral infarction foetal
		Intraventricular haemorrhage neonatal
		Perinatal stroke
		Periventricular haemorrhage neonatal
		Reversible cerebral vasoconstriction syndrome
		Subarachnoid haemorrhage neonatal
		Subdural haemorrhage neonatal
	Psychiatric disorders	Hemiasomatognosia
		Post stroke depression
		Vascular encephalopathy
	Respiratory, thoracic and mediastinal disorders	Brain hypoxia
		Hypoxic-ischaemic encephalopathy
	Surgical and medical procedures	Carotid angioplasty
		Carotid artery bypass
		Carotid artery stent insertion
		Carotid artery stent removal
		Carotid endarterectomy
		Carotid revascularisation
		Cerebral endovascular aneurysm repair
		Cerebral revascularisation
		Cerebrovascular accident prophylaxis
		Coronary angioplasty
		Coronary arterial stent insertion
		Coronary artery bypass
		Coronary brachytherapy
		Coronary endarterectomy
		Coronary revascularisation

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nn1218/nn1218-summary/pmda_nda_20180709_er
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Adverse event class	System organ class	Preferred term
Cardiovascular	Surgical and medical procedures	External counterpulsation
		Intra-cerebral aneurysm operation
		Intracerebral haematoma evacuation
		Percutaneous coronary intervention
		Subdural haematoma evacuation
	Vascular disorders	Acute coronary syndrome
		Acute myocardial infarction
		Amaurosis fugax
		Angina pectoris
		Angina unstable
		Anginal equivalent
		Arteriosclerosis coronary artery
		Arteriospasm coronary
		Basal ganglia haematoma
		Basal ganglia haemorrhage
		Basal ganglia infarction
		Basal ganglia stroke
		Basilar artery aneurysm
		Basilar artery occlusion
		Basilar artery perforation
		Basilar artery stenosis
		Basilar artery thrombosis
		Brachiocephalic arteriosclerosis
		Brachiocephalic artery occlusion
		Brachiocephalic artery stenosis
		Brain hypoxia
		Brain stem embolism
		Brain stem haematoma
		Brain stem haemorrhage
		Brain stem infarction
		Brain stem ischaemia
		Brain stem microhaemorrhage
		Brain stem stroke
		Brain stem thrombosis
		Capsular warning syndrome
		Carotid aneurysm rupture
		Carotid arterial embolus
		Carotid arteriosclerosis
		Carotid artery aneurysm
		Carotid artery calcification
		Carotid artery disease
		Carotid artery dissection
		Carotid artery insufficiency
		Carotid artery occlusion
		Carotid artery perforation
		Carotid artery restenosis
		Carotid artery stenosis
		Carotid artery thrombosis
		Central nervous system haemorrhage
		Cerebellar artery occlusion
		Cerebellar artery thrombosis
		Cerebellar embolism

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Adverse event class	System organ class	Preferred term
Cardiovascular	Vascular disorders	Cerebellar haematoma
		Cerebellar haemorrhage
		Cerebellar infarction
		Cerebellar ischaemia
		Cerebellar microhaemorrhage
		Cerebellar stroke
		Cerebral aneurysm perforation
		Cerebral aneurysm ruptured syphilitic
		Cerebral arteriosclerosis
		Cerebral arteriovenous malformation haemorrhagic
		Cerebral arteritis
		Cerebral artery embolism
		Cerebral artery occlusion
		Cerebral artery perforation
		Cerebral artery restenosis
		Cerebral artery stenosis
		Cerebral artery thrombosis
		Cerebral capillary telangiectasia
		Cerebral circulatory failure
		Cerebral congestion
		Cerebral gas embolism
		Cerebral haematoma
		Cerebral haemorrhage
		Cerebral haemorrhage foetal
		Cerebral haemorrhage neonatal
		Cerebral hypoperfusion
		Cerebral infarction
		Cerebral infarction foetal
		Cerebral ischaemia
		Cerebral microembolism
		Cerebral microhaemorrhage
		Cerebral reperfusion injury
		Cerebral septic infarct
		Cerebral small vessel ischaemic disease
		Cerebral thrombosis
		Cerebral vascular occlusion
		Cerebral vasoconstriction
		Cerebral venous thrombosis
		Cerebrovascular accident
		Cerebrovascular disorder
		Cerebrovascular insufficiency
		Cerebrovascular stenosis
		Charcot-Bouchard microaneurysms
		Coronary artery disease
		Coronary artery dissection
		Coronary artery embolism
		Coronary artery insufficiency
		Coronary artery occlusion
		Coronary artery reocclusion
		Coronary artery restenosis
		Coronary artery stenosis
		Coronary artery thrombosis

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Adverse event class	System organ class	Preferred term
Cardiovascular	Vascular disorders	Coronary bypass stenosis
		Coronary bypass thrombosis
		Coronary no-reflow phenomenon
		Coronary ostial stenosis
		Coronary vascular graft occlusion
		Coronary vascular graft stenosis
		Delayed ischaemic neurological deficit
		Dissecting coronary artery aneurysm
		Dural arteriovenous fistula
		Embolic cerebral infarction
		Embolic stroke
		Epidural haemorrhage
		Extra-axial haemorrhage
		Extradural haematoma
		Haemorrhage coronary artery
		Haemorrhage intracranial
		Haemorrhagic cerebral infarction
		Haemorrhagic stroke
		Haemorrhagic transformation stroke
		Hypoxic-ischaemic encephalopathy
		Inner ear infarction
		Intracranial aneurysm
		Intracranial haematoma
		Intracranial tumour haemorrhage
		Intracranial venous sinus thrombosis
		Intraventricular haemorrhage
		Intraventricular haemorrhage neonatal
		Ischaemic cardiomyopathy
		Ischaemic cerebral infarction
		Ischaemic stroke
		Kounis syndrome
		Lacunar infarction
		Lacunar stroke
		Lateral medullary syndrome
		Meningorrhagia
		Microvascular coronary artery disease
		Migrainous infarction
		Millard-Gubler syndrome
		Moyamoya disease
		Myocardial infarction
		Myocardial ischaemia
		Myocardial necrosis
		Myocardial reperfusion injury
		Myocardial stunning
		Papillary muscle infarction
		Perinatal stroke
		Periventricular haemorrhage neonatal
		Pituitary haemorrhage
		Post cardiac arrest syndrome
		Post procedural stroke
		Postinfarction angina
		Precerebral arteriosclerosis
		Precerebral artery occlusion

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Adverse event class	System organ class	Preferred term
Cardiovascular	Vascular disorders	Prinzmetal angina
		Putamen haemorrhage
		Reversible cerebral vasoconstriction syndrome
		Reversible ischaemic neurological deficit
		Ruptured cerebral aneurysm
		Silent myocardial infarction
		Spinal artery embolism
		Spinal artery thrombosis
		Spinal cord haematoma
		Spinal cord haemorrhage
		Spinal epidural haematoma
		Spinal epidural haemorrhage
		Spinal subarachnoid haemorrhage
		Spinal subdural haematoma
		Spinal subdural haemorrhage
		Stress cardiomyopathy
		Stroke in evolution
		Subarachnoid haematoma
		Subarachnoid haemorrhage
		Subarachnoid haemorrhage neonatal
		Subclavian coronary steal syndrome
		Subclavian steal syndrome
		Subdural haematoma
		Subdural haemorrhage
		Subdural haemorrhage neonatal
		Subendocardial ischaemia
		Superior sagittal sinus thrombosis
		Thalamic infarction
		Thalamus haemorrhage
		Thrombotic cerebral infarction
		Thrombotic stroke
		Transient ischaemic attack
		Transverse sinus thrombosis
		Vascular encephalopathy
		Vasculitis cerebral
		Vein of Galen aneurysmal malformation
		Vertebral artery aneurysm
		Vertebral artery dissection
		Vertebral artery occlusion
		Vertebral artery perforation
		Vertebral artery stenosis
		Vertebral artery thrombosis
		Vertebrobasilar insufficiency
Diabetic retinopathy	Endocrine disorders	Diabetic blindness
		Diabetic eye disease
		Diabetic glaucoma
		Diabetic retinal oedema
		Diabetic retinopathy
		Diabetic uveitis
		Retinal neovascularisation

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Adverse event class	System organ class	Preferred term
Diabetic retinopathy	Endocrine disorders	Retinopathy proliferative
	Eye disorders	Amaurosis
		Cystoid macular oedema
		Diabetic blindness
		Diabetic eye disease
		Diabetic glaucoma
		Diabetic retinal oedema
		Diabetic retinopathy
		Diabetic uveitis
		Exudative retinopathy
		Macular ischaemia
		Macular oedema
		Macular opacity
		Macular pseudohole
		Maculopathy
		Night blindness
		Papilloedema
		Papillophlebitis
		Retinal deposits
		Retinal detachment
		Retinal exudates
		Retinal haemorrhage
		Retinal ischaemia
		Retinal neovascularisation
		Retinal oedema
		Retinal pallor
		Retinal vascular occlusion
		Retinopathy
		Retinopathy proliferative
		Sudden visual loss
		Visual acuity reduced
		Visual acuity reduced transiently
		Vitreal cells
		Vitreous detachment
		Vitreous haemorrhage
		Vitreous opacities
	Injury, poisoning and procedural complications	Cystoid macular oedema
		Retinal detachment
		Vitreous detachment
	Metabolism and nutrition disorders	Diabetic blindness
		Diabetic eye disease
		Diabetic glaucoma
		Diabetic retinal oedema
		Diabetic retinopathy
		Diabetic uveitis
		Night blindness
		Retinal neovascularisation
		Retinopathy proliferative
	Nervous system disorders	Papilloedema
		Sudden visual loss
		Visual acuity reduced

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Adverse event class	System organ class	Preferred term
Diabetic retinopathy	Nervous system disorders	Visual acuity reduced transiently
	Vascular disorders	Diabetic retinopathy
		Exudative retinopathy
		Macular ischaemia
		Papilloedema
		Papillophlebitis
		Retinal exudates
		Retinal haemorrhage
		Retinal ischaemia
		Retinal neovascularisation
		Retinal oedema
		Retinal vascular occlusion
		Retinopathy
		Retinopathy proliferative
		Vitreous haemorrhage
Peripheral neuropathy	Congenital, familial and genetic disorders	Hereditary motor and sensory neuropathy
	Ear and labyrinth disorders	Paraesthesia ear
	Endocrine disorders	Acute painful neuropathy of rapid glycaemic control
		Diabetic autonomic neuropathy
		Diabetic mononeuropathy
		Diabetic neuropathy
		Small fibre neuropathy
	Eye disorders	Miller Fisher syndrome
	Gastrointestinal disorders	Autonomic failure syndrome
	General disorders and administration site conditions	Burning sensation
		Gait disturbance
	Immune system disorders	Angiopathic neuropathy
		Anti-myelin-associated glycoprotein associated polyneuropathy
		Autoimmune neuropathy
		Demyelinating polyneuropathy
		Guillain-Barre syndrome
		Multifocal motor neuropathy
	Infections and infestations	Guillain-Barre syndrome
		Tick paralysis
	Injury, poisoning and procedural complications	Neuromuscular toxicity
		Neurotoxicity
		Radiation neuropathy
		Tick paralysis
		Toxic neuropathy
	Investigations	Anti-ganglioside antibody positive
		Anti-myelin-associated glycoprotein antibodies positive
		Biopsy peripheral nerve abnormal

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Adverse event class	System organ class	Preferred term
Peripheral neuropathy	Investigations	Electromyogram abnormal
		Nerve conduction studies abnormal
		Peripheral nervous system function test abnormal
		Temperature perception test decreased
	Metabolism and nutrition disorders	Acute painful neuropathy of rapid glycaemic control
		Diabetic autonomic neuropathy
		Diabetic mononeuropathy
		Diabetic neuropathy
		Neuropathy vitamin B6 deficiency
		Small fibre neuropathy
	Musculoskeletal and connective tissue disorders	Amyotrophy
		Burning feet syndrome
		Decreased nasolabial fold
		Hypotonia
		Motor dysfunction
		Muscle atrophy
		Muscular weakness
		Neuromuscular pain
		Neuromyopathy
		Neuropathic muscular atrophy
	Nervous system disorders	Acute painful neuropathy of rapid glycaemic control
		Acute polyneuropathy
		Amyotrophy
		Angiopathic neuropathy
		Anti-myelin-associated glycoprotein associated polyneuropathy
		Areflexia
		Autoimmune neuropathy
		Autonomic failure syndrome
		Autonomic neuropathy
		Axonal neuropathy
		Burning feet syndrome
		Burning sensation
		Decreased nasolabial fold
		Decreased vibratory sense
		Demyelinating polyneuropathy
		Diabetic autonomic neuropathy
		Diabetic mononeuropathy
		Diabetic neuropathy
		Dysaesthesia
		Formication
		Gait disturbance
		Genital hypoaesthesia
		Guillain-Barre syndrome
		Hereditary motor and sensory neuropathy
		Hypoaesthesia
		Hyporeflexia

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Adverse event class	System organ class	Preferred term
Peripheral neuropathy	Nervous system disorders	Hypotonia
		Ischaemic neuropathy
		Loss of proprioception
		Miller Fisher syndrome
		Mononeuritis
		Mononeuropathy
		Mononeuropathy multiplex
		Motor dysfunction
		Multifocal motor neuropathy
		Muscle atrophy
		Muscular weakness
		Myelopathy
		Nerve degeneration
		Neuralgia
		Neuritis
		Neuromuscular pain
		Neuromuscular toxicity
		Neuromyopathy
		Neuronal neuropathy
		Neuropathic muscular atrophy
		Neuropathy peripheral
		Neuropathy vitamin B6 deficiency
		Neurotoxicity
		Notalgia paraesthetica
		Paraesthesia
		Paraesthesia ear
		Peripheral motor neuropathy
		Peripheral nerve lesion
		Peripheral nerve palsy
		Peripheral nerve paresis
		Peripheral sensorimotor neuropathy
		Peripheral sensory neuropathy
		Peroneal nerve palsy
		Phrenic nerve paralysis
		Polyneuropathy
		Polyneuropathy chronic
		Polyneuropathy idiopathic progressive
		Radiation neuropathy
		Sensorimotor disorder
		Sensory disturbance
		Sensory loss
		Skin burning sensation
		Small fibre neuropathy
		Synkinesis
		Tick paralysis
		Tinel's sign
		Toxic neuropathy
		Ulnar neuritis
		Vulvovaginal hypoaesthesia
	Psychiatric disorders	Formication
	Reproductive system and breast disorders	Genital hypoaesthesia

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Adverse event class	System organ class	Preferred term
Peripheral neuropathy	Reproductive system and breast disorders	Vulvovaginal hypoaesthesia
	Skin and subcutaneous tissue disorders	Burning feet syndrome
		Notalgia paraesthetica
		Skin burning sensation
	Vascular disorders	Angiopathic neuropathy
		Autonomic failure syndrome
		Ischaemic neuropathy
Rare	Blood and lymphatic system disorders	ABO haemolytic disease of newborn
		Aase syndrome
		Accessory spleen
		Acquired amegakaryocytic thrombocytopenia
		Agranulocytosis
		Amegakaryocytic thrombocytopenia
		Antithrombin III deficiency
		Aplastic anaemia
		Asplenia
		Autoimmune aplastic anaemia
		Autoimmune lymphoproliferative syndrome
		B-lymphocyte abnormalities
		Basophilopenia
		Bicytopenia
		Blood disorder
		Blood incompatibility haemolytic anaemia of newborn
		Bone marrow disorder
		Bone marrow failure
		Bone marrow infiltration
		Bone marrow necrosis
		Bone marrow toxicity
		CANDLE syndrome
		Cardiac lymphangioma
		Chediak-Higashi syndrome
		Chronic granulomatous disease
		Coagulation factor mutation
		Complement deficiency disease
		Congenital anaemia
		Congenital aplastic anaemia
		Congenital coagulopathy
		Congenital dysfibrinogenaemia
		Congenital dyskeratosis
		Congenital haematological disorder
		Congenital hypercoagulation
		Congenital lymphoedema
		Congenital malaria
		Congenital methaemoglobinaemia
		Congenital thrombocyte disorder
		Congenital thrombocytopenia
		Congenital thymus absence

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Adverse event class	System organ class	Preferred term
Rare	Blood and lymphatic system disorders	Congenital white blood cell disorder
		Cutaneovisceral angiomatosis with thrombocytopenia
		Cyclic neutropenia
		Cystic lymphangioma
		Cytopenia
		Delta-beta thalassaemia
		Disseminated intravascular coagulation
		Double heterozygous sickling disorders
		Dubowitz syndrome
		Elliptocytosis hereditary
		Eosinopenia
		Erythroblastosis foetalis
		Factor I deficiency
		Factor II deficiency
		Factor II mutation
		Factor III deficiency
		Factor IX deficiency
		Factor V Leiden mutation
		Factor V deficiency
		Factor VII deficiency
		Factor VIII deficiency
		Factor X deficiency
		Factor XI deficiency
		Factor XII deficiency
		Factor XIII deficiency
		Familial haemophagocytic lymphohistiocytosis
		Familial polycythaemia
		Febrile bone marrow aplasia
		Febrile neutropenia
		Gelatinous transformation of the bone marrow
		Gleich's syndrome
		Glucose-6-phosphate dehydrogenase deficiency
		Glutathione synthetase deficiency
		Granulocytes maturation arrest
		Granulocytopenia
		Granulocytopenia neonatal
		Haematotoxicity
		Haemoglobin C disease
		Haemoglobin C trait
		Haemoglobin D disease
		Haemoglobin D trait
		Haemoglobin E disease
		Haemoglobin E trait
		Haemoglobin E-thalassaemia disease
		Haemoglobinopathy
		Haemophilia
		Haemophilia A with anti factor VIII
		Haemophilia A without inhibitors

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Adverse event class	System organ class	Preferred term
Rare	Blood and lymphatic system disorders	Haemophilia B with anti factor IX
		Haemophilia B without inhibitors
		Henoch-Schonlein purpura nephritis
		Hepatic infiltration eosinophilic
		Hereditary haemolytic anaemia
		Hereditary sideroblastic anaemia
		Hereditary spherocytosis
		Hereditary stomatocytosis
		Hermansky-Pudlak syndrome
		Hexokinase deficiency anaemia
		Hyperbilirubinaemia
		Hypersplenism congenital
		Idiopathic neutropenia
		Infantile genetic agranulocytosis
		Jaundice
		Leukopenia
		Leukopenia neonatal
		Lymphangiectasia intestinal congenital
		Lymphocytopenia neonatal
		Lymphopenia
		MLASA syndrome
		MYH9-related disease
		Methylenetetrahydrofolate reductase deficiency
		Monocytopenia
		Myelodysplastic syndrome
		Myelodysplastic syndrome transformation
		Myelofibrosis
		Myeloid maturation arrest
		Myeloid metaplasia
		Myeloperoxidase deficiency
		Neonatal alloimmune thrombocytopenia
		Neonatal leukaemia
		Neutropenia
		Neutropenia neonatal
		Neutropenic colitis
		Neutropenic infection
		Neutropenic sepsis
		Ocular icterus
		Omenn syndrome
		Pancytopenia
		Panmyelopathy
		Pearson's syndrome
		Plasma cell disorder
		Platelet glycoprotein gene mutation
		Platelet maturation arrest
		Platelet production decreased
		Platelet toxicity
		Primary myelofibrosis
		Protein C deficiency
		Protein S deficiency
		Pulmonary lymphangiectasia

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Adverse event class	System organ class	Preferred term
Rare	Blood and lymphatic system disorders	Pure white cell aplasia
		Pyruvate kinase deficiency anaemia
		Radiation leukopenia
		Red blood cell enzymes abnormal
		Rhesus haemolytic disease of newborn
		Shwachman-Diamond syndrome
		Sickle cell anaemia
		Sickle cell trait
		Spleen malformation
		Splenic hamartoma
		Splenic varices
		Splenic varices haemorrhage
		Sticky platelet syndrome
		Thalassaemia
		Thalassaemia alpha
		Thalassaemia beta
		Thalassaemia sickle cell
		Thrombocytopenia
		Thrombocytopenia-absent radius syndrome
		Thymus hypoplasia
		Trisomy 12
		Von Willebrand's disease
		White blood cell disorder
		Wiskott-Aldrich syndrome
		X-linked lymphoproliferative syndrome
	Cardiac disorders	Acardia
		Accelerated idioventricular rhythm
		Accessory cardiac pathway
		Adams-Stokes syndrome
		Agonal rhythm
		Anomalous atrioventricular excitation
		Anomalous pulmonary venous connection
		Aortic valve atresia
		Arrhythmia
		Arrhythmia neonatal
		Arrhythmia supraventricular
		Arrhythmogenic right ventricular dysplasia
		Ascites
		Atrial conduction time prolongation
		Atrial fibrillation
		Atrial flutter
		Atrial parasystole
		Atrial septal defect
		Atrial tachycardia
		Atrioventricular block
		Atrioventricular block complete
		Atrioventricular block first degree
		Atrioventricular block second degree
		Atrioventricular conduction time shortened
		Atrioventricular dissociation

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Adverse event class	System organ class	Preferred term
Rare	Cardiac disorders	Atrioventricular node dispersion
		Atrioventricular septal defect
		Baseline foetal heart rate variability disorder
		Bezold-Jarisch reflex
		Bicuspid aortic valve
		Bicuspid pulmonary valve
		Bifascicular block
		Bradyarrhythmia
		Bradycardia
		Bradycardia foetal
		Bradycardia neonatal
		Brugada syndrome
		Bundle branch block
		Bundle branch block bilateral
		Bundle branch block left
		Bundle branch block right
		CHARGE syndrome
		Cardiac arrest
		Cardiac arrest neonatal
		Cardiac death
		Cardiac fibrillation
		Cardiac flutter
		Cardiac lymphangioma
		Cardiac malposition
		Cardiac septal defect
		Cardio-respiratory arrest
		Cardio-respiratory arrest neonatal
		Carney complex
		Central bradycardia
		Chiari network
		Chronotropic incompetence
		Conduction disorder
		Congenital aortic valve incompetence
		Congenital aortic valve stenosis
		Congenital cardiovascular anomaly
		Congenital great vessel anomaly
		Congenital heart valve disorder
		Congenital heart valve incompetence
		Congenital mitral valve incompetence
		Congenital mitral valve stenosis
		Congenital pulmonary valve atresia
		Congenital pulmonary valve disorder
		Congenital tricuspid valve atresia
		Congenital tricuspid valve incompetence
		Congenital tricuspid valve stenosis
		Cor biloculare
		Cor triatriatum
		Corrected transposition of great vessels
		Defect conduction intraventricular
		Dextrocardia
		DiGeorge's syndrome
		Double outlet right ventricle

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Adverse event class	System organ class	Preferred term
Rare	Cardiac disorders	Ductus arteriosus premature closure
		Ebstein's anomaly
		Ectopia cordis
		Emanuel syndrome
		Endocardial fibroelastosis
		Extrasystoles
		Fallot's pentalogy
		Fallot's tetralogy
		Fallot's trilogy
		Foetal arrhythmia
		Foetal heart rate acceleration abnormality
		Foetal heart rate deceleration abnormality
		Foetal heart rate disorder
		Foetal tachyarrhythmia
		Glycogen storage disease type II
		Heart alternation
		Heart block congenital
		Heart disease congenital
		Holt-Oram syndrome
		Hypertrophic cardiomyopathy
		Hypoplastic left heart syndrome
		Hypoplastic right heart syndrome
		Inherited cardiac conduction disorder
		Junctional ectopic tachycardia
		Kabuki make-up syndrome
		Kearns-Sayre syndrome
		Kleefstra syndrome
		Kounis syndrome
		Laevocardia
		Larsen syndrome
		Left ventricle outflow tract obstruction
		Left-to-right cardiac shunt
		Lenegre's disease
		Long QT syndrome
		Long QT syndrome congenital
		Lown-Ganong-Levine syndrome
		Mitral valve atresia
		Mitral valve hypoplasia
		Multiple cardiac defects
		Multiple lentigines syndrome
		Myocardial bridging
		Neonatal tachycardia
		Nodal arrhythmia
		Nodal rhythm
		Non-compaction cardiomyopathy
		Nonreassuring foetal heart rate pattern
		Noonan syndrome
		Pacemaker generated arrhythmia
		Pacemaker syndrome
		Palpitations
		Parachute mitral valve

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Adverse event class	System organ class	Preferred term
Rare	Cardiac disorders	Parasystole
		Paroxysmal arrhythmia
		Paroxysmal atrioventricular block
		Patent ductus arteriosus
		Persistent foetal circulation
		Primary ciliary dyskinesia
		Pulmonary artery atresia
		Pulmonary valve stenosis congenital
		Pulseless electrical activity
		Rebound tachycardia
		Reperfusion arrhythmia
		Rhythm idioventricular
		Right ventricle outflow tract obstruction
		Rubinstein-Taybi syndrome
		Shone complex
		Sinoatrial block
		Sinus arrest
		Sinus arrhythmia
		Sinus bradycardia
		Sinus node dysfunction
		Sinus tachycardia
		Sudden cardiac death
		Sudden death
		Supraventricular extrasystoles
		Supraventricular tachyarrhythmia
		Supraventricular tachycardia
		Syncope
		Tachyarrhythmia
		Tachycardia
		Tachycardia foetal
		Tachycardia paroxysmal
		Timothy syndrome
		Torsade de pointes
		Transposition of the great vessels
		Trifascicular block
		Trisomy 11
		Trisomy 13
		Trisomy 14
		Trisomy 17
		Trisomy 18
		Trisomy 21
		Trisomy 22
		Trisomy 9
		Truncus arteriosus persistent
		Twin reversed arterial perfusion sequence malformation
		Uhl's anomaly
		Univentricular heart
		VACTERL syndrome
		Velo-cardio-facial syndrome
		Ventricular arrhythmia
		Ventricular asystole

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Adverse event class	System organ class	Preferred term
Rare	Cardiac disorders	Ventricular dyssynchrony
		Ventricular extrasystoles
		Ventricular fibrillation
		Ventricular flutter
		Ventricular hypoplasia
		Ventricular parasystole
		Ventricular pre-excitation
		Ventricular septal defect
		Ventricular tachyarrhythmia
		Ventricular tachycardia
		Wandering pacemaker
		Williams syndrome
		Withdrawal arrhythmia
		Wolff-Parkinson-White syndrome
		Wolff-Parkinson-White syndrome congenital
	Congenital, familial and genetic disorders	11-beta-hydroxylase deficiency
		17,20-desmolase deficiency
		17-alpha-hydroxylase deficiency
		18q minus syndrome
		2-Hydroxyglutaric aciduria
		20,22-desmolase deficiency
		21-hydroxylase deficiency
		3-hydroxyacetyl-coenzyme A dehydrogenase deficiency
		5-alpha-reductase deficiency
		ABO haemolytic disease of newborn
		Aase syndrome
		Abdominal transposition
		Abdominal wall anomaly
		Abnormal palmar/plantar creases
		Acardia
		Accessory auricle
		Accessory breast
		Accessory carpal bone
		Accessory kidney
		Accessory liver lobe
		Accessory muscle
		Accessory navicular syndrome
		Accessory salivary gland
		Accessory spleen
		Acetylcholinesterase deficiency
		Achromotrichia congenital
		Acral peeling skin syndrome
		Acrodermatitis enteropathica
		Acrokeratosis verruciformis
		Activated PI3 kinase delta syndrome
		Adactyly
		Adams-Oliver syndrome
		Adenine phosphoribosyl transferase deficiency
		Adenomatous polyposis coli

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Adrenal insufficiency neonatal
		Adrenogenital syndrome
		Adrenoleukodystrophy
		Adult polyglucosan body disease
		Aglossia
		Aicardi's syndrome
		Alagille syndrome
		Albinism
		Albright's disease
		Alkaptonuria
		Allan-Herndon-Dudley syndrome
		Alpers' disease
		Alpha-1 anti-trypsin deficiency
		Alport's syndrome
		Alstroem syndrome
		Alternating hemiplegia of childhood
		Alveolar capillary dysplasia
		Amblyopia congenital
		Amegakaryocytic thrombocytopenia
		Aminoaciduria
		Amniotic band syndrome
		Amyotrophic lateral sclerosis gene carrier
		Anal atresia
		Androgen insensitivity syndrome
		Anencephaly
		Angelman's syndrome
		Angiotensin converting enzyme inhibitor foetopathy
		Aniridia
		Ankyloglossia congenital
		Annular pancreas
		Anodontia
		Anomalous arrangement of pancreaticobiliary duct
		Anomalous pulmonary venous connection
		Anomaly of external ear congenital
		Anomaly of middle ear congenital
		Anomaly of orbit, congenital
		Anophthalmos
		Anorchism
		Anorectal agenesis
		Anotia
		Anterior chamber cleavage syndrome
		Anterior displaced anus
		Antithrombin III deficiency
		Aorta hypoplasia
		Aortic valve atresia
		Aorticopulmonary septal defect
		Apert's syndrome
		Aphakia congenital
		Aplasia

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Aplasia cutis congenita
		Arachnodactyly
		Arcuate foramen
		Arginase deficiency
		Argininosuccinate lyase deficiency
		Argininosuccinate synthetase deficiency
		Arnold-Chiari malformation
		Arrhythmogenic right ventricular dysplasia
		Arteriovenous malformation
		Ash leaf macule
		Aspartate-glutamate-transporter deficiency
		Aspartylglucosaminuria
		Asphyxiating thoracic dystrophy
		Asplenia
		Asymptomatic gene carrier
		Ataxia telangiectasia
		Atrial septal defect
		Atrioventricular node dispersion
		Atrioventricular septal defect
		Auditory neuropathy spectrum disorder
		Autoimmune lymphoproliferative syndrome
		Autosomal chromosome anomaly
		Azygos lobe
		Baltic myoclonic epilepsy
		Baraitser Rodeck Garner syndrome
		Barakat syndrome
		Barth syndrome
		Bartter's syndrome
		Basal cell naevus syndrome
		Becker's muscular dystrophy
		Beckwith-Wiedemann syndrome
		Benign congenital hypotonia
		Benign familial haematuria
		Benign familial neonatal convulsions
		Benign familial pemphigus
		Berdon's syndrome
		Beta ketothiolase deficiency
		Bicuspid aortic valve
		Bicuspid pulmonary valve
		Biliary hamartoma
		Biotinidase deficiency
		Birt-Hogg-Dube syndrome
		Birth mark
		Bladder agenesis
		Blau syndrome
		Blepharophimosis congenital
		Blindness congenital
		Bloch-Sulzberger syndrome
		Blood incompatibility haemolytic anaemia of newborn

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Bloom syndrome
		Brachycephaly
		Brachydactyly
		Brain malformation
		Branchial cleft sinus
		Branchial cyst
		Branchio-oto-renal syndrome
		Branchiogenic syndrome
		Breast malformation
		Bronchogenic cyst
		Bruton's agammaglobulinaemia
		Bulbospinal muscular atrophy congenital
		Buried penis syndrome
		CANDLE syndrome
		CHARGE syndrome
		Camptodactyly congenital
		Camptomelia
		Canavan disease
		Cancer gene carrier
		Carbamoyl phosphate synthetase deficiency
		Carbohydrate metabolism disorder
		Carcinogenic effect in offspring
		Cardiac lymphangioma
		Cardiac malposition
		Cardiac septal defect
		Carney complex
		Carnitine palmitoyltransferase deficiency
		Carnitine-acylcarnitine translocase deficiency
		Carpus curvus
		Cartilage-hair hypoplasia
		Cataract congenital
		Caudal regression syndrome
		Central core disease
		Central nervous system dermoid tumour
		Cerebellar dysplasia
		Cerebellar hypoplasia
		Cerebral arteriovenous malformation haemorrhagic
		Cerebral atrophy congenital
		Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
		Cerebral dysgenesis
		Cerebral palsy
		Cerebrohepatorenal syndrome
		Cerebrovascular arteriovenous malformation
		Cervical auricle
		Cervical rib

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Chediak-Higashi syndrome
		Chiari network
		Chimerism
		Choanal atresia
		Choanal stenosis
		Cholangiectasis congenital
		Choledochal cyst
		Chondrodystrophy
		Chondroectodermal dysplasia
		Chordee
		Chorioretinal degeneration congenital
		Choroidal coloboma
		Chromosomal deletion
		Chromosomal mutation
		Chronic granulomatous disease
		Chronic infantile neurological cutaneous and articular syndrome
		Citrate transporter deficiency
		Cleft foot
		Cleft lip
		Cleft lip and palate
		Cleft palate
		Cleft uvula
		Cleidocranial dysostosis
		Clinodactyly
		Cloacal exstrophy
		Coagulation factor mutation
		Coarctation of the aorta
		Cobb syndrome
		Cockayne's syndrome
		Cohen syndrome
		Collodion baby
		Coloboma
		Colour blindness
		Combined immunodeficiency
		Complement deficiency disease
		Congenital Eustachian tube anomaly
		Congenital HIV infection
		Congenital Horner's syndrome
		Congenital abdominal hernia
		Congenital absence of bile ducts
		Congenital absence of cranial vault
		Congenital absence of vertebra
		Congenital acrochordon
		Congenital adrenal gland hypoplasia
		Congenital anaemia
		Congenital androgen deficiency
		Congenital anomalies of ear ossicles
		Congenital anomaly
		Congenital anomaly in offspring
		Congenital anomaly of adrenal gland
		Congenital anomaly of inner ear

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Congenital aortic anomaly
		Congenital aortic atresia
		Congenital aortic dilatation
		Congenital aortic stenosis
		Congenital aortic valve incompetence
		Congenital aortic valve stenosis
		Congenital aplastic anaemia
		Congenital aqueductal stenosis
		Congenital arterial malformation
		Congenital arteriovenous fistula
		Congenital astigmatism
		Congenital aural fistula
		Congenital benign neoplasm
		Congenital bladder anomaly
		Congenital bladder diverticulum
		Congenital bladder neck obstruction
		Congenital bowing of long bones
		Congenital brain damage
		Congenital bronchiectasis
		Congenital bronchomalacia
		Congenital calyceal diverticulum
		Congenital cardiovascular anomaly
		Congenital carnitine deficiency
		Congenital central diabetes insipidus
		Congenital central hypoventilation syndrome
		Congenital central nervous system anomaly
		Congenital cerebellar agenesis
		Congenital cerebral cyst
		Congenital cerebral haemangioma
		Congenital cerebrovascular anomaly
		Congenital choroid plexus cyst
		Congenital choroidal anomaly
		Congenital chylothorax
		Congenital clavicular agenesis
		Congenital claw toe
		Congenital cleft hand
		Congenital coagulopathy
		Congenital condyloma
		Congenital corneal anomaly
		Congenital coronary artery malformation
		Congenital cranial nerve paralysis
		Congenital cutis laxa
		Congenital cyst
		Congenital cystic disease of liver
		Congenital cystic kidney disease
		Congenital cystic lung
		Congenital cytomegalovirus infection
		Congenital deformity of clavicle
		Congenital dermal sinus
		Congenital diaphragmatic anomaly

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Congenital diaphragmatic eventration
		Congenital diaphragmatic hernia
		Congenital disorder of glycosylation
		Congenital dysfibrinogenaemia
		Congenital dyskeratosis
		Congenital ectodermal dysplasia
		Congenital ectopic bladder
		Congenital ectopic pancreas
		Congenital elevation of scapula
		Congenital emphysema
		Congenital endocrine anomaly
		Congenital epiblepharon
		Congenital epiglottal anomaly
		Congenital eye disorder
		Congenital eye naevus
		Congenital eyelid malformation
		Congenital facial nerve hypoplasia
		Congenital fallopian tube anomaly
		Congenital fibrosarcoma
		Congenital flaccid paralysis
		Congenital flat feet
		Congenital floppy infant
		Congenital foot malformation
		Congenital gastric anomaly
		Congenital gastrointestinal vessel anomaly
		Congenital generalised lipodystrophy
		Congenital genital malformation
		Congenital genital malformation female
		Congenital genital malformation male
		Congenital genitourinary abnormality
		Congenital great vessel anomaly
		Congenital haematological disorder
		Congenital hair disorder
		Congenital hand malformation
		Congenital hearing disorder
		Congenital heart valve disorder
		Congenital heart valve incompetence
		Congenital hemiparesis
		Congenital hepatic fibrosis
		Congenital hepatitis B infection
		Congenital hepatobiliary anomaly
		Congenital hepatomegaly
		Congenital herpes simplex infection
		Congenital hiatus hernia
		Congenital high airway obstruction syndrome
		Congenital hydrocele renalis
		Congenital hydrocephalus
		Congenital hydronephrosis
		Congenital hypercoagulation
		Congenital hyperextension of knee

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Congenital hyperextension of spine
		Congenital hyperthyroidism
		Congenital hypertrichosis
		Congenital hypogammaglobulinaemia
		Congenital hypoparathyroidism
		Congenital hypothyroidism
		Congenital infection
		Congenital inguinal hernia
		Congenital intestinal malformation
		Congenital intestinal obstruction
		Congenital intrinsic factor deficiency
		Congenital iris anomaly
		Congenital jaw malformation
		Congenital joint malformation
		Congenital knee deformity
		Congenital knee dislocation
		Congenital kyphoscoliosis
		Congenital labia pudendi adhesions
		Congenital lacrimal gland anomaly
		Congenital lacrimal passage anomaly
		Congenital large intestinal atresia
		Congenital laryngeal stridor
		Congenital lenticonus
		Congenital limb hyperextension
		Congenital lip fistula
		Congenital lymphoedema
		Congenital malaria
		Congenital malignant neoplasm
		Congenital megacolon
		Congenital megaureter
		Congenital melanocytic naevus
		Congenital melanosis
		Congenital methaemoglobinaemia
		Congenital mitochondrial cytopathy
		Congenital mitral valve incompetence
		Congenital mitral valve stenosis
		Congenital monorchidism
		Congenital multiplex arthrogryposis
		Congenital muscle absence
		Congenital musculoskeletal anomaly
		Congenital myopathy
		Congenital myopia
		Congenital naevus
		Congenital nail disorder
		Congenital neoplasm
		Congenital nephrogenic diabetes insipidus
		Congenital nephrotic syndrome
		Congenital neurological degeneration
		Congenital neurological disorder
		Congenital neuropathy
		Congenital night blindness

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Congenital nose malformation
		Congenital nystagmus
		Congenital oculomotor apraxia
		Congenital oesophageal anomaly
		Congenital oesophageal stenosis
		Congenital oesophageal web
		Congenital optic nerve anomaly
		Congenital oral malformation
		Congenital osteodystrophy
		Congenital ovarian anomaly
		Congenital oxalosis
		Congenital pancreatic anomaly
		Congenital perforated nasal septum
		Congenital pharyngeal anomaly
		Congenital pigmentation disorder
		Congenital pneumonia
		Congenital poikiloderma
		Congenital pseudarthrosis
		Congenital pulmonary artery anomaly
		Congenital pulmonary hypertension
		Congenital pulmonary valve atresia
		Congenital pulmonary valve disorder
		Congenital pyelocaliectasis
		Congenital renal cyst
		Congenital renal disorder
		Congenital retinoblastoma
		Congenital rubella infection
		Congenital salivary gland anomaly
		Congenital scleral disorder
		Congenital scoliosis
		Congenital scrotal hypertrophy
		Congenital skin dimples
		Congenital skin disorder
		Congenital small intestinal atresia
		Congenital spinal cord anomaly
		Congenital spinal fusion
		Congenital spinal stenosis
		Congenital spondylolisthesis
		Congenital spondylolysis
		Congenital syphilis
		Congenital syphilitic encephalitis
		Congenital syphilitic meningitis
		Congenital syphilitic osteochondritis
		Congenital teratoma
		Congenital thrombocyte disorder
		Congenital thrombocytopenia
		Congenital thymus absence
		Congenital thyroid disorder
		Congenital tongue anomaly
		Congenital torticollis
		Congenital toxoplasmosis
		Congenital tracheomalacia

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Congenital trichomegaly
		Congenital tricuspid valve atresia
		Congenital tricuspid valve incompetence
		Congenital tricuspid valve stenosis
		Congenital tuberculosis
		Congenital umbilical hernia
		Congenital ureteric anomaly
		Congenital ureterocele
		Congenital ureterovesical junction anomaly
		Congenital urethral anomaly
		Congenital urinary tract obstruction
		Congenital uterine anomaly
		Congenital vaginal cyst
		Congenital varicella infection
		Congenital varicocele
		Congenital vas deferens absence
		Congenital vesicoureteric reflux
		Congenital visual acuity reduced
		Congenital vitreous anomaly
		Congenital white blood cell disorder
		Conjoined twins
		Conjunctivitis gonococcal neonatal
		Constricted ear deformity
		Cor biloculare
		Cor triatriatum
		Corneal dystrophy
		Corneal opacity congenital
		Cornelia de Lange syndrome
		Corrected transposition of great vessels
		Cortical dysplasia
		Costello syndrome
		Cowden's disease
		Craniofacial deformity
		Craniofacial dysostosis
		Craniolacunia
		Craniorachischisis
		Craniosynostosis
		Craniotabes
		Cri du Chat syndrome
		Crigler-Najjar syndrome
		Cryopyrin associated periodic syndrome
		Cryptophthalmos
		Cryptorchism
		Cutaneovisceral angiomatosis with thrombocytopenia
		Cyclopia
		Cystathionine beta-synthase deficiency
		Cystic angiomatosis
		Cystic eyeball, congenital
		Cystic fibrosis
		Cystic fibrosis carrier

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Cystic fibrosis gastrointestinal disease
		Cystic fibrosis hepatic disease
		Cystic fibrosis lung
		Cystic fibrosis pancreatic
		Cystic fibrosis related diabetes
		Cystic lymphangioma
		Cystinosis
		Cystinuria
		Cytogenetic abnormality
		DNA mismatch repair protein gene mutation
		Dacryostenosis congenital
		Dandy-Walker syndrome
		Deaf mutism
		Deafness congenital
		Deficiency of the interleukin-1 receptor antagonist
		Deficiency of the interleukin-36 receptor antagonist
		Delta-beta thalassaemia
		Dent's disease
		Dentatorubral-pallidoluysian atrophy
		Dentinogenesis imperfecta
		Dentofacial anomaly
		Denys-Drash syndrome
		Dermatofibrosis lenticularis disseminata
		Dermatoglyphic anomaly
		Dermoid cyst
		Developmental glaucoma
		Developmental hip dysplasia
		Dextrocardia
		DiGeorge's syndrome
		Diabetic foetopathy
		Diaphragmatic aplasia
		Diastematomyelia
		Diencephalic syndrome of infancy
		Diethylstilboestrol syndrome
		Dihydropyrimidine dehydrogenase deficiency
		Dilatation intrahepatic duct congenital
		Disorder of sex development
		Distichiasis
		Diverticulitis Meckel's
		Diverticulum of pharynx, congenital
		Dolichocolon
		Double cortex syndrome
		Double heterozygous sickling disorders
		Double outlet right ventricle
		Double ureter
		Dowling-Degos disease
		Duane's syndrome
		Dubin-Johnson syndrome

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Dubowitz syndrome
		Duchenne muscular dystrophy
		Duchenne muscular dystrophy gene carrier
		Ductus arteriosus premature closure
		Ductus arteriosus stenosis foetal
		Ductus venosus agenesis
		Duodenal atresia
		Duplex appendix
		Dyschondrosteosis
		Dysgnathia
		Dysmorphism
		Dysmyelination
		Dysplastic naevus syndrome
		Eagle Barrett syndrome
		Ear malformation
		Early onset familial Alzheimer's disease
		Early onset primary dystonia
		Ebstein's anomaly
		Ectopia cordis
		Ectopic kidney
		Ectopic ovary
		Ectopic posterior pituitary gland
		Ectopic thyroid
		Ectopic ureter
		Ehlers-Danlos syndrome
		Elliptocytosis hereditary
		Ellis-van Creveld syndrome
		Emanuel syndrome
		Encephalocele
		Encephalocutaneous angiomatosis
		Endocardial fibroelastosis
		Enteric duplication
		Entropion congenital
		Epidermal naevus
		Epidermal naevus syndrome
		Epidermolysis
		Epidermolysis bullosa
		Epilepsy congenital
		Epispadias
		Erythroblastosis foetalis
		Erythrokeratodermia variabilis
		Essential fructosuria
		Exomphalos
		Exophthalmos congenital
		External auditory canal atresia
		Extrarenal pelvis
		Eye anterior chamber congenital anomaly
		Eyelid ptosis congenital
		Fabry's disease
		Faciodigitogenital dysplasia
		Facioscapulohumeral muscular dystrophy
		Factor I deficiency

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Factor II deficiency
		Factor II mutation
		Factor III deficiency
		Factor IX deficiency
		Factor V Leiden carrier
		Factor V Leiden mutation
		Factor V deficiency
		Factor VII deficiency
		Factor VIII deficiency
		Factor X deficiency
		Factor XI deficiency
		Factor XII deficiency
		Factor XIII deficiency
		Fallot's pentalogy
		Fallot's tetralogy
		Fallot's trilogy
		Familial amyloidosis
		Familial amyotrophic lateral sclerosis
		Familial cold autoinflammatory syndrome
		Familial haemophagocytic lymphohistiocytosis
		Familial hemiplegic migraine
		Familial high density lipoprotein deficiency
		Familial hypertriglyceridaemia
		Familial hypocalciuric hypercalcaemia
		Familial infantile bilateral striatal necrosis
		Familial mediterranean fever
		Familial medullary thyroid cancer
		Familial periodic paralysis
		Familial polycythaemia
		Familial renal glycosuria
		Familial scaphocephaly syndrome
		Familial tremor
		Fanconi syndrome
		Fatal familial insomnia
		Fatty acid oxidation disorder
		Femoral anteversion
		Femoral retroversion
		Femur-fibula-ulna complex
		Fibrodysplasia ossificans progressiva
		Fibrous dysplasia of bone
		Fibrous dysplasia of jaw
		Fibula agenesis
		Fissure of tongue, congenital
		Foetal alcohol syndrome
		Foetal anticonvulsant syndrome
		Foetal chromosome abnormality
		Foetal cystic hygroma
		Foetal malformation
		Foetal megacystis

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Foetal methotrexate syndrome
		Foetal retinoid syndrome
		Foetal warfarin syndrome
		Foramen magnum stenosis
		Fragile X carrier
		Fragile X syndrome
		Freeman-Sheldon syndrome
		Frenulum breve
		Friedreich's ataxia
		Fryns syndrome
		GNE myopathy
		Galactosaemia
		Gallbladder agenesis
		Gallbladder anomaly congenital
		Gastrointestinal arteriovenous malformation
		Gastrointestinal disorder congenital
		Gastrointestinal malformation
		Gastroschisis
		Gaucher's disease
		Gaucher's disease type I
		Gaucher's disease type II
		Gaucher's disease type III
		Gene mutation
		Generalised resistance to thyroid hormone
		Genitalia external ambiguous
		Gilbert's syndrome
		Gitelman's syndrome
		Glucose transporter type 1 deficiency syndrome
		Glucose-6-phosphate dehydrogenase deficiency
		Glucose-galactose malabsorption
		Glutathione synthetase deficiency
		Glycogen storage disease type I
		Glycogen storage disease type II
		Glycogen storage disease type III
		Glycogen storage disease type IV
		Glycogen storage disease type V
		Glycogen storage disease type VI
		Glycogen storage disease type VII
		Glycogen storage disease type VIII
		Glycogen storage disorder
		Gnathoschisis
		Goitre congenital
		Gonadal dysgenesis
		Gorham's disease
		Greig's syndrome
		Haemangioma congenital
		Haemangioma of retina
		Haemochromatosis trait

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Haemoglobin C disease
		Haemoglobin C trait
		Haemoglobin D disease
		Haemoglobin D trait
		Haemoglobin E disease
		Haemoglobin E trait
		Haemoglobin E-thalassaemia disease
		Haemoglobinopathy
		Haemophilia
		Haemophilia A with anti factor VIII
		Haemophilia A without inhibitors
		Haemophilia B with anti factor IX
		Haemophilia B without inhibitors
		Haemophilia carrier
		Haemorrhagic arteriovenous malformation
		Hamartoma
		Hamartoma vascular
		Hand-foot-genital syndrome
		Harlequin foetus
		Hartnup disease
		Heart block congenital
		Heart disease congenital
		Hemihypertrophy
		Hemimegalencephaly
		Hemivertebra
		Hepatic arteriovenous malformation
		Hepato-lenticular degeneration
		Hereditary angioedema
		Hereditary areflexic dystasia
		Hereditary cerebral degeneration
		Hereditary choroidal dystrophy
		Hereditary disorder
		Hereditary fructose intolerance
		Hereditary haemochromatosis
		Hereditary haemolytic anaemia
		Hereditary haemorrhagic telangiectasia
		Hereditary hypophosphataemic rickets
		Hereditary leiomyomatosis renal cell carcinoma
		Hereditary motor and sensory neuropathy
		Hereditary motor neurone disease
		Hereditary multiple osteochondromas
		Hereditary neuropathic amyloidosis
		Hereditary neuropathy with liability to pressure palsies
		Hereditary non-polyposis colorectal cancer syndrome
		Hereditary optic atrophy
		Hereditary palmoplantar keratoderma
		Hereditary pancreatitis
		Hereditary papillary renal carcinoma
		Hereditary retinal dystrophy

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Hereditary sideroblastic anaemia
		Hereditary spastic paraplegia
		Hereditary spherocytosis
		Hereditary stomatocytosis
		Hermansky-Pudlak syndrome
		Hermaphroditism
		Hernia congenital
		Heterochromia iridis
		Heterotaxia
		Hexokinase deficiency anaemia
		High arched palate
		Hollow visceral myopathy
		Holoprosencephaly
		Holt-Oram syndrome
		Homocystinaemia
		Homocystinuria
		Hooded prepuce
		Huntington's disease
		Hydranencephaly
		Hydrocele
		Hydroxyprolinaemia
		Hyper IgD syndrome
		Hyper IgE syndrome
		Hyper IgM syndrome
		Hyperexplexia
		Hyperinsulinism syndrome
		Hypermethioninaemia
		Hypermethioniuria
		Hyperprolinaemia
		Hypersplenism congenital
		Hypertelorism of orbit
		Hypertrophic cardiomyopathy
		Hypocalvaria
		Hypochondroplasia
		Hypodontia
		Hypomelanosis of Ito
		Hypophosphatasia
		Hypopituitarism foetal
		Hypoplastic left heart syndrome
		Hypoplastic nasal cartilage
		Hypoplastic right heart syndrome
		Hypospadias
		Hypotelorism of orbit
		Hypothalamic hamartoma
		Hypoxanthine-guanine phosphoribosyl transferase deficiency
		Ichthyosis
		Ileal atresia
		Immunodeficiency congenital
		Imperforate hymen
		Imperforate oesophagus

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Inborn error in primary bile acid synthesis
		Inborn error of bilirubin metabolism
		Inborn error of lipid metabolism
		Inborn error of metabolism
		Infantile cortical hyperostosis
		Infantile genetic agranulocytosis
		Infantile septic granulomatosis
		Inherited cardiac conduction disorder
		Iniencephaly
		Interferon gamma receptor deficiency
		Interruption of aortic arch
		Intestinal atresia
		Intestinal malrotation
		Intestinal neuronal dysplasia
		Intestinal transposition
		Intracranial arterial fenestration
		Intracranial lipoma
		Iris coloboma
		Johanson-Blizzard syndrome
		Joubert syndrome
		Juvenile Paget's disease
		Kabuki make-up syndrome
		Kaufman-McKusick syndrome
		Kearns-Sayre syndrome
		Kenny-Caffey syndrome
		Keratitis-ichthyosis-deafness syndrome
		Keratolysis exfoliativa congenital
		Keratosis follicular
		Kidney duplex
		Kidney malformation
		Kidney malrotation
		Kimmerle's anomaly
		Kinematic imbalances due to suboccipital strain
		Kleefstra syndrome
		Klinefelter's syndrome
		Klippel-Feil syndrome
		Klippel-Trenaunay syndrome
		Krabbe's disease
		Kyphosis congenital
		LDLR mutation
		Labial tie
		Lacrimal punctum agenesis
		Laevocardia
		Lafora's myoclonic epilepsy
		Lamin A/C gene mutation
		Langer-Giedion syndrome
		Laron syndrome
		Larsen syndrome
		Laryngeal cleft
		Laryngeal web
		Laryngo-onycho-cutaneous syndrome

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Laryngocele
		Laryngomalacia
		Laurence-Moon-Bardet-Biedl syndrome
		Leber's congenital amaurosis
		Lecithin-cholesterol acyltransferase deficiency
		Left ventricle outflow tract obstruction
		Left-to-right cardiac shunt
		Lens abnormality, congenital
		Leukodystrophy
		Li-Fraumeni syndrome
		Lichen spinulosus
		Liddle's syndrome
		Limb hypoplasia congenital
		Limb malformation
		Limb reduction defect
		Lipid proteinosis
		Lipidosis
		Lipodermoid tumour
		Lipomeningocele
		Lissencephaly
		Long QT syndrome congenital
		Long-chain acyl-coenzyme A dehydrogenase deficiency
		Low set ears
		Lown-Ganong-Levine syndrome
		Lowry-Wood syndrome
		Lumbarisation
		Lymphangiectasia intestinal congenital
		Lysinuric protein intolerance
		Lysosomal acid lipase deficiency
		MELAS syndrome
		MLASA syndrome
		MYH9-related disease
		Macrocephaly
		Macrocheilia
		Macrocornea
		Macrodactyly
		Macrogenia
		Macroglossia
		Macrognathia
		Macrostomia
		Macrotia
		Macular dystrophy congenital
		Majeed's syndrome
		Malformation biliary
		Malformation venous
		Mandibulofacial dysostosis
		Maple syrup disease
		Marcus Gunn syndrome
		Marfan's syndrome
		Maxillonasal dysplasia

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Mayer-Rokitansky-Kuster-Hauser syndrome
		Medium-chain acyl-coenzyme A dehydrogenase deficiency
		Meier-Gorlin syndrome
		Melkersson-Rosenthal syndrome
		Membranous lipodystrophy
		Meningocele
		Meningomyelocele
		Menkes' syndrome
		Mesoblastic nephroma
		Mesonephric duct cyst
		Metabolic myopathy
		Metachromatic leukodystrophy
		Metaphyseal dysplasia
		Metatarsus primus varus
		Methylenetetrahydrofolate reductase deficiency
		Methylenetetrahydrofolate reductase gene mutation
		Methylmalonic aciduria
		Mevalonate kinase deficiency
		Mevalonic aciduria
		Microcephaly
		Microcheilia
		Microcolon
		Microcornea
		Microencephaly
		Microgenia
		Microglossia
		Micrognathia
		Micropenis
		Microphthalmos
		Microstomia
		Microtia
		Microvillous inclusion disease
		Mismatch repair cancer syndrome
		Mitochondrial DNA deletion
		Mitochondrial DNA depletion
		Mitochondrial DNA duplication
		Mitochondrial DNA mutation
		Mitochondrial encephalomyopathy
		Mitochondrial enzyme deficiency
		Mitochondrial hepatopathy
		Mitochondrial myopathy
		Mitochondrial neurogastrointestinal encephalopathy
		Mitral valve atresia
		Mitral valve hypoplasia
		Mittendorf dot
		Mobile caecum syndrome
		Moebius II syndrome
		Molybdenum cofactor deficiency

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Monopodia
		Morning glory syndrome
		Morton's syndrome
		Mosaicism
		Mount-Reback syndrome
		Muckle-Wells syndrome
		Mucolipidosis
		Mucolipidosis type I
		Mucolipidosis type II
		Mucolipidosis type III
		Mucolipidosis type IV
		Mucopolysaccharidosis
		Mucopolysaccharidosis I
		Mucopolysaccharidosis II
		Mucopolysaccharidosis III
		Mucopolysaccharidosis IV
		Mucopolysaccharidosis V
		Mucopolysaccharidosis VI
		Mucopolysaccharidosis VII
		Muir-Torre syndrome
		Multiple carboxylase deficiency
		Multiple cardiac defects
		Multiple congenital abnormalities
		Multiple cutaneous and uterine leiomyomatosis
		Multiple endocrine neoplasia
		Multiple endocrine neoplasia Type 1
		Multiple endocrine neoplasia Type 2
		Multiple endocrine neoplasia Type 2A
		Multiple endocrine neoplasia Type 2B
		Multiple epiphyseal dysplasia
		Multiple gastrointestinal atresias
		Multiple lentigines syndrome
		Muscular dystrophy
		Mutagenic effect
		Myeloperoxidase deficiency
		Myocardial bridging
		Myoclonic epilepsy and ragged-red fibres
		Myotonia congenita
		Myotonic dystrophy
		N-acetylglutamate synthase deficiency
		Naevus anaemicus
		Naevus flammeus
		Naevus spider congenital
		Nail-patella syndrome
		Nasopharyngeal atresia
		Neonatal alloimmune thrombocytopenia
		Neonatal haemochromatosis
		Neonatal leukaemia
		Neonatal lupus erythematosus
		Netherton's syndrome
		Neural tube defect

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Neurofibromatosis
		Neuronal ceroid lipofuscinosis
		Neuronal migration disorder
		Neuropathy, ataxia, retinitis pigmentosa syndrome
		Niemann-Pick disease
		Nijmegen breakage syndrome
		Non-compaction cardiomyopathy
		Nonketotic hyperglycinaemia
		Noonan syndrome
		Norrie's disease
		Ocular albinism
		Oculoauriculovertebral dysplasia
		Oculocerebrorenal syndrome
		Oculodentodigital dysplasia
		Oculopharyngeal dystrophy
		Odontogenic cyst
		Oesophageal atresia
		Oesophageal cyst
		Olfacto genital dysplasia
		Olfactory nerve agenesis
		Olmsted syndrome
		Omenn syndrome
		Opitz-G/BBB syndrome
		Optic nerve hypoplasia
		Oral-facial-digital syndrome type II
		Ornithine transcarbamoylase deficiency
		Oroticaciduria congenital
		Os trigonum
		Osteogenesis imperfecta
		Osteopathia striata
		Osteopetrosis
		Osteopoikilosis
		Osteoporosis-pseudoglioma syndrome
		Ota's naevus
		Otocephaly
		Ovarian agenesis
		Ovarian hypoplasia
		PHACES syndrome
		Pachydermoperiostosis
		Pachygyria
		Pancreas divisum
		Parachute mitral valve
		Paranasal sinus aplasia
		Parkes-Weber syndrome
		Patent ductus arteriosus
		Pearson's syndrome
		Pectus carinatum
		Pectus excavatum
		Pelizaeus-Merzbacher disease
		Pelvic kidney
		Penile torsion

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Penoscrotal fusion
		Penoscrotal transposition
		Periodontal congenital anomaly
		Periventricular nodular heterotopia
		Perry syndrome
		Persistent cloaca
		Persistent foetal circulation
		Persistent left superior vena cava
		Persistent pupillary membrane
		Persistent urogenital sinus
		Peutz-Jeghers syndrome
		Phakomatosis
		Phalangeal agenesis
		Phalangeal hypoplasia
		Phenylketonuria
		Phimosis
		Phytosterolaemia
		Pierre Robin syndrome
		Pilonidal cyst congenital
		Plagiocephaly
		Platelet glycoprotein gene mutation
		Platonychia
		Platybasia
		Platyspondylia
		Poland's syndrome
		Polycystic liver disease
		Polydactyly
		Polymicrogyria
		Porencephaly
		Porokeratosis
		Porphyria
		Porphyria acute
		Porphyria non-acute
		Porphyrin metabolism disorder
		Porphyrinuria
		Portal venous system anomaly
		Postauricular fistula
		Posterior segment of eye anomaly congenital
		Potter's syndrome
		Prader-Willi syndrome
		Preauricular cyst
		Preduodenal portal vein
		Preternatural anus
		Primary cerebellar degeneration
		Primary ciliary dyskinesia
		Primary familial brain calcification
		Primary familial hypomagnesaemia
		Primary hypercholesterolaemia
		Primary immunodeficiency syndrome
		Primary insulin like growth factor-1 deficiency

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Progeria
		Progressive cerebellar degeneration
		Progressive external ophthalmoplegia
		Progressive familial intrahepatic cholestasis
		Prominent epicanthal folds
		Protein C deficiency
		Protein S deficiency
		Proteus syndrome
		Protuberant ear
		Proximal focal femoral deficiency
		Pseudocholinesterase deficiency
		Pseudohermaphroditism
		Pseudohermaphroditism female
		Pseudohermaphroditism male
		Pseudohypoparathyroidism
		Pseudotruncus arteriosus
		Pseudoxanthoma elasticum
		Pterygium colli
		Pulmonary aplasia
		Pulmonary arteriovenous fistula
		Pulmonary artery atresia
		Pulmonary artery stenosis congenital
		Pulmonary hypoplasia
		Pulmonary lymphangiectasia
		Pulmonary malformation
		Pulmonary sequestration
		Pulmonary valve stenosis congenital
		Pyloric stenosis
		Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome
		Pyruvate carboxylase deficiency
		Pyruvate kinase deficiency anaemia
		Radioulnar synostosis
		Rathke's cleft cyst
		Rectal atresia
		Red blood cell enzymes abnormal
		Refsum's disease
		Renal aplasia
		Renal arteriovenous malformation
		Renal dysplasia
		Renal fusion anomaly
		Renal hypoplasia
		Renal malposition
		Renal vessel congenital anomaly
		Reproductive tract hypoplasia, male
		Respiratory tract malformation
		Retinal anomaly congenital
		Retinal arteriovenous malformation
		Retinal coloboma
		Retinitis pigmentosa
		Retinopathy congenital

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Retinoschisis congenital
		Rett syndrome
		Rhesus haemolytic disease of newborn
		Rib hypoplasia
		Rib synostosis
		Right aortic arch
		Right ventricle outflow tract obstruction
		Right-to-left cardiac shunt
		Riley-Day syndrome
		Rippling muscle disease
		Rotor's syndrome
		Rubinstein-Taybi syndrome
		Sacral hypoplasia
		Sacralisation
		Sarcosinaemia
		Scaphocephaly
		Schimke immunoosseous dysplasia
		Schinzel-Giedion syndrome
		Schizencephaly
		Scimitar syndrome
		Sclerotylosis
		Sebaceous naevus
		Sensory neuropathy hereditary
		Septate hymen
		Septo-optic dysplasia
		Septum pellucidum agenesis
		Sertoli-cell-only syndrome
		Severe myoclonic epilepsy of infancy
		Sex chromosome abnormality
		Shone complex
		Short-chain acyl-coenzyme A dehydrogenase deficiency
		Shwachman-Diamond syndrome
		Sickle cell anaemia
		Sickle cell trait
		Silver-Russell syndrome
		Single umbilical artery
		Sirenomelia
		Sjogren-Larsson syndrome
		Skeletal dysplasia
		Skin hypoplasia
		Skin malformation
		Skull malformation
		Smith-Lemli-Opitz syndrome
		Sotos' syndrome
		Special senses congenital anomaly
		Spherophakia
		Spina bifida
		Spina bifida cystica
		Spina bifida occulta
		Spinal muscular atrophy

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Spinal vessel congenital anomaly
		Spine malformation
		Spinocerebellar ataxia
		Spleen malformation
		Splenic hamartoma
		Spondyloepiphyseal dysplasia
		Stargardt's disease
		Steatocystoma multiplex
		Stickler's syndrome
		Sticky platelet syndrome
		Strabismus congenital
		Sturge-Weber syndrome
		Subependymal nodular heterotopia
		Sucrase-isomaltase deficiency
		Supernumerary nipple
		Supernumerary vertebra
		Syndactyly
		Synostosis
		Syringomyelia
		Talipes
		Tangier disease
		Tay-Sachs disease
		Telangiectasia congenital
		Teratogenicity
		Testicular dysplasia
		Testotoxicosis
		Tetrahydrobiopterin deficiency
		Thalassaemia
		Thalassaemia alpha
		Thalassaemia beta
		Thalassaemia sickle cell
		Thalidomide embryopathy
		Thanatophoric dwarfism
		Thrombocytopenia-absent radius syndrome
		Thymus hypoplasia
		Thyroglossal cyst
		Thyroglossal fistula
		Thyroid hemiagenesis
		Thyroid malformation
		Tibial torsion
		Tilted disc syndrome
		Timothy syndrome
		Tooth discolouration congenital
		Tooth hypoplasia
		Tooth malformation hereditary
		Tornwaldt cyst
		Tourette's disorder
		Tracheal atresia
		Tracheal web
		Tracheo-oesophageal fistula
		Transitional vertebrae
		Transposition of the great vessels

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Trichorhinophalangeal syndrome
		Trifunctional protein deficiency
		Trimethylaminuria
		Triple A syndrome
		Trisomy 11
		Trisomy 12
		Trisomy 13
		Trisomy 14
		Trisomy 15
		Trisomy 17
		Trisomy 18
		Trisomy 21
		Trisomy 22
		Trisomy 8
		Trisomy 9
		Truncus arteriosus persistent
		Tuberous sclerosis
		Tumour necrosis factor receptor-associated periodic syndrome
		Turner's syndrome
		Twin reversed arterial perfusion sequence malformation
		Type I hyperlipidaemia
		Type II hyperlipidaemia
		Type III hyperlipidaemia
		Type IIa hyperlipidaemia
		Type IIb hyperlipidaemia
		Type IV hyperlipidaemia
		Type V hyperlipidaemia
		Tyrosinaemia
		Uhl's anomaly
		Umbilical artery hypoplasia
		Umbilical malformation
		Univentricular heart
		Urachal abnormality
		Ureteric atresia
		Urethral atresia
		Urethral valves
		Urinary tract malformation
		Usher's syndrome
		Uterine aplasia
		Uterine cervix hypoplasia
		Uterine hypoplasia
		Uvula aplasia
		VACTERL syndrome
		Vaginal atresia
		Vaginal hypoplasia
		Vaginal septum
		Vascular malformation
		Vein of Galen aneurysmal malformation
		Velo-cardio-facial syndrome
		Venous angioma of brain

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Ventricular hypoplasia
		Ventricular septal defect
		Vertebral artery hypoplasia
		Vertical talus
		Very long-chain acyl-coenzyme A dehydrogenase deficiency
		Virilism foetal
		Vitello-intestinal duct remnant
		Von Hippel-Lindau disease
		Von Willebrand's disease
		Waardenburg syndrome
		Wagner's disease
		Weill-Marchesani syndrome
		Welander distal myopathy
		Werner's syndrome
		Wildervanck syndrome
		Williams syndrome
		Winchester syndrome
		Wiskott-Aldrich syndrome
		Wolf-Hirschhorn syndrome
		Wolff-Parkinson-White syndrome congenital
		Wolfram syndrome
		Wyburn Mason's syndrome
		X-linked chromosomal disorder
		X-linked lymphoproliferative syndrome
		XXX syndrome
		XXXY syndrome
		XXYY syndrome
		XYY syndrome
		Xeroderma pigmentosum
		Y-linked chromosomal disorder
		Young's syndrome
	Ear and labyrinth disorders	Accessory auricle
		Alport's syndrome
		Alstroem syndrome
		Anomaly of external ear congenital
		Anomaly of middle ear congenital
		Anotia
		Auditory neuropathy spectrum disorder
		Barakat syndrome
		Branchio-oto-renal syndrome
		Branchiogenic syndrome
		CHARGE syndrome
		Cockayne's syndrome
		Congenital Eustachian tube anomaly
		Congenital anomalies of ear ossicles
		Congenital anomaly of inner ear
		Congenital aural fistula
		Congenital hearing disorder
		Constricted ear deformity

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Adverse event class	System organ class	Preferred term
Rare	Ear and labyrinth disorders	Deaf mutism
		Deafness congenital
		Ear malformation
		Emanuel syndrome
		External auditory canal atresia
		Johanson-Blizzard syndrome
		Keratitis-ichthyosis-deafness syndrome
		Low set ears
		MYH9-related disease
		Macrotia
		Meier-Gorlin syndrome
		Microtia
		Norrie's disease
		Preauricular cyst
		Protuberant ear
		Usher's syndrome
		Waardenburg syndrome
		Wildervanck syndrome
		Wolfram syndrome
	Endocrine disorders	18q minus syndrome
		Adrenal insufficiency neonatal
		Adrenogenital syndrome
		Adrenoleukodystrophy
		Albright's disease
		Androgen insensitivity syndrome
		Anorchism
		Barakat syndrome
		Bulbospinal muscular atrophy congenital
		Carney complex
		Congenital adrenal gland hypoplasia
		Congenital androgen deficiency
		Congenital anomaly of adrenal gland
		Congenital central diabetes insipidus
		Congenital endocrine anomaly
		Congenital generalised lipodystrophy
		Congenital hyperthyroidism
		Congenital hypoparathyroidism
		Congenital hypothyroidism
		Congenital thyroid disorder
		Cryptorchism
		Cystic fibrosis related diabetes
		Denys-Drash syndrome
		DiGeorge's syndrome
		Diabetic foetopathy
		Diabetic hepatopathy
		Diencephalic syndrome of infancy
		Ectopic posterior pituitary gland
		Ectopic thyroid
		Familial hypocalciuric hypercalcaemia
		Familial medullary thyroid cancer
		Generalised resistance to thyroid hormone

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Adverse event class	System organ class	Preferred term
Rare	Endocrine disorders	Goitre congenital
		Hermaphroditism
		Hyperinsulinism syndrome
		Hypopituitarism foetal
		Hypothalamic hamartoma
		Kenny-Caffey syndrome
		Klinefelter's syndrome
		Laron syndrome
		Multiple endocrine neoplasia
		Multiple endocrine neoplasia Type 1
		Multiple endocrine neoplasia Type 2
		Multiple endocrine neoplasia Type 2A
		Multiple endocrine neoplasia Type 2B
		Myotonic dystrophy
		Ovarian hypoplasia
		Pseudohermaphroditism
		Pseudohermaphroditism female
		Pseudohermaphroditism male
		Septo-optic dysplasia
		Sertoli-cell-only syndrome
		Thyroglossal cyst
		Thyroglossal fistula
		Thyroid hemiagenesis
		Thyroid malformation
		Triple A syndrome
		Turner's syndrome
		Virilism foetal
		Wolfram syndrome
		XXXY syndrome
		XXYY syndrome
	Eye disorders	Alstroem syndrome
		Amblyopia congenital
		Aniridia
		Anomaly of orbit, congenital
		Anophthalmos
		Anterior chamber cleavage syndrome
		Aphakia congenital
		Basal cell naevus syndrome
		Bickerstaff's encephalitis
		Blau syndrome
		Blepharophimosis congenital
		Blindness congenital
		Bloch-Sulzberger syndrome
		CHARGE syndrome
		Cataract congenital
		Chorioretinal degeneration congenital
		Choroidal coloboma
		Cockayne's syndrome
		Cohen syndrome
		Coloboma
		Colour blindness
		Congenital Horner's syndrome
		Congenital astigmatism

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Adverse event class	System organ class	Preferred term
Rare	Eye disorders	Congenital choroidal anomaly
		Congenital corneal anomaly
		Congenital epiblepharon
		Congenital eye disorder
		Congenital eye naevus
		Congenital eyelid malformation
		Congenital iris anomaly
		Congenital lacrimal gland anomaly
		Congenital lacrimal passage anomaly
		Congenital lenticonus
		Congenital myopia
		Congenital night blindness
		Congenital nystagmus
		Congenital oculomotor apraxia
		Congenital optic nerve anomaly
		Congenital retinoblastoma
		Congenital scleral disorder
		Congenital trichomegaly
		Congenital visual acuity reduced
		Congenital vitreous anomaly
		Conjunctivitis gonococcal neonatal
		Corneal dystrophy
		Corneal opacity congenital
		Cri du Chat syndrome
		Cryptophthalmos
		Cyclopia
		Cystic eyeball, congenital
		Dacryostenosis congenital
		Developmental glaucoma
		Distichiasis
		Duane's syndrome
		Emanuel syndrome
		Entropion congenital
		Exophthalmos congenital
		Eye anterior chamber congenital anomaly
		Eyelid oedema
		Eyelid ptosis congenital
		Faciodigitogenital dysplasia
		Haemangioma of retina
		Hepato-lenticular degeneration
		Hereditary choroidal dystrophy
		Hereditary optic atrophy
		Hereditary retinal dystrophy
		Hermansky-Pudlak syndrome
		Heterochromia iridis
		Hypertelorism of orbit
		Hypotelorism of orbit
		Iris coloboma
		Kearns-Sayre syndrome
		Keratitis-ichthyosis-deafness syndrome
		Lacrimal punctum agenesis
		Laurence-Moon-Bardet-Biedl syndrome
		Leber's congenital amaurosis

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Adverse event class	System organ class	Preferred term
Rare	Eye disorders	Lecithin-cholesterol acyltransferase deficiency
		Lens abnormality, congenital
		Lipodermoid tumour
		MYH9-related disease
		Macrocornea
		Macular dystrophy congenital
		Marcus Gunn syndrome
		Marfan's syndrome
		Microcornea
		Microphthalmos
		Miller Fisher syndrome
		Mittendorf dot
		Morning glory syndrome
		Neuropathy, ataxia, retinitis pigmentosa syndrome
		Norrie's disease
		Ocular albinism
		Ocular icterus
		Oculocerebrorenal syndrome
		Oculodentodigital dysplasia
		Oculomucocutaneous syndrome
		Oculopharyngeal dystrophy
		Oculorespiratory syndrome
		Opitz-G/BBB syndrome
		Optic nerve hypoplasia
		Osteoporosis-pseudoglioma syndrome
		Ota's naevus
		PHACES syndrome
		Periorbital oedema
		Persistent pupillary membrane
		Phakomatosis
		Posterior segment of eye anomaly congenital
		Progressive external ophthalmoplegia
		Prominent epicanthal folds
		Pseudoxanthoma elasticum
		Retinal anomaly congenital
		Retinal arteriovenous malformation
		Retinal coloboma
		Retinitis pigmentosa
		Retinopathy congenital
		Retinoschisis congenital
		Septo-optic dysplasia
		Spherophakia
		Stargardt's disease
		Stickler's syndrome
		Strabismus congenital
		Sturge-Weber syndrome
		Tilted disc syndrome
		Triple A syndrome
		Trisomy 13
		Trisomy 22

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Adverse event class	System organ class	Preferred term
Rare	Eye disorders	Tuberous sclerosis
		Tubulointerstitial nephritis and uveitis syndrome
		Usher's syndrome
		Waardenburg syndrome
		Wagner's disease
		Weill-Marchesani syndrome
		Wildervanck syndrome
		Winchester syndrome
		Wolfram syndrome
		Wyburn Mason's syndrome
	Gastrointestinal disorders	Abdominal transposition
		Abdominal wall anomaly
		Accessory salivary gland
		Acrodermatitis enteropathica
		Adenomatous polyposis coli
		Aglossia
		Alcoholic pancreatitis
		Alcoholic pancreopathy
		Anal atresia
		Ankyloglossia congenital
		Annular pancreas
		Anodontia
		Anomalous arrangement of pancreaticobiliary duct
		Anorectal agenesis
		Anterior displaced anus
		Ascites
		Autoimmune pancreatitis
		Bacterascites
		Basal cell naevus syndrome
		Beckwith-Wiedemann syndrome
		Cleft lip
		Cleft lip and palate
		Cleft palate
		Cleft uvula
		Cloacal exstrophy
		Clostridium colitis
		Clostridium difficile colitis
		Congenital abdominal hernia
		Congenital diaphragmatic hernia
		Congenital dyskeratosis
		Congenital ectopic pancreas
		Congenital gastric anomaly
		Congenital gastrointestinal vessel anomaly
		Congenital hiatus hernia
		Congenital inguinal hernia
		Congenital intestinal malformation
		Congenital intestinal obstruction
		Congenital intrinsic factor deficiency
		Congenital large intestinal atresia

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Adverse event class	System organ class	Preferred term
Rare	Gastrointestinal disorders	Congenital lip fistula
		Congenital megacolon
		Congenital oesophageal anomaly
		Congenital oesophageal stenosis
		Congenital oesophageal web
		Congenital oral malformation
		Congenital pancreatic anomaly
		Congenital salivary gland anomaly
		Congenital small intestinal atresia
		Congenital tongue anomaly
		Congenital umbilical hernia
		Cullen's sign
		Cutaneovisceral angiomatosis with thrombocytopenia
		Cystic fibrosis
		Cystic fibrosis gastrointestinal disease
		Cystic fibrosis pancreatic
		Cytomegalovirus pancreatitis
		Dentinogenesis imperfecta
		Dentofacial anomaly
		Diverticulitis Meckel's
		Dolichocolon
		Duodenal atresia
		Duodenal varices
		Duplex appendix
		Encapsulating peritoneal sclerosis
		Enteric duplication
		Exomphalos
		Fissure of tongue, congenital
		Fryns syndrome
		Gastric varices
		Gastric varices haemorrhage
		Gastroenteritis clostridial
		Gastrointestinal arteriovenous malformation
		Gastrointestinal disorder congenital
		Gastrointestinal malformation
		Gastroschisis
		Glucose-galactose malabsorption
		Gnathoschisis
		Grey Turner's sign
		Haemorrhagic necrotic pancreatitis
		Hepatic hydrothorax
		Hereditary haemorrhagic telangiectasia
		Hereditary non-polyposis colorectal cancer syndrome
		Hereditary pancreatitis
		High arched palate
		Hollow visceral myopathy
		Hypodontia
		Ileal atresia
		Imperforate oesophagus

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Adverse event class	System organ class	Preferred term
Rare	Gastrointestinal disorders	Intestinal angioedema
		Intestinal atresia
		Intestinal malrotation
		Intestinal neuronal dysplasia
		Intestinal sepsis
		Intestinal transposition
		Intestinal varices
		Intestinal varices haemorrhage
		Ischaemic pancreatitis
		Johanson-Blizzard syndrome
		Labial tie
		Lip oedema
		Lip swelling
		Lupus pancreatitis
		Lymphangiectasia intestinal congenital
		Macroglossia
		Melkersson-Rosenthal syndrome
		Mesenteric fibrosis
		Microcolon
		Microglossia
		Microvillous inclusion disease
		Mobile caecum syndrome
		Mouth swelling
		Muir-Torre syndrome
		Multiple gastrointestinal atresias
		Neutropenic colitis
		Oculomucocutaneous syndrome
		Odontogenic cyst
		Oedema mouth
		Oedematous pancreatitis
		Oesophageal atresia
		Oesophageal cyst
		Oesophageal varices haemorrhage
		Oropharyngeal oedema
		Oropharyngeal swelling
		Pancreas divisum
		Pancreas infection
		Pancreatic abscess
		Pancreatic haemorrhage
		Pancreatic necrosis
		Pancreatic phlegmon
		Pancreatic pseudocyst
		Pancreatitis
		Pancreatitis acute
		Pancreatitis bacterial
		Pancreatitis chronic
		Pancreatitis fungal
		Pancreatitis haemorrhagic
		Pancreatitis helminthic
		Pancreatitis mumps
		Pancreatitis necrotising
		Pancreatitis relapsing

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Adverse event class	System organ class	Preferred term
Rare	Gastrointestinal disorders	Pancreatitis viral
		Pancreatorenal syndrome
		Pearson's syndrome
		Periodontal congenital anomaly
		Peripancreatic varices
		Persistent cloaca
		Peutz-Jeghers syndrome
		Portal hypertensive colopathy
		Portal hypertensive enteropathy
		Portal hypertensive gastropathy
		Preduodenal portal vein
		Preternatural anus
		Pseudomembranous colitis
		Pyloric stenosis
		Rectal atresia
		Retroperitoneal fibrosis
		Retroperitonitis
		Shwachman-Diamond syndrome
		Sucrase-isomaltase deficiency
		Swollen tongue
		Tongue oedema
		Tooth discolouration congenital
		Tooth hypoplasia
		Tooth malformation hereditary
		Tracheo-oesophageal fistula
		Traumatic pancreatitis
		Triple A syndrome
		Uvula aplasia
		VACTERL syndrome
		Varices oesophageal
		Varicose veins of abdominal wall
		Vitello-intestinal duct remnant
		White nipple sign
	General disorders and administration site conditions	Aplasia
		Cardiac death
		Chronic infantile neurological cutaneous and articular syndrome
		Congenital cyst
		Cryopyrin associated periodic syndrome
		Deficiency of the interleukin-1 receptor antagonist
		Deficiency of the interleukin-36 receptor antagonist
		Dentatorubral-pallidoluysian atrophy
		Face oedema
		Familial cold autoinflammatory syndrome
		Familial mediterranean fever
		Febrile bone marrow aplasia
		Febrile neutropenia
		Friedreich's ataxia

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Adverse event class	System organ class	Preferred term
Rare	General disorders and administration site conditions	Hernia congenital
		Hyper IgD syndrome
		Hyperthermia malignant
		Joubert syndrome
		Majeed's syndrome
		Mevalonate kinase deficiency
		Mevalonic aciduria
		Multiple organ dysfunction syndrome
		Neuroleptic malignant syndrome
		Oedema due to hepatic disease
		Pacemaker generated arrhythmia
		Pacemaker syndrome
		Pelvic fibrosis
		Rebound tachycardia
		Spinocerebellar ataxia
		Sudden cardiac death
		Sudden death
		Tumour necrosis factor receptor-associated periodic syndrome
		Withdrawal arrhythmia
		Yellow skin
	Hepatobiliary disorders	Accessory liver lobe
		Acute graft versus host disease in liver
		Acute hepatic failure
		Acute on chronic liver failure
		Acute yellow liver atrophy
		Alagille syndrome
		Allergic hepatitis
		Alpha-1 anti-trypsin deficiency
		Anomalous arrangement of pancreaticobiliary duct
		Ascites
		Asterixis
		Autoimmune hepatitis
		Bacterascites
		Biliary cirrhosis
		Biliary cirrhosis primary
		Biliary fibrosis
		Biliary hamartoma
		Bilirubin excretion disorder
		Cerebrohepatorenal syndrome
		Cholaemia
		Cholangiectasis congenital
		Cholangitis
		Choledochal cyst
		Cholestasis
		Cholestatic liver injury
		Cholestatic pruritus
		Chronic graft versus host disease in liver
		Chronic hepatic failure

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Adverse event class	System organ class	Preferred term
Rare	Hepatobiliary disorders	Chronic hepatitis
		Coma hepatic
		Congenital absence of bile ducts
		Congenital cystic disease of liver
		Congenital hepatic fibrosis
		Congenital hepatitis B infection
		Congenital hepatobiliary anomaly
		Congenital hepatomegaly
		Crigler-Najjar syndrome
		Cryptogenic cirrhosis
		Cystic fibrosis hepatic disease
		Deficiency of bile secretion
		Diabetic hepatopathy
		Dilatation intrahepatic duct congenital
		Drug-induced liver injury
		Dubin-Johnson syndrome
		Duodenal varices
		Gallbladder agenesis
		Gallbladder anomaly congenital
		Gallbladder varices
		Gastric varices
		Gastric varices haemorrhage
		Gilbert's syndrome
		Glycogen storage disease type I
		Glycogen storage disease type III
		Glycogen storage disease type IV
		Glycogen storage disease type VI
		Graft versus host disease in liver
		Granulomatous liver disease
		Haemochromatosis trait
		Hepatic arteriovenous malformation
		Hepatic atrophy
		Hepatic calcification
		Hepatic cirrhosis
		Hepatic encephalopathy
		Hepatic failure
		Hepatic fibrosis
		Hepatic hydrothorax
		Hepatic infiltration eosinophilic
		Hepatic lesion
		Hepatic necrosis
		Hepatic steato-fibrosis
		Hepatic steatosis
		Hepatitis
		Hepatitis acute
		Hepatitis cholestatic
		Hepatitis chronic active
		Hepatitis chronic persistent
		Hepatitis fulminant
		Hepatitis toxic
		Hepato-lenticular degeneration
		Hepatobiliary disease
		Hepatocellular foamy cell syndrome

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Adverse event class	System organ class	Preferred term
Rare	Hepatobiliary disorders	Hepatocellular injury
		Hepatopulmonary syndrome
		Hepatorenal failure
		Hepatorenal syndrome
		Hepatotoxicity
		Hereditary haemochromatosis
		Hyperbilirubinaemia
		Intestinal varices
		Ischaemic hepatitis
		Jaundice
		Jaundice cholestatic
		Jaundice hepatocellular
		Liver disorder
		Liver injury
		Liver sarcoidosis
		Lupoid hepatic cirrhosis
		Lupus hepatitis
		Lysosomal acid lipase deficiency
		Malformation biliary
		Minimal hepatic encephalopathy
		Mitochondrial hepatopathy
		Mixed liver injury
		Nodular regenerative hyperplasia
		Non-alcoholic fatty liver
		Non-alcoholic steatohepatitis
		Non-cirrhotic portal hypertension
		Ocular icterus
		Oedema due to hepatic disease
		Oesophageal varices haemorrhage
		Parenteral nutrition associated liver disease
		Peripancreatic varices
		Polycystic liver disease
		Porphyria acute
		Porphyria non-acute
		Porphyrin metabolism disorder
		Porphyrinuria
		Portal fibrosis
		Portal hypertension
		Portal hypertensive colopathy
		Portal hypertensive enteropathy
		Portal hypertensive gastropathy
		Portal tract inflammation
		Portal vein cavernous transformation
		Portal vein dilatation
		Portal venous system anomaly
		Portopulmonary hypertension
		Progressive familial intrahepatic cholestasis
		Radiation hepatitis
		Retrograde portal vein flow
		Reye's syndrome
		Reynold's syndrome

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Adverse event class	System organ class	Preferred term
Rare	Hepatobiliary disorders	Rotor's syndrome
		Splenic varices
		Splenic varices haemorrhage
		Steatohepatitis
		Subacute hepatic failure
		Varices oesophageal
		Varicose veins of abdominal wall
		White nipple sign
		Yellow skin
	Immune system disorders	ABO haemolytic disease of newborn
		Acquired amegakaryocytic thrombocytopenia
		Activated PI3 kinase delta syndrome
		Acute graft versus host disease in liver
		Acute motor axonal neuropathy
		Acute motor-sensory axonal neuropathy
		Allergic hepatitis
		Amegakaryocytic thrombocytopenia
		Anaphylactic reaction
		Anaphylactic shock
		Anaphylactic transfusion reaction
		Anaphylactoid reaction
		Anaphylactoid shock
		Angioedema
		Ataxia telangiectasia
		Autoimmune aplastic anaemia
		Autoimmune hepatitis
		Autoimmune lymphoproliferative syndrome
		Autoimmune nephritis
		Autoimmune pancreatitis
		Benign familial pemphigus
		Bickerstaff's encephalitis
		Biliary cirrhosis primary
		Blau syndrome
		Bruton's agammaglobulinaemia
		C3 glomerulopathy
		CANDLE syndrome
		Cartilage-hair hypoplasia
		Chediak-Higashi syndrome
		Chronic autoimmune glomerulonephritis
		Chronic graft versus host disease in liver
		Chronic granulomatous disease
		Chronic infantile neurological cutaneous and articular syndrome
		Chronic inflammatory demyelinating polyradiculoneuropathy
		Circumoral oedema
		Combined immunodeficiency
		Complement deficiency disease
		Congenital HIV infection
		Congenital hypogammaglobulinaemia
		Congenital thrombocytopenia

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Adverse event class	System organ class	Preferred term
Rare	Immune system disorders	Cryopyrin associated periodic syndrome
		Cutaneous vasculitis
		Deficiency of the interleukin-1 receptor antagonist
		Deficiency of the interleukin-36 receptor antagonist
		Demyelinating polyneuropathy
		Dermatitis exfoliative
		Dermatitis exfoliative generalised
		DiGeorge's syndrome
		Dialysis membrane reaction
		Drug reaction with eosinophilia and systemic symptoms
		Erythema multiforme
		Eyelid oedema
		Face oedema
		Familial amyloidosis
		Familial cold autoinflammatory syndrome
		Familial mediterranean fever
		Fibrillary glomerulonephritis
		Gleich's syndrome
		Glomerulonephritis
		Glomerulonephritis rapidly progressive
		Goodpasture's syndrome
		Graft versus host disease in liver
		Granulomatosis with polyangiitis
		Guillain-Barre syndrome
		HIV associated nephropathy
		Henoch-Schonlein purpura nephritis
		Hereditary angioedema
		Hereditary neuropathic amyloidosis
		Hyper IgD syndrome
		Hyper IgE syndrome
		Hyper IgM syndrome
		Idiopathic angioedema
		IgA nephropathy
		IgM nephropathy
		Immunodeficiency congenital
		Interferon gamma receptor deficiency
		Intestinal angioedema
		Kounis syndrome
		Laryngeal oedema
		Laryngotracheal oedema
		Lip oedema
		Lip swelling
		Liver sarcoidosis
		Lupoid hepatic cirrhosis
		Lupus hepatitis
		Lupus nephritis
		Lupus pancreatitis
		Majeed's syndrome
		Mevalonate kinase deficiency
		Mevalonic aciduria

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Adverse event class	System organ class	Preferred term
Rare	Immune system disorders	Microscopic polyangiitis
		Mouth swelling
		Muckle-Wells syndrome
		Myeloperoxidase deficiency
		Neonatal alloimmune thrombocytopenia
		Neonatal lupus erythematosus
		Nephritis allergic
		Oculorespiratory syndrome
		Oedema mouth
		Omenn syndrome
		Oropharyngeal oedema
		Oropharyngeal swelling
		Periorbital oedema
		Pharyngeal oedema
		Primary immunodeficiency syndrome
		Pulmonary renal syndrome
		Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome
		Retroperitoneal fibrosis
		Reynold's syndrome
		Rhesus haemolytic disease of newborn
		Schimke immunoosseous dysplasia
		Stevens-Johnson syndrome
		Swelling face
		Swollen tongue
		Tongue oedema
		Toxic epidermal necrolysis
		Toxic skin eruption
		Tubulointerstitial nephritis and uveitis syndrome
		Tumour necrosis factor receptor-associated periodic syndrome
		Type I hypersensitivity
		Wiskott-Aldrich syndrome
		X-linked lymphoproliferative syndrome
	Infections and infestations	Activated PI3 kinase delta syndrome
		Acute focal bacterial nephritis
		Acute motor axonal neuropathy
		Acute motor-sensory axonal neuropathy
		Bacterascites
		Bickerstaff's encephalitis
		Cataract congenital
		Chronic hepatitis
		Clostridial infection
		Clostridial sepsis
		Clostridium bacteraemia
		Clostridium colitis
		Clostridium difficile colitis
		Clostridium difficile infection
		Congenital HIV infection
		Congenital condyloma
		Congenital cytomegalovirus infection

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Adverse event class	System organ class	Preferred term
Rare	Infections and infestations	Congenital hepatitis B infection
		Congenital herpes simplex infection
		Congenital infection
		Congenital malaria
		Congenital pneumonia
		Congenital rubella infection
		Congenital syphilis
		Congenital syphilitic encephalitis
		Congenital syphilitic meningitis
		Congenital syphilitic osteochondritis
		Congenital toxoplasmosis
		Congenital tuberculosis
		Congenital varicella infection
		Conjunctivitis gonococcal neonatal
		Cytomegalovirus nephritis
		Cytomegalovirus pancreatitis
		Fatal familial insomnia
		Gastroenteritis clostridial
		Guillain-Barre syndrome
		HIV associated nephropathy
		Hepatitis chronic active
		Hepatitis chronic persistent
		Hepatitis fulminant
		Hepatitis virus-associated nephropathy
		Infantile septic granulomatosis
		Intestinal sepsis
		Neutropenic infection
		Neutropenic sepsis
		Pancreas infection
		Pancreatic abscess
		Pancreatitis bacterial
		Pancreatitis fungal
		Pancreatitis helminthic
		Pancreatitis mumps
		Pancreatitis viral
		Pilonidal cyst congenital
		Post infection glomerulonephritis
		Post streptococcal glomerulonephritis
		Pseudomembranous colitis
		Retroperitonitis
		Reye's syndrome
		Shigella sepsis
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
		X-linked lymphoproliferative syndrome
		Young's syndrome
	Injury, poisoning and procedural complications	Acute generalised exanthematous pustulosis
		Acute graft versus host disease in liver
		Anaphylactic transfusion reaction
		Angiotensin converting enzyme inhibitor foetopathy

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Adverse event class	System organ class	Preferred term
Rare	Injury, poisoning and procedural complications	Bacterascites
		Bone marrow toxicity
		Chronic graft versus host disease in liver
		Dialysis membrane reaction
		Diethylstilboestrol syndrome
		Drug-induced liver injury
		Foetal alcohol syndrome
		Foetal anticonvulsant syndrome
		Foetal methotrexate syndrome
		Foetal retinoid syndrome
		Foetal warfarin syndrome
		Graft versus host disease in liver
		Haematotoxicity
		Hepatitis toxic
		Hepatotoxicity
		Junctional ectopic tachycardia
		Liver injury
		Nephritis radiation
		Nephropathy toxic
		Neuroleptic malignant syndrome
		Parenteral nutrition associated liver disease
		Platelet toxicity
		Radiation hepatitis
		Radiation leukopenia
		Serotonin syndrome
		Stevens-Johnson syndrome
		Teratogenicity
		Thalidomide embryopathy
		Toxic epidermal necrolysis
		Traumatic pancreatitis
	Investigations	Aspiration bone marrow abnormal
		B-lymphocyte count abnormal
		B-lymphocyte count decreased
		Band neutrophil count decreased
		Band neutrophil percentage decreased
		Basophil count abnormal
		Basophil count decreased
		Basophil percentage decreased
		Biopsy bone marrow abnormal
		Blood count abnormal
		Bone marrow myelogram abnormal
		Cardiac telemetry abnormal
		Clostridium test positive
		Differential white blood cell count abnormal
		ECG P wave inverted
		Electrocardiogram P wave abnormal
		Electrocardiogram PQ interval prolonged
		Electrocardiogram PQ interval shortened
		Electrocardiogram PR prolongation

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Adverse event class	System organ class	Preferred term
Rare	Investigations	Electrocardiogram PR shortened
		Electrocardiogram QRS complex prolonged
		Electrocardiogram QT prolonged
		Electrocardiogram RR interval prolonged
		Electrocardiogram U-wave abnormality
		Electrocardiogram abnormal
		Electrocardiogram ambulatory abnormal
		Electrocardiogram change
		Electrocardiogram delta waves abnormal
		Electrocardiogram repolarisation abnormality
		Eosinophil count abnormal
		Eosinophil count decreased
		Eosinophil percentage decreased
		Full blood count abnormal
		Full blood count decreased
		Granulocyte count decreased
		Granulocytes abnormal
		Heart rate abnormal
		Heart rate decreased
		Heart rate increased
		Heart rate irregular
		Icterus index increased
		Lymphocyte count abnormal
		Lymphocyte count decreased
		Lymphocyte percentage abnormal
		Lymphocyte percentage decreased
		Megakaryocytes decreased
		Metamyelocyte count decreased
		Monoblast count decreased
		Monocyte count abnormal
		Monocyte count decreased
		Monocyte percentage decreased
		Myeloblast count decreased
		Myeloblast percentage decreased
		Myelocyte count decreased
		Myelocyte percentage decreased
		Neutrophil count abnormal
		Neutrophil count decreased
		Neutrophil percentage decreased
		Plasma cells absent
		Plasmablast count decreased
		Platelet count decreased
		Promyelocyte count decreased
		Respiratory sinus arrhythmia magnitude abnormal
		Respiratory sinus arrhythmia magnitude decreased
		Respiratory sinus arrhythmia magnitude increased
		Retrograde p-waves
		Scan bone marrow abnormal
		T-lymphocyte count abnormal

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Adverse event class	System organ class	Preferred term
Rare	Investigations	T-lymphocyte count decreased
		White blood cell analysis abnormal
		White blood cell count abnormal
		White blood cell count decreased
	Metabolism and nutrition disorders	11-beta-hydroxylase deficiency
		17,20-desmolase deficiency
		17-alpha-hydroxylase deficiency
		2-Hydroxyglutaric aciduria
		20,22-desmolase deficiency
		21-hydroxylase deficiency
		3-hydroxyacetyl-coenzyme A dehydrogenase deficiency
		5-alpha-reductase deficiency
		Acetylcholinesterase deficiency
		Acrodermatitis enteropathica
		Acute phosphate nephropathy
		Adenine phosphoribosyl transferase deficiency
		Adrenal insufficiency neonatal
		Albinism
		Alkaptonuria
		Alpha-1 anti-trypsin deficiency
		Aminoaciduria
		Arginase deficiency
		Argininosuccinate lyase deficiency
		Argininosuccinate synthetase deficiency
		Aspartate-glutamate-transporter deficiency
		Aspartylglucosaminuria
		Barth syndrome
		Bartter's syndrome
		Beta ketothiolase deficiency
		Bilirubin excretion disorder
		Biotinidase deficiency
		CANDLE syndrome
		Canavan disease
		Carbamoyl phosphate synthetase deficiency
		Carbohydrate metabolism disorder
		Carnitine palmitoyltransferase deficiency
		Carnitine-acylcarnitine translocase deficiency
		Citrate transporter deficiency
		Congenital carnitine deficiency
		Congenital central diabetes insipidus
		Congenital disorder of glycosylation
		Congenital generalised lipodystrophy
		Congenital hyperthyroidism
		Congenital hypothyroidism
		Congenital intrinsic factor deficiency
		Congenital mitochondrial cytopathy

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Adverse event class	System organ class	Preferred term
Rare	Metabolism and nutrition disorders	Congenital nephrogenic diabetes insipidus
		Congenital oxalosis
		Craniotabes
		Crigler-Najjar syndrome
		Cystathionine beta-synthase deficiency
		Cystic fibrosis related diabetes
		Cystinosis
		Cystinuria
		Dent's disease
		Diabetic foetopathy
		Diabetic hepatopathy
		Diencephalic syndrome of infancy
		Dihydropyrimidine dehydrogenase deficiency
		Dubin-Johnson syndrome
		Dysmyelination
		Essential fructosuria
		Fabry's disease
		Familial high density lipoprotein deficiency
		Familial hypertriglyceridaemia
		Familial hypocalciuric hypercalcaemia
		Fanconi syndrome
		Fatty acid oxidation disorder
		Galactosaemia
		Gaucher's disease
		Gaucher's disease type I
		Gaucher's disease type II
		Gaucher's disease type III
		Gilbert's syndrome
		Gitelman's syndrome
		Glucose-6-phosphate dehydrogenase deficiency
		Glucose-galactose malabsorption
		Glutathione synthetase deficiency
		Glycogen storage disease type I
		Glycogen storage disease type II
		Glycogen storage disease type III
		Glycogen storage disease type IV
		Glycogen storage disease type V
		Glycogen storage disease type VI
		Glycogen storage disease type VII
		Glycogen storage disease type VIII
		Glycogen storage disorder
		Gorham's disease
		Haemochromatosis trait
		Hartnup disease
		Hepatic steato-fibrosis
		Hepatic steatosis
		Hepato-lenticular degeneration
		Hereditary fructose intolerance
		Hereditary haemochromatosis

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Adverse event class	System organ class	Preferred term
Rare	Metabolism and nutrition disorders	Hereditary hypophosphataemic rickets
		Hermansky-Pudlak syndrome
		Homocystinaemia
		Homocystinuria
		Hydroxyprolinaemia
		Hyper IgD syndrome
		Hyperbilirubinaemia
		Hyperinsulinism syndrome
		Hypermethioninaemia
		Hypermethioniuria
		Hyperprolinaemia
		Hypochondroplasia
		Hyponatriuria
		Hypophosphatasia
		Hypoxanthine-guanine phosphoribosyl transferase deficiency
		Inborn error in primary bile acid synthesis
		Inborn error of bilirubin metabolism
		Inborn error of lipid metabolism
		Inborn error of metabolism
		Krabbe's disease
		Lecithin-cholesterol acyltransferase deficiency
		Leukodystrophy
		Liddle's syndrome
		Lipid proteinosis
		Lipidosis
		Long-chain acyl-coenzyme A dehydrogenase deficiency
		Lysinuric protein intolerance
		Lysosomal acid lipase deficiency
		MELAS syndrome
		MLASA syndrome
		Maple syrup disease
		Medium-chain acyl-coenzyme A dehydrogenase deficiency
		Menkes' syndrome
		Metabolic myopathy
		Metachromatic leukodystrophy
		Methylenetetrahydrofolate reductase deficiency
		Methylenetetrahydrofolate reductase gene mutation
		Methylmalonic aciduria
		Mevalonate kinase deficiency
		Mitochondrial DNA deletion
		Mitochondrial DNA depletion
		Mitochondrial DNA mutation
		Mitochondrial enzyme deficiency
		Molybdenum cofactor deficiency
		Mucolipidosis

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Adverse event class	System organ class	Preferred term
Rare	Metabolism and nutrition disorders	Mucolipidosis type I
		Mucolipidosis type II
		Mucolipidosis type III
		Mucolipidosis type IV
		Mucopolysaccharidosis
		Mucopolysaccharidosis I
		Mucopolysaccharidosis II
		Mucopolysaccharidosis III
		Mucopolysaccharidosis IV
		Mucopolysaccharidosis V
		Mucopolysaccharidosis VI
		Mucopolysaccharidosis VII
		Multiple carboxylase deficiency
		N-acetylglutamate synthase deficiency
		Neonatal haemochromatosis
		Neuronal ceroid lipofuscinosis
		Niemann-Pick disease
		Non-alcoholic fatty liver
		Non-alcoholic steatohepatitis
		Nonketotic hyperglycinaemia
		Ornithine transcarbamoylase deficiency
		Oroticaciduria congenital
		Pelizaeus-Merzbacher disease
		Phenylketonuria
		Phytosterolaemia
		Porphyria
		Porphyria acute
		Porphyria non-acute
		Porphyrin metabolism disorder
		Porphyrinuria
		Prader-Willi syndrome
		Primary familial brain calcification
		Primary familial hypomagnesaemia
		Primary hypercholesterolaemia
		Primary insulin like growth factor-1 deficiency
		Pseudocholinesterase deficiency
		Pseudohypoparathyroidism
		Pyruvate carboxylase deficiency
		Refsum's disease
		Rett syndrome
		Rotor's syndrome
		Sarcosinaemia
		Short-chain acyl-coenzyme A dehydrogenase deficiency
		Steatohepatitis
		Sucrase-isomaltase deficiency
		Tangier disease
		Tay-Sachs disease
		Tetrahydrobiopterin deficiency
		Trifunctional protein deficiency
		Trimethylaminuria

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Adverse event class	System organ class	Preferred term
Rare	Metabolism and nutrition disorders	Type I hyperlipidaemia
		Type II hyperlipidaemia
		Type III hyperlipidaemia
		Type IIa hyperlipidaemia
		Type IIb hyperlipidaemia
		Type IV hyperlipidaemia
		Type V hyperlipidaemia
		Tyrosinaemia
		Very long-chain acyl-coenzyme A dehydrogenase deficiency
		Williams syndrome
		Wolfram syndrome
	Musculoskeletal and connective tissue disorders	18q minus syndrome
		3-hydroxyacetyl-coenzyme A dehydrogenase deficiency
		Aase syndrome
		Accessory carpal bone
		Accessory muscle
		Accessory navicular syndrome
		Adactyly
		Adult polyglucosan body disease
		Albright's disease
		Allan-Herndon-Dudley syndrome
		Amniotic band syndrome
		Apert's syndrome
		Arachnodactyly
		Arcuate foramen
		Asphyxiating thoracic dystrophy
		Becker's muscular dystrophy
		Benign congenital hypotonia
		Blau syndrome
		Bloom syndrome
		Brachycephaly
		Brachydactyly
		Branchial cleft sinus
		Branchial cyst
		Branchiogenic syndrome
		Bulbospinal muscular atrophy congenital
		Camptodactyly congenital
		Camptomelia
		Carpus curvus
		Cartilage-hair hypoplasia
		Caudal regression syndrome
		Central core disease
		Cervical auricle
		Cervical rib
		Chondrodystrophy
		Chondroectodermal dysplasia
		Chronic infantile neurological cutaneous and articular syndrome

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Adverse event class	System organ class	Preferred term
Rare	Musculoskeletal and connective tissue disorders	Cleft foot
		Cleft lip
		Cleidocranial dysostosis
		Clinodactyly
		Cohen syndrome
		Congenital absence of cranial vault
		Congenital absence of vertebra
		Congenital bowing of long bones
		Congenital clavicular agenesis
		Congenital claw toe
		Congenital cleft hand
		Congenital cutis laxa
		Congenital deformity of clavicle
		Congenital elevation of scapula
		Congenital fibrosarcoma
		Congenital flat feet
		Congenital floppy infant
		Congenital foot malformation
		Congenital hand malformation
		Congenital hyperextension of knee
		Congenital hyperextension of spine
		Congenital jaw malformation
		Congenital joint malformation
		Congenital knee deformity
		Congenital knee dislocation
		Congenital kyphoscoliosis
		Congenital limb hyperextension
		Congenital lip fistula
		Congenital multiplex arthrogryposis
		Congenital muscle absence
		Congenital musculoskeletal anomaly
		Congenital myopathy
		Congenital osteodystrophy
		Congenital pseudarthrosis
		Congenital scoliosis
		Congenital spinal fusion
		Congenital spinal stenosis
		Congenital spondylolisthesis
		Congenital spondylolysis
		Congenital syphilitic osteochondritis
		Congenital torticollis
		Cornelia de Lange syndrome
		Costello syndrome
		Craniofacial deformity
		Craniofacial dysostosis
		Craniolacunia
		Craniorachischisis
		Craniosynostosis
		Craniotabes
		Cryopyrin associated periodic syndrome
		Cyclopia

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Adverse event class	System organ class	Preferred term
Rare	Musculoskeletal and connective tissue disorders	Cystic angiomatosis
		Deficiency of the interleukin-1 receptor antagonist
		Dentofacial anomaly
		Dermatofibrosis lenticularis disseminata
		Developmental hip dysplasia
		Dubowitz syndrome
		Duchenne muscular dystrophy
		Dyschondrosteosis
		Dysgnathia
		Dysmorphism
		Ehlers-Danlos syndrome
		Ellis-van Creveld syndrome
		Epidermal naevus syndrome
		Faciodigitogenital dysplasia
		Facioscapulohumeral muscular dystrophy
		Familial cold autoinflammatory syndrome
		Familial scaphocephaly syndrome
		Familial tremor
		Femoral anteversion
		Femoral retroversion
		Femur-fibula-ulna complex
		Fibrodysplasia ossificans progressiva
		Fibrous dysplasia of bone
		Fibrous dysplasia of jaw
		Fibula agenesis
		Foramen magnum stenosis
		Freeman-Sheldon syndrome
		GNE myopathy
		Glycogen storage disease type II
		Glycogen storage disease type III
		Glycogen storage disease type V
		Glycogen storage disease type VII
		Gnathoschisis
		Gorham's disease
		Greig's syndrome
		Hand-foot-genital syndrome
		Hemivertebra
		Hereditary hypophosphataemic rickets
		Hereditary motor neurone disease
		Hereditary multiple osteochondromas
		Hyper IgD syndrome
		Hypertelorism of orbit
		Hypocalvaria
		Hypochondroplasia
		Hypoplastic nasal cartilage
		Hypotelorism of orbit
		Infantile cortical hyperostosis
		Iniencephaly
		Juvenile Paget's disease
		Kabuki make-up syndrome

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Adverse event class	System organ class	Preferred term
Rare	Musculoskeletal and connective tissue disorders	Kearns-Sayre syndrome
		Kenny-Caffey syndrome
		Kimmerle's anomaly
		Kinematic imbalances due to suboccipital strain
		Kleefstra syndrome
		Klippel-Feil syndrome
		Klippel-Trenaunay syndrome
		Kyphosis congenital
		Laron syndrome
		Larsen syndrome
		Limb hypoplasia congenital
		Limb malformation
		Limb reduction defect
		Long-chain acyl-coenzyme A dehydrogenase deficiency
		Lowry-Wood syndrome
		Lumbarisation
		Lupoid hepatic cirrhosis
		Lupus hepatitis
		Lupus nephritis
		Lupus pancreatitis
		MELAS syndrome
		MLASA syndrome
		Macrocephaly
		Macrocheilia
		Macrodactyly
		Macrogenia
		Macrognathia
		Macrostomia
		Majeed's syndrome
		Mandibulofacial dysostosis
		Marfan's syndrome
		Maxillonasal dysplasia
		Medium-chain acyl-coenzyme A dehydrogenase deficiency
		Meier-Gorlin syndrome
		Metabolic myopathy
		Metaphyseal dysplasia
		Metatarsus primus varus
		Microcephaly
		Microcheilia
		Microgenia
		Micrognathia
		Microstomia
		Mitochondrial encephalomyopathy
		Mitochondrial myopathy
		Monopodia
		Morton's syndrome
		Muckle-Wells syndrome
		Multiple epiphyseal dysplasia

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Adverse event class	System organ class	Preferred term
Rare	Musculoskeletal and connective tissue disorders	Muscular dystrophy
		Myoclonic epilepsy and ragged-red fibres
		Myotonia congenita
		Myotonic dystrophy
		Nail-patella syndrome
		Neonatal lupus erythematosus
		Neuroleptic malignant syndrome
		Nijmegen breakage syndrome
		Noonan syndrome
		Oculoauriculovertebral dysplasia
		Oculodentodigital dysplasia
		Opitz-G/BBB syndrome
		Oral-facial-digital syndrome type II
		Os trigonum
		Osteogenesis imperfecta
		Osteopathia striata
		Osteopetrosis
		Osteopoikilosis
		Osteoporosis-pseudoglioma syndrome
		Otocephaly
		PHACES syndrome
		Pachydermoperiostosis
		Parkes-Weber syndrome
		Pectus carinatum
		Pectus excavatum
		Phalangeal agenesis
		Phalangeal hypoplasia
		Pierre Robin syndrome
		Plagiocephaly
		Platybasia
		Platyspondylia
		Poland's syndrome
		Polydactyly
		Potter's syndrome
		Preauricular cyst
		Proteus syndrome
		Proximal focal femoral deficiency
		Pseudoxanthoma elasticum
		Pterygium colli
		Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome
		Radioulnar synostosis
		Reynold's syndrome
		Rib hypoplasia
		Rib synostosis
		Rippling muscle disease
		Rubinstein-Taybi syndrome
		Sacral hypoplasia
		Sacralisation
		Scaphocephaly
		Schimke immunoosseous dysplasia

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Adverse event class	System organ class	Preferred term
Rare	Musculoskeletal and connective tissue disorders	Schinzel-Giedion syndrome
		Serotonin syndrome
		Short-chain acyl-coenzyme A dehydrogenase deficiency
		Silver-Russell syndrome
		Sirenomelia
		Skeletal dysplasia
		Skull malformation
		Smith-Lemli-Opitz syndrome
		Sotos' syndrome
		Spinal muscular atrophy
		Spine malformation
		Spondyloepiphyseal dysplasia
		Stickler's syndrome
		Supernumerary vertebra
		Syndactyly
		Synostosis
		Talipes
		Thalidomide embryopathy
		Thanatophoric dwarfism
		Thrombocytopenia-absent radius syndrome
		Tibial torsion
		Transitional vertebrae
		Trichorhinophalangeal syndrome
		VACTERL syndrome
		Velo-cardio-facial syndrome
		Vertical talus
		Very long-chain acyl-coenzyme A dehydrogenase deficiency
		Weill-Marchesani syndrome
		Welander distal myopathy
		Werner's syndrome
		Wildervanck syndrome
		Winchester syndrome
		Wolf-Hirschhorn syndrome
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenomatous polyposis coli
		Basal cell naevus syndrome
		Biliary hamartoma
		Birt-Hogg-Dube syndrome
		Branchial cyst
		Carcinogenic effect in offspring
		Cardiac lymphangioma
		Carney complex
		Central nervous system dermoid tumour
		Choledochal cyst
		Congenital acrochordon
		Congenital benign neoplasm
		Congenital cerebral cyst

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Adverse event class	System organ class	Preferred term
Rare	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Congenital cerebral haemangioma
		Congenital choroid plexus cyst
		Congenital cyst
		Congenital cystic disease of liver
		Congenital cystic kidney disease
		Congenital eye naevus
		Congenital fibrosarcoma
		Congenital malignant neoplasm
		Congenital melanocytic naevus
		Congenital naevus
		Congenital neoplasm
		Congenital renal cyst
		Congenital retinoblastoma
		Congenital teratoma
		Congenital vaginal cyst
		Cowden's disease
		Cystic angiomatosis
		Cystic eyeball, congenital
		Cystic lymphangioma
		Denys-Drash syndrome
		Dermoid cyst
		Dysplastic naevus syndrome
		Epidermal naevus syndrome
		Familial haemophagocytic lymphohistiocytosis
		Familial medullary thyroid cancer
		Foetal cystic hygroma
		Gorham's disease
		Haemangioma congenital
		Haemangioma of retina
		Hamartoma
		Hamartoma vascular
		Hereditary leiomyomatosis renal cell carcinoma
		Hereditary multiple osteochondromas
		Hereditary non-polyposis colorectal cancer syndrome
		Hereditary papillary renal carcinoma
		Hypothalamic hamartoma
		Infantile septic granulomatosis
		Inferior vena cava syndrome
		Lipodermoid tumour
		Mesoblastic nephroma
		Mesonephric duct cyst
		Mismatch repair cancer syndrome
		Muir-Torre syndrome
		Multiple cutaneous and uterine leiomyomatosis
		Multiple endocrine neoplasia
		Multiple endocrine neoplasia Type 1

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Adverse event class	System organ class	Preferred term
Rare	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Multiple endocrine neoplasia Type 2
		Multiple endocrine neoplasia Type 2A
		Multiple endocrine neoplasia Type 2B
		Myelodysplastic syndrome
		Myelodysplastic syndrome transformation
		Myelofibrosis
		Myeloid metaplasia
		Neonatal leukaemia
		Neurofibromatosis
		Odontogenic cyst
		Oesophageal cyst
		Omenn syndrome
		Ota's naevus
		PHACES syndrome
		Paraneoplastic glomerulonephritis
		Paraneoplastic nephrotic syndrome
		Peutz-Jeghers syndrome
		Phakomatosis
		Primary myelofibrosis
		Splenic hamartoma
		Steatocystoma multiplex
		Thyroglossal cyst
		Tornwaldt cyst
		Trisomy 12
		Venous angioma of brain
		X-linked lymphoproliferative syndrome
	Nervous system disorders	18q minus syndrome
		2-Hydroxyglutaric aciduria
		Acute motor axonal neuropathy
		Acute motor-sensory axonal neuropathy
		Adams-Stokes syndrome
		Adrenoleukodystrophy
		Adult polyglucosan body disease
		Aicardi's syndrome
		Allan-Herndon-Dudley syndrome
		Alpers' disease
		Alternating hemiplegia of childhood
		Anencephaly
		Angelman's syndrome
		Arnold-Chiari malformation
		Asterixis
		Ataxia telangiectasia
		Auditory neuropathy spectrum disorder
		Baltic myoclonic epilepsy
		Basal cell naevus syndrome
		Becker's muscular dystrophy
		Benign congenital hypotonia
		Benign familial neonatal convulsions
		Bezold-Jarisch reflex
		Bickerstaff's encephalitis

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Adverse event class	System organ class	Preferred term
Rare	Nervous system disorders	Biotinidase deficiency
		Bloch-Sulzberger syndrome
		Brain malformation
		Bulbospinal muscular atrophy congenital
		CHARGE syndrome
		Canavan disease
		Caudal regression syndrome
		Central bradycardia
		Central nervous system dermoid tumour
		Cerebellar dysplasia
		Cerebellar hypoplasia
		Cerebral arteriovenous malformation haemorrhagic
		Cerebral atrophy congenital
		Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
		Cerebral dysgenesis
		Cerebral palsy
		Cerebrohepatorenal syndrome
		Cerebrovascular arteriovenous malformation
		Chronic infantile neurological cutaneous and articular syndrome
		Chronic inflammatory demyelinating polyradiculoneuropathy
		Citrate transporter deficiency
		Cobb syndrome
		Cockayne's syndrome
		Cohen syndrome
		Coma hepatic
		Congenital aqueductal stenosis
		Congenital brain damage
		Congenital central hypoventilation syndrome
		Congenital central nervous system anomaly
		Congenital cerebellar agenesis
		Congenital cerebral cyst
		Congenital cerebral haemangioma
		Congenital cerebrovascular anomaly
		Congenital choroid plexus cyst
		Congenital cranial nerve paralysis
		Congenital facial nerve hypoplasia
		Congenital flaccid paralysis
		Congenital floppy infant
		Congenital hemiparesis
		Congenital hydrocephalus
		Congenital neurological degeneration
		Congenital neurological disorder
		Congenital neuropathy
		Congenital nystagmus
		Congenital oculomotor apraxia

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Adverse event class	System organ class	Preferred term
Rare	Nervous system disorders	Congenital optic nerve anomaly
		Congenital spinal cord anomaly
		Congenital spinal stenosis
		Congenital syphilitic encephalitis
		Congenital syphilitic meningitis
		Congenital torticollis
		Congenital visual acuity reduced
		Cornelia de Lange syndrome
		Cortical dysplasia
		Craniolacunia
		Craniorachischisis
		Cri du Chat syndrome
		Dandy-Walker syndrome
		Deaf mutism
		Demyelinating polyneuropathy
		Dentatorubral-pallidoluysian atrophy
		Diastematomyelia
		Diencephalic syndrome of infancy
		Double cortex syndrome
		Duane's syndrome
		Dubowitz syndrome
		Duchenne muscular dystrophy
		Dysmyelination
		Early onset familial Alzheimer's disease
		Early onset primary dystonia
		Emanuel syndrome
		Encephalocele
		Epidermal naevus syndrome
		Epilepsy congenital
		Eyelid ptosis congenital
		Fabry's disease
		Facioscapulohumeral muscular dystrophy
		Familial amyloidosis
		Familial amyotrophic lateral sclerosis
		Familial hemiplegic migraine
		Familial infantile bilateral striatal necrosis
		Familial periodic paralysis
		Familial scaphocephaly syndrome
		Familial tremor
		Fatal familial insomnia
		Foetal alcohol syndrome
		Fragile X syndrome
		Friedreich's ataxia
		Galactosaemia
		Gaucher's disease
		Gaucher's disease type II
		Gaucher's disease type III
		Glucose transporter type 1 deficiency syndrome
		Glycogen storage disease type II
		Glycogen storage disease type III
		Glycogen storage disease type V

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Adverse event class	System organ class	Preferred term
Rare	Nervous system disorders	Glycogen storage disease type VII
		Greig's syndrome
		Guillain-Barre syndrome
		Hemimegalencephaly
		Hepatic encephalopathy
		Hepato-lenticular degeneration
		Hereditary areflexic dystasia
		Hereditary cerebral degeneration
		Hereditary motor and sensory neuropathy
		Hereditary motor neurone disease
		Hereditary neuropathic amyloidosis
		Hereditary neuropathy with liability to pressure palsies
		Hereditary spastic paraplegia
		Holoprosencephaly
		Huntington's disease
		Hydranencephaly
		Hyperexplexia
		Hypothalamic hamartoma
		Iniencephaly
		Intracranial arterial fenestration
		Intracranial lipoma
		Johanson-Blizzard syndrome
		Joubert syndrome
		Kabuki make-up syndrome
		Kearns-Sayre syndrome
		Kleefstra syndrome
		Krabbe's disease
		Lafora's myoclonic epilepsy
		Langer-Giedion syndrome
		Laurence-Moon-Bardet-Biedl syndrome
		Leukodystrophy
		Lipomeningocele
		Lissencephaly
		Loss of consciousness
		Lowry-Wood syndrome
		MELAS syndrome
		Marcus Gunn syndrome
		Melkersson-Rosenthal syndrome
		Membranous lipodystrophy
		Meningocele
		Meningomyelocele
		Menkes' syndrome
		Metabolic myopathy
		Metachromatic leukodystrophy
		Methylenetetrahydrofolate reductase deficiency
		Mevalonic aciduria
		Microencephaly
		Miller Fisher syndrome
		Minimal hepatic encephalopathy
		Mitochondrial encephalomyopathy

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Adverse event class	System organ class	Preferred term
Rare	Nervous system disorders	Mitochondrial neurogastrointestinal encephalopathy
		Moebius II syndrome
		Molybdenum cofactor deficiency
		Morning glory syndrome
		Mount-Reback syndrome
		Muscular dystrophy
		Myoclonic epilepsy and ragged-red fibres
		Myotonia congenita
		Myotonic dystrophy
		Neural tube defect
		Neurofibromatosis
		Neuroleptic malignant syndrome
		Neuronal ceroid lipofuscinosis
		Neuronal migration disorder
		Neuropathy, ataxia, retinitis pigmentosa syndrome
		Niemann-Pick disease
		Nonketotic hyperglycinaemia
		Norrie's disease
		Oculocerebrorenal syndrome
		Olfacto genital dysplasia
		Olfactory nerve agenesis
		Optic nerve hypoplasia
		Oral-facial-digital syndrome type II
		Osteoporosis-pseudoglioma syndrome
		PHACES syndrome
		Pachygyria
		Pelizaeus-Merzbacher disease
		Periventricular nodular heterotopia
		Perry syndrome
		Phakomatosis
		Phenylketonuria
		Polymicrogyria
		Porencephaly
		Porphyria acute
		Prader-Willi syndrome
		Primary cerebellar degeneration
		Primary familial brain calcification
		Progressive cerebellar degeneration
		Progressive external ophthalmoplegia
		Rathke's cleft cyst
		Refsum's disease
		Rett syndrome
		Reye's syndrome
		Riley-Day syndrome
		Rippling muscle disease
		Rubinstein-Taybi syndrome
		Schinzel-Giedion syndrome
		Schizencephaly
		Sensory neuropathy hereditary
		Septo-optic dysplasia
		Septum pellucidum agenesis

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Adverse event class	System organ class	Preferred term
Rare	Nervous system disorders	Serotonin syndrome
		Severe myoclonic epilepsy of infancy
		Sjogren-Larsson syndrome
		Smith-Lemli-Opitz syndrome
		Spina bifida
		Spina bifida cystica
		Spina bifida occulta
		Spinal muscular atrophy
		Spinal vessel congenital anomaly
		Spinocerebellar ataxia
		Strabismus congenital
		Sturge-Weber syndrome
		Subependymal nodular heterotopia
		Syncope
		Syringomyelia
		Tay-Sachs disease
		Tetrahydrobiopterin deficiency
		Timothy syndrome
		Tourette's disorder
		Trisomy 13
		Trisomy 14
		Trisomy 17
		Trisomy 18
		Trisomy 21
		Trisomy 22
		Tuberous sclerosis
		Vein of Galen aneurysmal malformation
		Velo-cardio-facial syndrome
		Venous angioma of brain
		Vertebral artery hypoplasia
		Von Hippel-Lindau disease
		Welander distal myopathy
		Williams syndrome
		Wolf-Hirschhorn syndrome
		Wyburn Mason's syndrome
	Pregnancy, puerperium and perinatal conditions	ABO haemolytic disease of newborn
		Acardia
		Adrenal insufficiency neonatal
		Alveolar capillary dysplasia
		Amniotic band syndrome
		Angiotensin converting enzyme inhibitor foetopathy
		Arrhythmia neonatal
		Atrioventricular node dispersion
		Baseline foetal heart rate variability disorder
		Benign familial neonatal convulsions
		Blood incompatibility haemolytic anaemia of newborn
		Bradycardia foetal
		Bradycardia neonatal
		Cardiac arrest neonatal

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Adverse event class	System organ class	Preferred term
Rare	Pregnancy, puerperium and perinatal conditions	Cardio-respiratory arrest neonatal
		Cerebral palsy
		Collodion baby
		Congenital HIV infection
		Congenital chylothorax
		Congenital condyloma
		Congenital cytomegalovirus infection
		Congenital floppy infant
		Congenital hepatitis B infection
		Congenital herpes simplex infection
		Congenital infection
		Congenital malaria
		Congenital pneumonia
		Congenital pulmonary hypertension
		Congenital rubella infection
		Congenital syphilis
		Congenital syphilitic encephalitis
		Congenital syphilitic meningitis
		Congenital toxoplasmosis
		Congenital tuberculosis
		Congenital varicella infection
		Conjoined twins
		Conjunctivitis gonococcal neonatal
		Craniotabes
		Diabetic foetopathy
		Diethylstilboestrol syndrome
		Ductus arteriosus premature closure
		Ductus venosus agenesis
		Erythroblastosis foetalis
		Foetal alcohol syndrome
		Foetal anticonvulsant syndrome
		Foetal arrhythmia
		Foetal chromosome abnormality
		Foetal heart rate acceleration abnormality
		Foetal heart rate deceleration abnormality
		Foetal heart rate disorder
		Foetal malformation
		Foetal methotrexate syndrome
		Foetal renal impairment
		Foetal retinoid syndrome
		Foetal tachyarrhythmia
		Foetal warfarin syndrome
		Granulocytopenia neonatal
		Harlequin foetus
		Hypopituitarism foetal
		Inferior vena cava syndrome
		Junctional ectopic tachycardia
		Leukopenia neonatal
		Lymphocytopenia neonatal
		Neonatal alloimmune thrombocytopenia

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Adverse event class	System organ class	Preferred term
Rare	Pregnancy, puerperium and perinatal conditions	Neonatal anuria
		Neonatal haemochromatosis
		Neonatal leukaemia
		Neonatal lupus erythematosus
		Neonatal tachycardia
		Netherton's syndrome
		Neutropenia neonatal
		Nonketotic hyperglycinaemia
		Nonreassuring foetal heart rate pattern
		Persistent foetal circulation
		Primary familial hypomagnesaemia
		Pulmonary lymphangiectasia
		Renal failure neonatal
		Renal impairment neonatal
		Rhesus haemolytic disease of newborn
		Single umbilical artery
		Tachycardia foetal
		Thalidomide embryopathy
		Twin reversed arterial perfusion sequence malformation
		Umbilical artery hypoplasia
		Umbilical malformation
		Virilism foetal
	Psychiatric disorders	2-Hydroxyglutaric aciduria
		Allan-Herndon-Dudley syndrome
		Baltic myoclonic epilepsy
		CHARGE syndrome
		Cohen syndrome
		Congenital brain damage
		Cornelia de Lange syndrome
		Cri du Chat syndrome
		Deaf mutism
		Diencephalic syndrome of infancy
		Dubowitz syndrome
		Early onset familial Alzheimer's disease
		Emanuel syndrome
		Familial scaphocephaly syndrome
		Fragile X syndrome
		Galactosaemia
		Greig's syndrome
		Johanson-Blizzard syndrome
		Kabuki make-up syndrome
		Kleefstra syndrome
		Langer-Giedion syndrome
		Laurence-Moon-Bardet-Biedl syndrome
		Membranous lipodystrophy
		Mevalonic aciduria
		Norrie's disease
		Oculocerebrorenal syndrome
		Osteoporosis-pseudoglioma syndrome
		Perry syndrome
		Phenylketonuria

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Adverse event class	System organ class	Preferred term
Rare	Psychiatric disorders	Porphyria acute
		Prader-Willi syndrome
		Primary familial brain calcification
		Rett syndrome
		Rubinstein-Taybi syndrome
		Schinzel-Giedion syndrome
		Sjogren-Larsson syndrome
		Smith-Lemli-Opitz syndrome
		Tetrahydrobiopterin deficiency
		Timothy syndrome
		Tourette's disorder
		Trisomy 14
		Trisomy 17
		Trisomy 18
		Trisomy 21
		Trisomy 22
		Velo-cardio-facial syndrome
		Williams syndrome
		Wolf-Hirschhorn syndrome
	Renal and urinary disorders	2-Hydroxyglutaric aciduria
		Accessory kidney
		Acute focal bacterial nephritis
		Acute kidney injury
		Acute phosphate nephropathy
		Acute prerenal failure
		Adult polyglucosan body disease
		Alkaptonuria
		Alport's syndrome
		Aminoaciduria
		Anuria
		Aspartylglucosaminuria
		Autoimmune nephritis
		Azotaemia
		Barakat syndrome
		Bartter's syndrome
		Benign familial haematuria
		Berdon's syndrome
		Bladder agenesis
		Branchio-oto-renal syndrome
		C3 glomerulopathy
		CHARGE syndrome
		Chronic autoimmune glomerulonephritis
		Cloacal exstrophy
		Congenital bladder anomaly
		Congenital bladder diverticulum
		Congenital bladder neck obstruction
		Congenital calyceal diverticulum
		Congenital cystic kidney disease
		Congenital ectopic bladder
		Congenital genitourinary abnormality
		Congenital hydrocele renalis
		Congenital hydronephrosis

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Adverse event class	System organ class	Preferred term
Rare	Renal and urinary disorders	Congenital megaureter
		Congenital nephrogenic diabetes insipidus
		Congenital nephrotic syndrome
		Congenital oxalosis
		Congenital pyelocaliectasis
		Congenital renal cyst
		Congenital renal disorder
		Congenital ureteric anomaly
		Congenital ureterocele
		Congenital ureterovesical junction anomaly
		Congenital urethral anomaly
		Congenital urinary tract obstruction
		Congenital vesicoureteric reflux
		Cystinosis
		Cystinuria
		Cytomegalovirus nephritis
		Dent's disease
		Denys-Drash syndrome
		Double ureter
		Eagle Barrett syndrome
		Ectopic kidney
		Ectopic ureter
		Epispadias
		Essential fructosuria
		Extrarenal pelvis
		Familial hypocalciuric hypercalcaemia
		Familial renal glycosuria
		Fanconi syndrome
		Fibrillary glomerulonephritis
		Focal segmental glomerulosclerosis
		Foetal megacystis
		Foetal renal impairment
		Gitelman's syndrome
		Glomerulonephritis
		Glomerulonephritis acute
		Glomerulonephritis chronic
		Glomerulonephritis membranoproliferative
		Glomerulonephritis membranous
		Glomerulonephritis minimal lesion
		Glomerulonephritis proliferative
		Glomerulonephritis rapidly progressive
		Goodpasture's syndrome
		Granulomatosis with polyangiitis
		HIV associated nephropathy
		Hand-foot-genital syndrome
		Henoch-Schonlein purpura nephritis
		Hepatitis virus-associated nephropathy
		Hepatorenal failure
		Hepatorenal syndrome

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Adverse event class	System organ class	Preferred term
Rare	Renal and urinary disorders	Hereditary leiomyomatosis renal cell carcinoma
		Hereditary papillary renal carcinoma
		Hollow visceral myopathy
		Homocystinuria
		Hydronephrosis
		Hydroureter
		Hypermethioniuria
		Hyponatriuria
		Hypospadias
		IgA nephropathy
		IgM nephropathy
		Immunotactoid glomerulonephritis
		Kaufman-McKusick syndrome
		Kidney duplex
		Kidney malformation
		Kidney malrotation
		Liddle's syndrome
		Lupus nephritis
		MYH9-related disease
		Mesangioproliferative glomerulonephritis
		Methylmalonic aciduria
		Microscopic polyangiitis
		Nail-patella syndrome
		Neonatal anuria
		Nephritic syndrome
		Nephritis
		Nephritis allergic
		Nephritis haemorrhagic
		Nephritis radiation
		Nephropathy toxic
		Nephrotic syndrome
		Obstructive uropathy
		Oculocerebrorenal syndrome
		Oliguria
		Opitz-G/BBB syndrome
		Oroticaciduria congenital
		Pancreatorenal syndrome
		Paraneoplastic glomerulonephritis
		Paraneoplastic nephrotic syndrome
		Pelvi-ureteric obstruction
		Pelvic kidney
		Perinephritis
		Persistent cloaca
		Persistent urogenital sinus
		Phenylketonuria
		Porphyrinuria
		Post infection glomerulonephritis
		Post streptococcal glomerulonephritis
		Potter's syndrome
		Prerenal failure
		Primary familial hypomagnesaemia
		Pulmonary renal syndrome

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Adverse event class	System organ class	Preferred term
Rare	Renal and urinary disorders	Renal aplasia
		Renal arteriovenous malformation
		Renal dysplasia
		Renal failure
		Renal failure neonatal
		Renal fusion anomaly
		Renal hypoplasia
		Renal impairment
		Renal impairment neonatal
		Renal malposition
		Retroperitoneal fibrosis
		Schinzel-Giedion syndrome
		Sirenomelia
		Tubulointerstitial nephritis
		Tubulointerstitial nephritis and uveitis syndrome
		Urachal abnormality
		Ureteric atresia
		Ureteric compression
		Ureteric dilatation
		Ureteric obstruction
		Ureteric stenosis
		Urethral atresia
		Urethral valves
		Urinary tract malformation
	Reproductive system and breast disorders	Accessory breast
		Adrenogenital syndrome
		Albright's disease
		Androgen insensitivity syndrome
		Anorchism
		Breast malformation
		Buried penis syndrome
		Chordee
		Cloacal exstrophy
		Congenital androgen deficiency
		Congenital fallopian tube anomaly
		Congenital genital malformation
		Congenital genital malformation female
		Congenital genital malformation male
		Congenital genitourinary abnormality
		Congenital labia pudendi adhesions
		Congenital monorchidism
		Congenital ovarian anomaly
		Congenital scrotal hypertrophy
		Congenital teratoma
		Congenital uterine anomaly
		Congenital vaginal cyst
		Congenital varicocele
		Congenital vas deferens absence
		Cryptorchism
		Denys-Drash syndrome

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Adverse event class	System organ class	Preferred term
Rare	Reproductive system and breast disorders	Diethylstilboestrol syndrome
		Disorder of sex development
		Ectopic ovary
		Epispadias
		Faciodigitogenital dysplasia
		Frenulum breve
		Fryns syndrome
		Genitalia external ambiguous
		Hermaphroditism
		Hooded prepuce
		Hydrocele
		Hypospadias
		Imperforate hymen
		Mayer-Rokitansky-Kuster-Hauser syndrome
		Mesonephric duct cyst
		Micropenis
		Multiple cutaneous and uterine leiomyomatosis
		Olfacto genital dysplasia
		Ovarian agenesis
		Ovarian hypoplasia
		Penile torsion
		Penoscrotal fusion
		Penoscrotal transposition
		Persistent cloaca
		Persistent urogenital sinus
		Phimosis
		Primary ciliary dyskinesia
		Pseudohermaphroditism
		Pseudohermaphroditism female
		Pseudohermaphroditism male
		Reproductive tract hypoplasia, male
		Septate hymen
		Sertoli-cell-only syndrome
		Testicular dysplasia
		Testotoxicosis
		Uterine aplasia
		Uterine cervix hypoplasia
		Uterine hypoplasia
		Vaginal atresia
		Vaginal hypoplasia
		Vaginal septum
		Virilism foetal
		Young's syndrome
	Respiratory, thoracic and mediastinal disorders	Alveolar capillary dysplasia
		Angioedema
		Azygos lobe
		Bronchogenic cyst
		CHARGE syndrome
		Cardio-respiratory arrest
		Cardio-respiratory arrest neonatal

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Adverse event class	System organ class	Preferred term
Rare	Respiratory, thoracic and mediastinal disorders	Choanal atresia
		Choanal stenosis
		Congenital bronchiectasis
		Congenital bronchomalacia
		Congenital central hypoventilation syndrome
		Congenital chylothorax
		Congenital cystic lung
		Congenital diaphragmatic anomaly
		Congenital diaphragmatic eventration
		Congenital diaphragmatic hernia
		Congenital emphysema
		Congenital epiglottal anomaly
		Congenital hiatus hernia
		Congenital high airway obstruction syndrome
		Congenital laryngeal stridor
		Congenital nose malformation
		Congenital perforated nasal septum
		Congenital pharyngeal anomaly
		Congenital pneumonia
		Congenital pulmonary hypertension
		Congenital tracheomalacia
		Cystic fibrosis
		Cystic fibrosis lung
		Diaphragmatic aplasia
		Diverticulum of pharynx, congenital
		Fryns syndrome
		Goodpasture's syndrome
		Granulomatosis with polyangiitis
		Hepatic hydrothorax
		Hepatopulmonary syndrome
		Laryngeal cleft
		Laryngeal oedema
		Laryngeal web
		Laryngo-onycho-cutaneous syndrome
		Laryngocele
		Laryngomalacia
		Laryngotracheal oedema
		Nasopharyngeal atresia
		Oculopharyngeal dystrophy
		Oculorespiratory syndrome
		Oropharyngeal oedema
		Oropharyngeal swelling
		Paranasal sinus aplasia
		Pectus carinatum
		Pectus excavatum
		Perry syndrome
		Pharyngeal oedema
		Portopulmonary hypertension
		Primary ciliary dyskinesia
		Pulmonary aplasia

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Adverse event class	System organ class	Preferred term
Rare	Respiratory, thoracic and mediastinal disorders	Pulmonary arteriovenous fistula
		Pulmonary artery stenosis congenital
		Pulmonary hypoplasia
		Pulmonary lymphangiectasia
		Pulmonary malformation
		Pulmonary renal syndrome
		Pulmonary sequestration
		Respiratory tract malformation
		Right-to-left cardiac shunt
		Tornwaldt cyst
		Tracheal atresia
		Tracheal web
		Tracheo-oesophageal fistula
		VACTERL syndrome
		Young's syndrome
	Skin and subcutaneous tissue disorders	Abnormal palmar/plantar creases
		Achromotrichia congenital
		Acral peeling skin syndrome
		Acrodermatitis enteropathica
		Acrokeratosis verruciformis
		Acute generalised exanthematous pustulosis
		Adams-Oliver syndrome
		Albinism
		Albright's disease
		Angioedema
		Aplasia cutis congenita
		Ash leaf macule
		Ataxia telangiectasia
		Basal cell naevus syndrome
		Benign familial pemphigus
		Birt-Hogg-Dube syndrome
		Birth mark
		Blau syndrome
		Bloch-Sulzberger syndrome
		Bloom syndrome
		CANDLE syndrome
		Carney complex
		Cholestatic pruritus
		Chronic infantile neurological cutaneous and articular syndrome
		Circumoral oedema
		Cobb syndrome
		Collodion baby
		Congenital acrochordon
		Congenital cutis laxa
		Congenital dermal sinus
		Congenital dyskeratosis
		Congenital ectodermal dysplasia
		Congenital eyelid malformation
		Congenital generalised lipodystrophy

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Adverse event class	System organ class	Preferred term
Rare	Skin and subcutaneous tissue disorders	Congenital hair disorder
		Congenital hypertrichosis
		Congenital melanocytic naevus
		Congenital melanosis
		Congenital naevus
		Congenital nail disorder
		Congenital pigmentation disorder
		Congenital poikiloderma
		Congenital skin dimples
		Congenital skin disorder
		Congenital trichomegaly
		Cullen's sign
		Cutaneous vasculitis
		Cutaneovisceral angiomatosis with thrombocytopenia
		Deficiency of the interleukin-36 receptor antagonist
		Dermatitis bullous
		Dermatitis exfoliative
		Dermatitis exfoliative generalised
		Dermatofibrosis lenticularis disseminata
		Dermatoglyphic anomaly
		Dowling-Degos disease
		Drug reaction with eosinophilia and systemic symptoms
		Dysplastic naevus syndrome
		Ehlers-Danlos syndrome
		Epidermal naevus
		Epidermal naevus syndrome
		Epidermal necrosis
		Epidermolysis
		Epidermolysis bullosa
		Erythema multiforme
		Erythrokeratodermia variabilis
		Exfoliative rash
		Eyelid oedema
		Fabry's disease
		Face oedema
		Familial cold autoinflammatory syndrome
		Gleich's syndrome
		Grey Turner's sign
		Harlequin foetus
		Hartnup disease
		Henoch-Schonlein purpura nephritis
		Hereditary angioedema
		Hereditary haemorrhagic telangiectasia
		Hereditary palmoplantar keratoderma
		Hermansky-Pudlak syndrome
		Hyper IgD syndrome
		Hypomelanosis of Ito
		Ichthyosis
		Idiopathic angioedema

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Adverse event class	System organ class	Preferred term
Rare	Skin and subcutaneous tissue disorders	Intestinal angioedema
		Jaundice
		Keratitis-ichthyosis-deafness syndrome
		Keratolysis exfoliativa congenital
		Keratosis follicular
		Laryngeal oedema
		Laryngo-onycho-cutaneous syndrome
		Laryngotracheal oedema
		Lichen spinulosus
		Lip oedema
		Lip swelling
		Melkersson-Rosenthal syndrome
		Menkes' syndrome
		Mouth swelling
		Muir-Torre syndrome
		Multiple cutaneous and uterine leiomyomatosis
		Multiple lentigines syndrome
		Naevus anaemicus
		Naevus flammeus
		Naevus spider congenital
		Nail-patella syndrome
		Neonatal lupus erythematosus
		Netherton's syndrome
		Oculomucocutaneous syndrome
		Oculorespiratory syndrome
		Oedema mouth
		Olmsted syndrome
		Oropharyngeal oedema
		Oropharyngeal swelling
		Ota's naevus
		Periorbital oedema
		Peutz-Jeghers syndrome
		Phakomatosis
		Pharyngeal oedema
		Pilonidal cyst congenital
		Platonychia
		Porokeratosis
		Porphyria non-acute
		Postauricular fistula
		Progeria
		Proteus syndrome
		Pseudoxanthoma elasticum
		Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome
		Reynold's syndrome
		Sclerotylosis
		Sebaceous naevus
		Sjogren-Larsson syndrome
		Skin hypoplasia
		Skin malformation
		Skin necrosis

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Adverse event class	System organ class	Preferred term
Rare	Skin and subcutaneous tissue disorders	Steatocystoma multiplex
		Stevens-Johnson syndrome
		Sturge-Weber syndrome
		Supernumerary nipple
		Swelling face
		Swollen tongue
		Telangiectasia congenital
		Tongue oedema
		Toxic epidermal necrolysis
		Toxic skin eruption
		Tuberous sclerosis
		Tumour necrosis factor receptor-associated periodic syndrome
		Umbilical malformation
		Waardenburg syndrome
		Wiskott-Aldrich syndrome
		Xeroderma pigmentosum
		Yellow skin
	Surgical and medical procedures	Continuous haemodiafiltration
		Dialysis
		Gastric variceal injection
		Gastric variceal ligation
		Haemodialysis
		Haemofiltration
		Hepatectomy
		Hepatic encephalopathy prophylaxis
		Liver and small intestine transplant
		Liver dialysis
		Liver operation
		Liver transplant
		Pancreatic pseudocyst drainage
		Peritoneal dialysis
		Renal and liver transplant
	Vascular disorders	Acute prerenal failure
		Alveolar capillary dysplasia
		Anaphylactic reaction
		Anaphylactic shock
		Anaphylactoid reaction
		Anaphylactoid shock
		Anomalous pulmonary venous connection
		Aorta hypoplasia
		Aorticopulmonary septal defect
		Arteriovenous malformation
		Benign familial haematuria
		Bezold-Jarisch reflex
		Bone marrow necrosis
		Cerebral arteriovenous malformation haemorrhagic
		Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

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Adverse event class	System organ class	Preferred term
Rare	Vascular disorders	Cerebrovascular arteriovenous malformation
		Circulatory collapse
		Coarctation of the aorta
		Cobb syndrome
		Congenital aortic anomaly
		Congenital aortic atresia
		Congenital aortic dilatation
		Congenital aortic stenosis
		Congenital arterial malformation
		Congenital arteriovenous fistula
		Congenital cardiovascular anomaly
		Congenital cerebral haemangioma
		Congenital cerebrovascular anomaly
		Congenital coronary artery malformation
		Congenital gastrointestinal vessel anomaly
		Congenital great vessel anomaly
		Congenital lymphoedema
		Congenital pulmonary artery anomaly
		Congenital varicocele
		Corrected transposition of great vessels
		Cullen's sign
		Cutaneous vasculitis
		Diencephalic syndrome of infancy
		Disseminated intravascular coagulation
		Ductus arteriosus premature closure
		Ductus arteriosus stenosis foetal
		Ductus venosus agenesis
		Duodenal varices
		Encephalocutaneous angiomatosis
		Familial hemiplegic migraine
		Gallbladder varices
		Gastric varices
		Gastric varices haemorrhage
		Gastrointestinal arteriovenous malformation
		Gorham's disease
		Granulomatosis with polyangiitis
		Grey Turner's sign
		Haemangioma congenital
		Haemangioma of retina
		Haemorrhagic arteriovenous malformation
		Haemorrhagic necrotic pancreatitis
		Hamartoma vascular
		Henoch-Schonlein purpura nephritis
		Hepatic arteriovenous malformation
		Hepatic fibrosis
		Hepatic steato-fibrosis
		Hereditary haemorrhagic telangiectasia
		Inferior vena cava syndrome
		Interruption of aortic arch
		Intestinal varices

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Adverse event class	System organ class	Preferred term
Rare	Vascular disorders	Intestinal varices haemorrhage
		Intracranial arterial fenestration
		Ischaemic hepatitis
		Ischaemic pancreatitis
		Klippel-Trenaunay syndrome
		Kounis syndrome
		Left ventricle outflow tract obstruction
		Liddle's syndrome
		Malformation venous
		Marfan's syndrome
		Microscopic polyangiitis
		Naevus anaemicus
		Naevus flammeus
		Naevus spider congenital
		Nephritis haemorrhagic
		Non-cirrhotic portal hypertension
		Oesophageal varices haemorrhage
		PHACES syndrome
		Pancreatic haemorrhage
		Parkes-Weber syndrome
		Patent ductus arteriosus
		Peripancreatic varices
		Persistent foetal circulation
		Persistent left superior vena cava
		Portal fibrosis
		Portal hypertension
		Portal hypertensive colopathy
		Portal hypertensive enteropathy
		Portal hypertensive gastropathy
		Portal vein cavernous transformation
		Portal vein dilatation
		Portal venous system anomaly
		Portopulmonary hypertension
		Preduodenal portal vein
		Prerenal failure
		Proximal focal femoral deficiency
		Pseudotruncus arteriosus
		Pseudoxanthoma elasticum
		Pulmonary arteriovenous fistula
		Pulmonary artery stenosis congenital
		Pulmonary lymphangiectasia
		Renal arteriovenous malformation
		Renal vessel congenital anomaly
		Retinal arteriovenous malformation
		Retinopathy congenital
		Retrograde portal vein flow
		Right aortic arch
		Right ventricle outflow tract obstruction
		Right-to-left cardiac shunt
		Scimitar syndrome
		Shock
		Shock symptom

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Adverse event class	System organ class	Preferred term
Rare	Vascular disorders	Single umbilical artery
		Spinal vessel congenital anomaly
		Splenic hamartoma
		Splenic varices
		Splenic varices haemorrhage
		Sturge-Weber syndrome
		Syncope
		Telangiectasia congenital
		Transposition of the great vessels
		Truncus arteriosus persistent
		Umbilical artery hypoplasia
		VACTERL syndrome
		Varices oesophageal
		Varicose veins of abdominal wall
		Vascular malformation
		Vein of Galen aneurysmal malformation
		Venous angioma of brain
		Vertebral artery hypoplasia
		Von Hippel-Lindau disease
		White nipple sign
		Wyburn Mason's syndrome
Refraction disorders	Eye disorders	Accommodation disorder
		Acute myopia
		Altered visual depth perception
		Aniseikonia
		Anisometropia
		Antimetropia
		Astigmatism
		Hypermetropia
		Myopia
		Pathologic myopia
		Presbyopia
		Pseudomyopia
		Refraction disorder
Suspected transmission of infectious agent	Infections and infestations	Air-borne transmission
		Bacterial disease carrier
		Community acquired infection
		Diphtheria carrier
		Direct infection transmission
		Faecal-oral transmission of infection
		HIV carrier
		HTLV-1 carrier
		Human immunodeficiency virus transmission
		Iatrogenic infection
		Indirect infection transmission
		Infection transmission via personal contact
		Infection via vaccinee

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Adverse event class	System organ class	Preferred term
Suspected transmission of infectious agent	Infections and infestations	Infectious disease carrier
		Mycobacterial disease carrier
		Nosocomial infection
		Primary transmission
		Secondary transmission
		Sexual transmission of infection
		Sexually transmitted disease carrier
		Suspected transmission of an infectious agent via product
		Transmission of an infectious agent via product
		Typhoid carrier
		Vaccine virus shedding
		Vector-borne transmission of infection
		Vertical infection transmission
		Viral hepatitis carrier

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フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.4.7. 付録
2. 有害事象
2. 海外併合データにおける
特に注目すべき安全性領域

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2.7.4.7.2.2.16. 治験薬投与下で発現した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 - Cochran-Mantel-Haenszel 法を用いた調整 – 海外併合データ - 安全性解析対象集団....47

2.7.4.7.2.2.17. 治験薬投与下で発現した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（器官別大分類別及び基本語別） - Cochran-Mantel-Haenszel 法を用いた調整 – 海外併合データ - 安全性解析対象集団 48

2.7.4.7.2.2.18. 治験薬投与下で発現した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 – 海外併合データ - 安全性解析対象集団 48

2.7.4.7.2.2.1. 治験薬投与下で発現した糖尿病網膜症に関連する有害事象の要約 - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart				Comparator				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	1244				853				2097			
Total exposure (yrs)	741.2				566.3				1307.5			
Total Events	39	(2.9)	41	5.5	22	(2.7)	24	4.3	61	(2.9)	65	5.0
Serious												
Yes	0				1	(0.1)	1	0.2	1	(0.0)	1	0.1
No	39	(2.9)	41	5.5	21	(2.6)	23	4.1	60	(2.9)	64	4.9
Missing	0				0				0			
Severity												
Severe	2	(0.1)	2	0.3	0				2	(0.1)	2	0.2
Moderate	10	(0.8)	11	1.6	8	(1.0)	9	1.6	18	(0.9)	20	1.5
Mild	28	(2.1)	28	3.7	15	(1.8)	15	2.7	43	(2.1)	43	3.3
Missing	0				0				0			
Related to investigational products												
Probable	0				0				0			
Possible	0				1	(0.1)	1	0.2	1	(0.0)	1	0.1
Unlikely	36	(2.7)	38	5.1	18	(2.3)	20	3.6	54	(2.6)	58	4.4

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure,
yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

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	Faster aspart				Comparator				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Missing	3	(0.2)	3	0.4	3	(0.3)	3	0.5	6	(0.3)	6	0.5
Outcome												
Recovered/resolved	8	(0.6)	9	1.2	5	(0.6)	6	1.1	13	(0.6)	15	1.1
Recovering/resolving	1	(0.1)	1	0.2	2	(0.2)	2	0.3	3	(0.1)	3	0.2
Recovered/resolved with sequelae	1	(0.1)	1	0.1	0				1	(0.0)	1	0.1
Not recovered/not resolved	30	(2.3)	30	4.0	15	(1.9)	16	2.8	45	(2.1)	46	3.5
Fatal	0				0				0			
Unknown	0				0				0			
Missing	0				0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

2.7.4.7.2.2.2. 治験薬投与下で発現した糖尿病網膜症に関連する有害事象の要約（器官別大分類別及び基本語別） - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R	RD	[95% CI]
Number of subjects	1244				853				2097					
Total exposure (yrs)	741.2				566.3				1307.5					
Total events	39	(2.9)	41	5.5	22	(2.7)	24	4.3	61	(2.9)	65	5.0		
Eye disorders	39	(3.1)	41	5.5	22	(2.6)	24	4.2	61	(2.9)	65	5.0		
Diabetic retinopathy	25	(1.8)	25	3.3	9	(1.2)	9	1.7	34	(1.6)	34	2.6	1.60	[-0.08; 3.27]
Retinopathy	6	(0.5)	6	0.9	5	(0.6)	5	0.9	11	(0.5)	11	0.8	-0.02	[-1.05; 1.02]
Vitreous haemorrhage	2	(0.2)	4	0.6	0				2	(0.1)	4	0.3	0.60	[0.01; 1.19]
Macular oedema	1	(0.1)	1	0.1	2	(0.3)	2	0.4	3	(0.1)	3	0.2	-0.25	[-0.83; 0.33]
Diabetic retinal oedema	0				1	(0.1)	2	0.4	1	(0.0)	2	0.2	-0.38	[-0.90; 0.15]
Maculopathy	1	(0.1)	1	0.1	1	(0.1)	1	0.2	2	(0.1)	2	0.2	-0.03	[-0.42; 0.36]
Retinal detachment	2	(0.1)	2	0.3	0				2	(0.1)	2	0.2	0.25	[-0.10; 0.60]
Retinopathy proliferative	1	(0.1)	1	0.2	1	(0.1)	1	0.2	2	(0.1)	2	0.2	-0.03	[-0.51; 0.45]
Retinal exudates	0				1	(0.1)	1	0.2	1	(0.0)	1	0.1	-0.16	[-0.46; 0.15]
Retinal haemorrhage	1	(0.1)	1	0.1	0				1	(0.0)	1	0.1	0.13	[-0.12; 0.37]
Visual acuity reduced	0				1	(0.1)	1	0.2	1	(0.0)	1	0.1	-0.16	[-0.46; 0.15]
Vitreous detachment	0				1	(0.1)	1	0.2	1	(0.0)	1	0.1	-0.16	[-0.46; 0.15]
Vitreous opacities	0				1	(0.1)	1	0.2	1	(0.0)	1	0.1	-0.19	[-0.56; 0.18]

%: Percentage of subjects, CI: Confidence interval, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, RD: Rate difference, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

2.7.4.7.2.2.3. 治験薬投与下で発現した糖尿病網膜症に関連する有害事象の一覧 - 海外併合データ - 安全性解析対象集団

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 103006/ NovoRapid/ 39/M/24.3	2	Eye disorders/ Retinopathy/ Clinically Significant Mild Retinopathy Left And Right Eye	13MAY2014
NN1218-3852/ 221003/ Faster aspart (postmeal)/ 64/M/27.9	2	Eye disorders/ Diabetic retinopathy/ Worsening Diabetic Retinopathy	29MAY2014
NN1218-3852/ 400012/ Faster aspart (mealtime)/ 62/F/23.4	14	Eye disorders/ Diabetic retinopathy/ Diabetic Retinopathy Not Proliferative	10MAR2015
NN1218-3852/ 402016/ Faster aspart (mealtime)/ 38/M/25.3	5	Eye disorders/ Diabetic retinopathy/ Incipient Diabetic Retinopathy Left Eye	11AUG2014
NN1218-3852/ 405004/ NovoRapid/ 37/M/27.9	5	Eye disorders/ Diabetic retinopathy/ Diabetic Maculapathy	13NOV2014
NN1218-3852/ 405006/ NovoRapid/ 36/M/30.1	16	Eye disorders/ Diabetic retinopathy/ Worsening Of Diab. Retinopathia = Proliferative Retinopathy	01FEB2014
NN1218-3852/ 406006/ Faster aspart (postmeal)/ 62/M/26.2	1	Eye disorders/ Diabetic retinopathy/ Diabetic Retinopathy	02JUN2014
NN1218-3852/ 408004/ NovoRapid/ 41/M/29.7	3	Eye disorders/ Vitreous opacities/ Vitreous Body Opacities	21NOV2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0 .
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

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Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 408008/ Faster aspart (mealtime)/ 52/F/29.8	3	Eye disorders/ Diabetic retinopathy/ Retinopathy Diabetica	27JAN2015
NN1218-3852/ 409002/ Faster aspart (postmeal)/ 37/F/26.4	5	Eye disorders/ Diabetic retinopathy/ Non-Proliferative Diabetic Retinopathy	08MAY2014
NN1218-3852/ 413002/ Faster aspart (mealtime)/ 48/F/22.8	14	Eye disorders/ Retinopathy/ Not Proliferative Retinopathy	19NOV2014
NN1218-3852/ 415003/ Faster aspart (postmeal)/ 57/M/22.0	5	Eye disorders/ Diabetic retinopathy/ Non-Proleferartive Diabetic Retinopathy	09JUL2014
NN1218-3852/ 415008/ Faster aspart (postmeal)/ 37/F/23.6	4	Eye disorders/ Diabetic retinopathy/ Diabetic Maculopathy	22JUL2014
NN1218-3852/ 417002/ NovoRapid/ 50/M/25.1	2	Eye disorders/ Diabetic retinopathy/ Non Proliferative Diabetic Retinopathy Left Eye	14APR2014
NN1218-3852/ 417011/ Faster aspart (postmeal)/ 32/F/24.6	2	Eye disorders/ Diabetic retinopathy/ Proliferative Diabetic Retinopathy Right Eye	17JUN2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0 .
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

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Diabetic retinopathy adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 419005/ Faster aspart (mealtime)/ 47/M/31.6	3	Eye disorders/ Diabetic retinopathy/ Non-Proliferative Diabetic Retinopathy	10NOV2014
NN1218-3852/ 421003/ Faster aspart (mealtime)/ 65/F/27.5	9	Eye disorders/ Maculopathy/ Maculopathy	11DEC2013
NN1218-3852/ 425001/ Faster aspart (mealtime)/ 41/M/26.1	7	Eye disorders/ Diabetic retinopathy/ Diabetic Retinopathy Not Proliferativ Rigth Eye	12AUG2014
NN1218-3852/ 505009/ Faster aspart (mealtime)/ 36/F/20.1	2	Eye disorders/ Diabetic retinopathy/ Newly Discovered Diabetic Retinopathy In Left Eye	09DEC2014
NN1218-3852/ 506009/ NovoRapid/ 49/M/30.5	2	Eye disorders/ Diabetic retinopathy/ Incipient Non-Proliferative Diabetic Retinopathy	02JUN2014
NN1218-3852/ 552001/ NovoRapid/ 37/F/22.1	8	Eye disorders/ Retinopathy/ Retinopathia Simplex	04JUN2014
NN1218-3852/ 552004/ Faster aspart (mealtime)/ 35/F/23.6	2	Eye disorders/ Diabetic retinopathy/ Diabetic Retinopathy Simple	10DEC2014
NN1218-3852/ 556015/ NovoRapid/ 45/F/25.6	4	Eye disorders/ Retinopathy/ Worsening Of Retinopathy	14JUL2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

Diabetic retinopathy adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 603008/ NovoRapid/ 68/M/27.7	13	Eye disorders/ Diabetic retinal oedema/ Injection Into Left Eye For Diabetic Macular Oedema	10DEC2014
	14	Eye disorders/ Diabetic retinal oedema/ Injection In The Left Eye For Diabetic Macular Oedema	21JAN2015
NN1218-3852/ 605006/ Faster aspart (mealtime)/ 69/M/25.5	4	Eye disorders/ Macular oedema/ Macular Oedema Va Cf Only	17NOV2014
NN1218-3852/ 605008/ Faster aspart (mealtime)/ 30/F/28.7	43	Eye disorders/ Diabetic retinopathy/ Diabetic Maculopathy	05NOV2014
NN1218-3852/ 606004/ Faster aspart (mealtime)/ 44/F/29.6	12	Eye disorders/ Diabetic retinopathy/ Bilateral Background Diabetic Retinopathy	02OCT2014
NN1218-3852/ 606005/ Faster aspart (postmeal)/ 69/F/26.0	5	Eye disorders/ Diabetic retinopathy/ Deterioration In Bilateral Diabetic Retinopathy	28MAY2014
NN1218-3852/ 609003/ Faster aspart (mealtime)/ 58/F/23.5	4	Eye disorders/ Diabetic retinopathy/ Background Retinopathy	04DEC2013
NN1218-3852/ 703006/ Faster aspart (postmeal)/ 30/M/31.6	1	Eye disorders/ Diabetic retinopathy/ Background Retinopathy - Left Eye	31JAN2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

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Diabetic retinopathy adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 704036/ NovoRapid/ 40/M/25.9	1	Eye disorders/ Macular oedema/ Macular Edema Left Eye	20JUN2014
NN1218-3852/ 716001/ NovoRapid/ 56/F/26.8	3	Eye disorders/ Diabetic retinopathy/ Mild Diabetic Retinopathy (Ou)	13NOV2013
NN1218-3852/ 716004/ Faster aspart (postmeal)/ 31/F/28.4	2	Eye disorders/ Diabetic retinopathy/ Diabetic Retinopathy (Mild; Background; Left Eye)	06JUN2014
NN1218-3852/ 716009/ Faster aspart (postmeal)/ 50/M/25.2	1	Eye disorders/ Diabetic retinopathy/ Mild Non-Proliferative Diabetic Retinopathy (Ou)	30JAN2014
NN1218-3852/ 717015/ Faster aspart (mealtime)/ 39/F/30.9	25	Eye disorders/ Diabetic retinopathy/ Mild Non Proliferative Diabetic Retinopathy Right Eye	01APR2015
NN1218-3852/ 717016/ Faster aspart (postmeal)/ 58/M/24.1	6	Eye disorders/ Retinopathy/ Retinopathy Grade Ii Worsening	06OCT2014
NN1218-3852/ 725005/ Faster aspart (mealtime)/ 46/M/26.5	3	Eye disorders/ Retinal haemorrhage/ Retinal Hemmorage	06MAR2014
NN1218-3852/ 727010/ Faster aspart (postmeal)/ 49/F/24.4	2	Eye disorders/ Retinal detachment/ Detached Retina (Right Eye)	31JUL2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

Diabetic retinopathy adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 743007/ Faster aspart (postmeal)/ 52/M/29.6	3	Eye disorders/ Vitreous haemorrhage/ Left Eye Vitreous Hemorrhage	22MAR2014
NN1218-3852/ 762007/ Faster aspart (mealtime)/ 64/M/29.5	1	Eye disorders/ Diabetic retinopathy/ Laser Treatment On Left Eye For Diabetic Retinopathy.	16MAY2014
NN1218-3852/ 766007/ NovoRapid/ 55/F/30.8	4	Eye disorders/ Retinopathy proliferative/ Proliferative Retinopathy	13JAN2015
	5	Eye disorders/ Macular oedema/ Macular Edema	13JAN2015
NN1218-3852/ 768005/ Faster aspart (mealtime)/ 72/F/21.8	1	Eye disorders/ Retinopathy/ Non Proliferative Retinopathy	09JUN2014
NN1218-3852/ 775003/ Faster aspart (postmeal)/ 35/F/22.8	9	Eye disorders/ Retinal detachment/ Right Eye Retinal Detachment	07MAR2014
NN1218-3852/ 787007/ NovoRapid/ 26/F/21.8	4	Eye disorders/ Diabetic retinopathy/ Bilateral Proliferative Diabetic Retinopathy	16JAN2015
NN1218-3853/ 120003/ Faster aspart (mealtime)/ 56/M/31.3	3	Eye disorders/ Diabetic retinopathy/ Abnormal Eye Exam Moderate Background Retinopathy	08AUG2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

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Diabetic retinopathy adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3853/ 124019/ NovoRapid/ 59/M/38.2	2	Eye disorders/ Diabetic retinopathy/ Non-Proliferative Diabetic Retinopathy Of Right Eye	29OCT2014
NN1218-3853/ 154002/ Faster aspart (mealtime)/ 54/F/32.6	4	Eye disorders/ Retinopathy/ Minimal Retinopathy	17SEP2014
NN1218-3853/ 157007/ NovoRapid/ 70/M/37.1	4	Eye disorders/ Visual acuity reduced/ Decreased Vision Acuity	17JUL2014
NN1218-3853/ 169003/ Faster aspart (mealtime)/ 78/M/29.4	10	Eye disorders/ Retinopathy proliferative/ Proliferative Retinopathy Change Left Eye	19SEP2014
NN1218-3853/ 202004/ NovoRapid/ 66/M/28.4	1	Eye disorders/ Maculopathy/ Worsening Maculopathy Of Left Eye	23MAR2014
NN1218-3853/ 205002/ Faster aspart (mealtime)/ 61/M/34.6	2	Eye disorders/ Vitreous haemorrhage/ Vitreous Haemorrhage Left Eye	26DEC2013
	6	Eye disorders/ Vitreous haemorrhage/ Right Eye Vitreous Haemorrhage	19MAR2014
	7	Eye disorders/ Vitreous haemorrhage/ Right Eye Recurrent Vitreous Haemmorhage	14JUN2014
NN1218-3853/ 208002/ NovoRapid/ 38/M/28.5	2	Eye disorders/ Retinopathy/ Worsening Of Retinopathy	28JUN2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

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Diabetic retinopathy adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3853/ 209004/ NovoRapid/ 72/F/28.3	4	Eye disorders/ Retinal exudates/ Cotton Wool Spots Right Eye	08MAY2014
NN1218-3853/ 403015/ NovoRapid/ 55/F/29.3	2	Eye disorders/ Diabetic retinopathy/ Left Eye Nonproliferative Diabetic Retinopathy	15OCT2014
NN1218-3853/ 602016/ Faster aspart (mealtime)/ 66/M/32.4	1	Eye disorders/ Retinopathy/ Suspected Retinopathy Of Rt Eye	18AUG2014
NN1218-3853/ 603008/ Faster aspart (mealtime)/ 66/M/25.5	2	Eye disorders/ Diabetic retinopathy/ Diabetic Retinopathy	04NOV2014
NN1218-3853/ 706014/ Faster aspart (mealtime)/ 59/F/25.0	2	Eye disorders/ Diabetic retinopathy/ Moderate Non Proliferative Dibetic Retinopathy	24JUN2014
NN1218-3853/ 911002/ NovoRapid/ 61/F/30.2	17	Eye disorders/ Vitreous detachment/ Right Eye Posterior Vitreous Detachment	09MAY2014
NN1218-3931/ 505020/ NovoRapid/ 28/M/24.6	1	Eye disorders/ Diabetic retinopathy/ Non Proliferative Diabetic Retinopathia	10MAR2014
NN1218-4049/ 301016/ Faster aspart (mealtime)/ 62/F/30.1	3	Eye disorders/ Retinopathy/ Worsening Of Retinopathy	09APR2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

nn1218/nn1218-summary/pmda_nda_20180709_er
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Diabetic retinopathy adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-4049/ 503003/ Basal/ 66/M/34.0	5	Eye disorders/ Retinopathy/ Nonprolipherative Retinopathy Of The Right Eye	02JUL2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0 .
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:18 - l_ae_over.sas/l_dia_ae_sas.txt

2.7.4.7.2.2.4. 治験薬投与下で発現した屈折障害に関連する有害事象の要約 - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Number of subjects	1244				853				2097			
Total exposure (yrs)	741.2				566.3				1307.5			
Total Events	2	(0.1)	4	0.5	7	(0.9)	11	2.0	9	(0.4)	15	1.1
Serious												
Yes	0				0				0			
No	2	(0.1)	4	0.5	7	(0.9)	11	2.0	9	(0.4)	15	1.1
Missing	0				0				0			
Severity												
Severe	0				0				0			
Moderate	0				0				0			
Mild	2	(0.1)	4	0.5	7	(0.9)	11	2.0	9	(0.4)	15	1.1
Missing	0				0				0			
Related to investigational products												
Probable	0				0				0			
Possible	0				0				0			
Unlikely	2	(0.1)	4	0.5	5	(0.7)	9	1.7	7	(0.3)	13	1.0

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure,
yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

Refraction disorders adverse events – Cochran-Mantel Haenszel adjusted - treatment emergent – summary – overseas pooled data - safety analysis set

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Missing	0				2	(0.2)	2	0.3	2	(0.1)	2	0.2
Outcome												
Recovered/resolved	0				0				0			
Recovering/resolving	0				0				0			
Recovered/resolved with sequelae	0				0				0			
Not recovered/not resolved	2	(0.1)	4	0.5	7	(0.9)	11	2.0	9	(0.4)	15	1.1
Fatal	0				0				0			
Unknown	0				0				0			
Missing	0				0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

2.7.4.7.2.2.5. 治験薬投与下で発現した屈折障害に関連する有害事象の要約（器官別大分類別及び基本語別） - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart N (%)	E	R	Comparator N (%)	E	R	Total N (%)	E	R	RD [95% CI]
Number of subjects	1244			853			2097			
Total exposure (yrs)	741.2			566.3			1307.5			
Total events	2 (0.1)	4	0.5	7 (0.9)	11	2.0	9 (0.4)	15	1.1	
Eye disorders	2 (0.2)	4	0.5	7 (0.8)	11	1.9	9 (0.4)	15	1.1	
Astigmatism	1 (0.1)	1	0.1	4 (0.5)	4	0.7	5 (0.2)	5	0.4	-0.59 [-1.34; 0.16]
Hypermetropia	1 (0.1)	1	0.1	3 (0.4)	3	0.5	4 (0.2)	4	0.3	-0.40 [-1.05; 0.25]
Myopia	1 (0.1)	1	0.1	2 (0.3)	2	0.4	3 (0.1)	3	0.2	-0.25 [-0.83; 0.33]
Presbyopia	1 (0.1)	1	0.1	2 (0.3)	2	0.4	3 (0.1)	3	0.2	-0.25 [-0.83; 0.33]

%: Percentage of subjects, CI: Confidence interval, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, RD: Rate difference, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

2.7.4.7.2.2.6. 治験薬投与下で発現した屈折障害に関連する有害事象の一覧 - 海外併合データ - 安全性解析対象集団

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 400007/ NovoRapid/ 38/M/28.2	8	Eye disorders/ Hypermetropia/ Hyperopie	06JAN2014
	9	Eye disorders/ Astigmatism/ Astigmatism	06JAN2014
NN1218-3852/ 405006/ NovoRapid/ 36/M/30.1	17	Eye disorders/ Hypermetropia/ Hypermetropia	20MAY2014
NN1218-3852/ 405009/ NovoRapid/ 25/F/21.1	8	Eye disorders/ Myopia/ Myopie Right Eye, Left Eye	06FEB2015
NN1218-3852/ 408002/ Faster aspart (mealtime)/ 47/F/24.7	3	Eye disorders/ Myopia/ Myopie	06MAY2014
	4	Eye disorders/ Astigmatism/ Astigmatismus	06MAY2014
NN1218-3852/ 415001/ Faster aspart (postmeal)/ 62/F/26.5	3	Eye disorders/ Hypermetropia/ Hyperopia	16JUN2014
	4	Eye disorders/ Presbyopia/ Presbyopia	16JUN2014
NN1218-3852/ 415007/ NovoRapid/ 51/F/27.6	1	Eye disorders/ Presbyopia/ Presbyopia	28JAN2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0 .
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

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Refraction disorders adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 415007/ NovoRapid/ 51/F/27.6	2	Eye disorders/ Astigmatism/ Astigmatism	28JAN2014
	3	Eye disorders/ Myopia/ Myopia	27JAN2015
NN1218-3852/ 415009/ NovoRapid/ 46/F/21.0	4	Eye disorders/ Astigmatism/ Astigmatism	19AUG2014
	5	Eye disorders/ Presbyopia/ Prespyopia	19AUG2014
NN1218-4049/ 405007/ Basal/ 64/M/23.7	2	Eye disorders/ Hypermetropia/ Hypermetropy Right Eye	21MAY2014
NN1218-4049/ 405010/ Basal/ 59/M/25.6	1	Eye disorders/ Astigmatism/ Astigmatism Both Eyes	03JUN2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0 .
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:18 - l_ae_over.sas/l_ref_ae_sas.txt

2.7.4.7.2.2.7. 治験薬投与下で発現した末梢性ニューロパチーに関連する有害事象の要約 - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Number of subjects	1244				853				2097			
Total exposure (yrs)	741.2				566.3				1307.5			
Total Events	21	(1.6)	24	3.3	18	(2.2)	19	3.3	39	(1.9)	43	3.3
Serious												
Yes	0				0				0			
No	21	(1.6)	24	3.3	18	(2.2)	19	3.3	39	(1.9)	43	3.3
Missing	0				0				0			
Severity												
Severe	0				0				0			
Moderate	5	(0.4)	6	0.8	5	(0.7)	5	0.9	10	(0.5)	11	0.8
Mild	16	(1.3)	18	2.5	13	(1.5)	14	2.3	29	(1.4)	32	2.4
Missing	0				0				0			
Related to investigational products												
Probable	0				0				0			
Possible	0				1	(0.1)	1	0.2	1	(0.0)	1	0.1
Unlikely	20	(1.6)	23	3.2	16	(2.0)	17	3.0	36	(1.7)	40	3.1

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure,
yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

Peripheral neuropathy adverse events - Cochran-Mantel Haenszel adjusted - treatment emergent - summary - overseas pooled data - safety analysis set

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Missing	1	(0.1)	1	0.1	1	(0.1)	1	0.2	2	(0.1)	2	0.2
Outcome												
Recovered/resolved	8	(0.6)	9	1.2	9	(1.1)	9	1.5	17	(0.8)	18	1.4
Recovering/resolving	5	(0.4)	6	0.9	1	(0.1)	1	0.2	6	(0.3)	7	0.5
Recovered/resolved with sequelae	0				0				0			
Not recovered/not resolved	9	(0.6)	9	1.2	7	(0.9)	8	1.4	16	(0.8)	17	1.3
Fatal	0				0				0			
Unknown	0				0				0			
Missing	0				1	(0.1)	1	0.2	1	(0.0)	1	0.1

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

2.7.4.7.2.2.8. 治験薬投与下で発現した末梢性ニューロパチーに関連する有害事象の要約（器官別大分類別及び基本語別） - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart N (%)	E	R	Comparator N (%)	E	R	Total N (%)	E	R	RD [95% CI]
Number of subjects	1244			853			2097			
Total exposure (yrs)	741.2			566.3			1307.5			
Total events	21 (1.6)	24	3.3	18 (2.2)	19	3.3	39 (1.9)	43	3.3	
Nervous system disorders	20 (1.6)	22	3.0	17 (2.0)	17	3.0	37 (1.8)	39	3.0	
Paraesthesia	6 (0.5)	7	1.1	7 (0.9)	7	1.3	13 (0.6)	14	1.1	-0.20 [-1.42; 1.02]
Neuropathy peripheral	5 (0.4)	5	0.7	3 (0.3)	3	0.5	8 (0.4)	8	0.6	0.16 [-0.65; 0.98]
Hypoaesthesia	4 (0.3)	4	0.5	3 (0.3)	3	0.5	7 (0.3)	7	0.5	0.04 [-0.73; 0.82]
Diabetic neuropathy	3 (0.2)	3	0.4	0			3 (0.1)	3	0.2	0.41 [-0.06; 0.88]
Polyneuropathy	1 (0.1)	1	0.1	1 (0.1)	1	0.2	2 (0.1)	2	0.2	-0.06 [-0.51; 0.38]
Decreased vibratory sense	1 (0.1)	1	0.1	0			1 (0.0)	1	0.1	0.13 [-0.12; 0.37]
Hyporeflexia	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.19 [-0.56; 0.18]
Neuralgia	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.16 [-0.46; 0.15]
Neuronal neuropathy	1 (0.1)	1	0.1	0			1 (0.0)	1	0.1	0.13 [-0.12; 0.37]
Peroneal nerve palsy	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.19 [-0.56; 0.18]
Musculoskeletal and connective tissue disorders	2 (0.2)	2	0.3	2 (0.2)	2	0.4	4 (0.2)	4	0.3	
Muscular weakness	2 (0.1)	2	0.3	2 (0.2)	2	0.3	4 (0.2)	4	0.3	-0.06 [-0.62; 0.50]

%: Percentage of subjects, CI: Confidence interval, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, RD: Rate difference, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

2.7.4.7.2.2.9. 治験薬投与下で発現した末梢性ニューロパチーに関連する有害事象の一覧 - 海外併合データ - 安全性解析対象集団

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 105004/ NovoRapid/ 68/F/26.5	5	Nervous system disorders/ Paraesthesia/ Paresthesia Fingers Both Hands	27MAR2014
NN1218-3852/ 218006/ Faster aspart (mealtime)/ 44/M/26.7	3	Nervous system disorders/ Paraesthesia/ Tingling In Right Hand	09MAR2014
NN1218-3852/ 303009/ Faster aspart (mealtime)/ 53/M/29.1	2	Nervous system disorders/ Diabetic neuropathy/ Vorsening Of Diabetic Polyneuropathy	14AUG2014
NN1218-3852/ 413002/ Faster aspart (mealtime)/ 48/F/22.8	8	Nervous system disorders/ Polyneuropathy/ Worsening Polyneuropathy	13FEB2014
NN1218-3852/ 413008/ Faster aspart (postmeal)/ 50/M/23.1	1	Nervous system disorders/ Diabetic neuropathy/ Diabetic Polyneuropathy	09DEC2013
NN1218-3852/ 421001/ NovoRapid/ 60/F/22.4	9	Nervous system disorders/ Polyneuropathy/ Polyneuropathy	10APR2014
NN1218-3852/ 422006/ Faster aspart (mealtime)/ 69/F/29.6	12	Nervous system disorders/ Neuronal neuropathy/ Neuronal Dysfunktion Of The Feet	11JUN2014
NN1218-3852/ 425005/ NovoRapid/ 47/M/28.9	3	Nervous system disorders/ Paraesthesia/ Paresthesia Left Arm	04JUN2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0 .
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

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Peripheral neuropathy adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 501002/ Faster aspart (postmeal)/ 34/F/26.6	11	Nervous system disorders/ Hypoaesthesia/ Numbness	21FEB2014
NN1218-3852/ 604005/ Faster aspart (postmeal)/ 29/F/22.9	2	Nervous system disorders/ Hypoaesthesia/ Numbness Over Left Big Toe	25NOV2013
NN1218-3852/ 701007/ NovoRapid/ 42/F/32.8	21	Nervous system disorders/ Paraesthesia/ Prickling In Feet	17SEP2014
NN1218-3852/ 701011/ NovoRapid/ 53/M/25.7	6	Nervous system disorders/ Peroneal nerve palsy/ Decreased Circulation To Left Foot Secondary To Repair Of Drop Foot	05JAN2015
NN1218-3852/ 704004/ NovoRapid/ 59/F/23.0	6	Nervous system disorders/ Hyporeflexia/ Absent Achilles Reflexes. Low Sensation To Vibration In Feet	05DEC2014
NN1218-3852/ 717015/ Faster aspart (mealtime)/ 39/F/30.9	16	Nervous system disorders/ Neuropathy peripheral/ Neuropathy	12JUL2014
NN1218-3852/ 717016/ Faster aspart (postmeal)/ 58/M/24.1	7	Nervous system disorders/ Decreased vibratory sense/ Decreased Vibration On Great Big Toes	10OCT2014
NN1218-3852/ 720014/ Faster aspart (postmeal)/ 47/M/33.3	11	Musculoskeletal and connective tissue disorders/ Muscular weakness/ Right Ankle Weakness (No Pain)	10JUN2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:19 - l_ae_over.sas/l_per_neu_ae_sas.txt

Peripheral neuropathy adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 720014/ Faster aspart (postmeal)/ 47/M/33.3	12	Nervous system disorders/ Hypoaesthesia/ Left Thigh Numbness	10JUN2014
NN1218-3852/ 721009/ NovoRapid/ 19/F/20.8	1	Nervous system disorders/ Hypoaesthesia/ Intermittent Bilateral Leg Numbness. Unknown Etiology.	08MAY2014
NN1218-3852/ 743002/ Faster aspart (mealtime)/ 47/F/21.6	5	Nervous system disorders/ Paraesthesia/ Left Great Toe Paresthesias	10OCT2014
NN1218-3852/ 743006/ Faster aspart (mealtime)/ 51/M/26.0	5	Nervous system disorders/ Neuropathy peripheral/ Worsening Of Neuropathy	25APR2014
NN1218-3852/ 749013/ NovoRapid/ 43/F/25.4	8	Nervous system disorders/ Paraesthesia/ Sensory Disturbance Skin: Paresthesia In The Left Side	05AUG2014
NN1218-3852/ 763005/ NovoRapid/ 48/M/29.0	3	Nervous system disorders/ Paraesthesia/ Paresthesia Left Hand 5th Digit	01AUG2014
NN1218-3852/ 779009/ Faster aspart (mealtime)/ 53/F/34.1	12	Nervous system disorders/ Neuropathy peripheral/ Worsening Neuropathy (Bilateral Feet)	01OCT2014
NN1218-3852/ 793008/ Faster aspart (mealtime)/ 50/F/32.8	6	Nervous system disorders/ Neuropathy peripheral/ Worsening Neuropathy	09JUN2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

nn1218/nn1218-summary/pmda_nda_20180709_er
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Peripheral neuropathy adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 808001/ NovoRapid/ 39/M/23.3	4	Nervous system disorders/ Neuropathy peripheral/ Worsening Neuropathy	28JUL2014
NN1218-3852/ 809014/ Faster aspart (postmeal)/ 53/F/21.2	2	Musculoskeletal and connective tissue disorders/ Muscular weakness/ Left Arm Weakness	29SEP2014
NN1218-3853/ 106007/ NovoRapid/ 63/F/21.3	1	Nervous system disorders/ Neuralgia/ Nerve Pain	01MAR2014
NN1218-3853/ 126009/ NovoRapid/ 58/F/37.3	8	Nervous system disorders/ Neuropathy peripheral/ Worsening Of Bilateral Lower Extremity Peripheral Neuropathy	15MAY2014
	9	Musculoskeletal and connective tissue disorders/ Muscular weakness/ Leg Weakness	21MAY2014
NN1218-3853/ 126013/ Faster aspart (mealtime)/ 72/M/30.5	17	Nervous system disorders/ Diabetic neuropathy/ Diabetic Peripheral Neuropathy Left Foot	08NOV2014
NN1218-3853/ 127007/ Faster aspart (mealtime)/ 59/M/37.9	2	Nervous system disorders/ Paraesthesia/ Paresthesia (Hand)	16JUL2014
	4	Nervous system disorders/ Paraesthesia/ Paraesthesia (Leg)	15OCT2014
NN1218-3853/ 157007/ NovoRapid/ 70/M/37.1	5	Musculoskeletal and connective tissue disorders/ Muscular weakness/ Right Leg Weakness	17AUG2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

Peripheral neuropathy adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3853/ 165003/ NovoRapid/ 49/F/34.5	2	Nervous system disorders/ Paraesthesia/ Paresthesia Rle	19MAR2014
NN1218-3853/ 165006/ NovoRapid/ 57/F/20.6	5	Nervous system disorders/ Hypoaesthesia/ Left Anterior Upper Arm Numbness	04JUL2014
NN1218-3853/ 172004/ NovoRapid/ 56/F/29.7	4	Nervous system disorders/ Hypoaesthesia/ Bilateral Arm Numbness	14FEB2014
NN1218-3853/ 185004/ NovoRapid/ 50/M/37.9	2	Nervous system disorders/ Paraesthesia/ Tingling Of Arm/Legs	11JUN2014
NN1218-3853/ 705003/ NovoRapid/ 62/F/33.0	3	Nervous system disorders/ Neuropathy peripheral/ Neuropathy	10JUN2014
NN1218-3853/ 705021/ Faster aspart (mealtime)/ 54/M/23.5	1	Nervous system disorders/ Neuropathy peripheral/ Neuropathy	08MAY2014
NN1218-4049/ 212009/ Faster aspart (mealtime)/ 51/F/21.7	3	Nervous system disorders/ Paraesthesia/ Tingling Rt. Leg	18AUG2014
	4	Nervous system disorders/ Hypoaesthesia/ Numbness Rt. Leg	18AUG2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0 .
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

nn1218/nn1218-summary/pmda_nda_20180709_er
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Peripheral neuropathy adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-4049/ 502008/ Faster aspart (mealtime)/ 75/M/29.4	3	Nervous system disorders/ Paraesthesia/ Parestesiae Of Legs	23DEC2013
NN1218-4049/ 612001/ Faster aspart (mealtime)/ 67/M/28.6	7	Nervous system disorders/ Paraesthesia/ Paresthesias With Subjective Weakness - Extremities	13FEB2014
NN1218-4049/ 630002/ Basal/ 50/F/34.2	2	Nervous system disorders/ Hypoaesthesia/ Numbness (Right Cheek, Right Hand, Right Buttock)	06MAY2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0 .
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

2.7.4.7.2.2.10. 治験薬投与下で発現した末梢性浮腫に関連する有害事象の要約 - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Number of subjects	1244				853				2097			
Total exposure (yrs)	741.2				566.3				1307.5			
Total Events	10	(0.8)	10	1.4	6	(0.6)	6	1.0	16	(0.8)	16	1.2
Serious												
Yes	0				0				0			
No	10	(0.8)	10	1.4	6	(0.6)	6	1.0	16	(0.8)	16	1.2
Missing	0				0				0			
Severity												
Severe	0				0				0			
Moderate	3	(0.2)	3	0.4	1	(0.1)	1	0.2	4	(0.2)	4	0.3
Mild	7	(0.6)	7	1.0	5	(0.5)	5	0.8	12	(0.6)	12	0.9
Missing	0				0				0			
Related to investigational products												
Probable	1	(0.1)	1	0.1	0				1	(0.0)	1	0.1
Possible	1	(0.1)	1	0.1	0				1	(0.0)	1	0.1
Unlikely	8	(0.7)	8	1.1	6	(0.6)	6	1.0	14	(0.7)	14	1.1

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure,
yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

Peripheral oedema adverse events - Cochran-Mantel Haenszel adjusted - treatment emergent - summary - overseas pooled data - safety analysis set

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Missing	0				0				0			
Outcome												
Recovered/resolved	8	(0.6)	8	1.1	5	(0.5)	5	0.8	13	(0.6)	13	1.0
Recovering/resolving	1	(0.1)	1	0.2	0				1	(0.0)	1	0.1
Recovered/resolved with sequelae	0				0				0			
Not recovered/not resolved	1	(0.1)	1	0.1	1	(0.1)	1	0.2	2	(0.1)	2	0.2
Fatal	0				0				0			
Unknown	0				0				0			
Missing	0				0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

2.7.4.7.2.2.11. 治験薬投与下で発現した末梢性浮腫に関連する有害事象の要約（器官別大分類別及び基本語別） - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R	RD [95% CI]
Number of subjects	1244				853				2097				
Total exposure (yrs)	741.2				566.3				1307.5				
Total events	10	(0.8)	10	1.4	6	(0.6)	6	1.0	16	(0.8)	16	1.2	
General disorders and administration site conditions	10	(0.8)	10	1.3	6	(0.7)	6	1.1	16	(0.8)	16	1.2	
Oedema peripheral	8	(0.7)	8	1.1	6	(0.6)	6	1.0	14	(0.7)	14	1.1	0.17 [-0.94; 1.28]
Oedema	2	(0.1)	2	0.3	0				2	(0.1)	2	0.2	0.25 [-0.10; 0.60]

%: Percentage of subjects, CI: Confidence interval, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, RD: Rate difference, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

2.7.4.7.2.2.12. 治験薬投与下で発現した末梢性浮腫に関連する有害事象の一覧 - 海外併合データ - 安全性解析対象集団

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 423004/ Faster aspart (mealtime)/ 61/M/26.0	3	General disorders and administration site conditions/ Oedema/ Edemata	21JUL2014
NN1218-3852/ 703002/ Faster aspart (mealtime)/ 61/F/29.2	10	General disorders and administration site conditions/ Oedema peripheral/ 1-2+ Bilateral Lower Leg Edema	11JUN2014
NN1218-3852/ 747004/ Faster aspart (mealtime)/ 60/F/26.3	1	General disorders and administration site conditions/ Oedema peripheral/ Lower Extremities - Edema	27MAY2014
NN1218-3852/ 758015/ Faster aspart (mealtime)/ 53/F/28.6	9	General disorders and administration site conditions/ Oedema peripheral/ Worsening Of Lower Extremities Edema	22JAN2015
NN1218-3852/ 771004/ NovoRapid/ 67/M/32.0	5	General disorders and administration site conditions/ Oedema peripheral/ Peripheral Edema	05JUL2014
NN1218-3852/ 790009/ Faster aspart (postmeal)/ 44/M/29.4	1	General disorders and administration site conditions/ Oedema/ 2+ Pitting Edema Bilateral Le	03JAN2014
NN1218-3852/ 799002/ Faster aspart (postmeal)/ 49/M/34.2	1	General disorders and administration site conditions/ Oedema peripheral/ Bilateral Leg Edema	05AUG2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0 .
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

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Peripheral oedema adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3853/ 105004/ Faster aspart (mealtime)/ 51/M/31.9	2	General disorders and administration site conditions/ Oedema peripheral/ Left Lower Extremity Peripheral Edema. Not An Allergic Reaction.	20JUL2014
NN1218-3853/ 108001/ NovoRapid/ 59/F/22.4	4	General disorders and administration site conditions/ Oedema peripheral/ Bilateral Edema Ankles To Thighs	28JUN2014
NN1218-3853/ 120001/ NovoRapid/ 64/M/38.0	2	General disorders and administration site conditions/ Oedema peripheral/ Bilateral Lower Extremity Edema	21MAY2014
NN1218-3853/ 126004/ Faster aspart (mealtime)/ 56/M/29.2	10	General disorders and administration site conditions/ Oedema peripheral/ Bilateral Lower Extremity Edema - (Not Cardiac Related, No Sob, No Chest Pain)	04JUN2014
NN1218-3853/ 157008/ Faster aspart (mealtime)/ 70/F/37.2	6	General disorders and administration site conditions/ Oedema peripheral/ Bilateral Lower Extremity Edema	01OCT2014
NN1218-3853/ 165003/ NovoRapid/ 49/F/34.5	1	General disorders and administration site conditions/ Oedema peripheral/ Intermittent Bilateral Lower Extremity Edema	18MAR2014
NN1218-3853/ 173008/ NovoRapid/ 60/F/38.3	8	General disorders and administration site conditions/ Oedema peripheral/ Lower Leg Edema	17JUL2014
NN1218-3853/ 174002/ Faster aspart (mealtime)/ 52/M/39.9	8	General disorders and administration site conditions/ Oedema peripheral/ Worsening Edema Of Both Legs	25JUL2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

nn1218/nn1218-summary/pmda_nda_20180709_er
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Peripheral oedema adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3853/ 706012/ NovoRapid/ 74/M/25.0	1	General disorders and administration site conditions/ Oedema peripheral/ Pedal Edema	02SEP2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0 .
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:20 - l_ae_over.sas/l_per_oed_ae_sas.txt

2.7.4.7.2.2.13. 治験薬投与下で発現した稀な事象に関連する有害事象の要約 - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Number of subjects	1244				853				2097			
Total exposure (yrs)	741.2				566.3				1307.5			
Total Events	19	(1.5)	22	3.0	20	(2.3)	23	3.8	39	(1.9)	45	3.4
Serious												
Yes	2	(0.1)	2	0.3	2	(0.2)	2	0.3	4	(0.2)	4	0.3
No	17	(1.4)	20	2.8	18	(2.1)	21	3.5	35	(1.7)	41	3.1
Missing	0				0				0			
Severity												
Severe	2	(0.1)	2	0.3	1	(0.1)	1	0.2	3	(0.1)	3	0.2
Moderate	4	(0.3)	4	0.5	5	(0.5)	5	0.8	9	(0.4)	9	0.7
Mild	13	(1.1)	16	2.2	15	(1.8)	17	2.9	28	(1.3)	33	2.5
Missing	0				0				0			
Related to investigational products												
Probable	0				1	(0.1)	1	0.2	1	(0.0)	1	0.1
Possible	4	(0.3)	4	0.6	0				4	(0.2)	4	0.3
Unlikely	12	(0.9)	14	1.8	14	(1.7)	16	2.7	26	(1.2)	30	2.3

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure,
yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

Rare events adverse events – Cochran-Mantel Haenszel adjusted - treatment emergent – summary – overseas pooled data - safety analysis set

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Missing	3	(0.3)	4	0.6	5	(0.5)	6	0.9	8	(0.4)	10	0.8
Outcome												
Recovered/resolved	8	(0.6)	9	1.2	10	(1.2)	12	2.0	18	(0.9)	21	1.6
Recovering/resolving	2	(0.2)	2	0.3	1	(0.1)	1	0.2	3	(0.1)	3	0.2
Recovered/resolved with sequelae	0				0				0			
Not recovered/not resolved	9	(0.8)	10	1.4	9	(1.0)	10	1.6	18	(0.9)	20	1.5
Fatal	1	(0.1)	1	0.1	0				1	(0.0)	1	0.1
Unknown	0				0				0			
Missing	0				0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Relationship is based on investigators assessment.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

2.7.4.7.2.2.14. 治験薬投与下で発現した稀な事象に関連する有害事象の要約（器官別大分類別及び基本語別） - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart N (%)	E	R	Comparator N (%)	E	R	Total N (%)	E	R	RD [95% CI]
Number of subjects	1244			853			2097			
Total exposure (yrs)	741.2			566.3			1307.5			
Total events	19 (1.5)	22	3.0	20 (2.3)	23	3.8	39 (1.9)	45	3.4	
Cardiac disorders	10 (0.8)	11	1.5	6 (0.7)	6	1.1	16 (0.8)	17	1.3	
Palpitations	3 (0.2)	3	0.4	2 (0.2)	2	0.3	5 (0.2)	5	0.4	0.03 [-0.61; 0.68]
Atrioventricular block first degree	1 (0.1)	1	0.2	1 (0.1)	1	0.2	2 (0.1)	2	0.2	0.01 [-0.43; 0.45]
Sinus bradycardia	1 (0.1)	1	0.1	1 (0.1)	1	0.2	2 (0.1)	2	0.2	-0.06 [-0.51; 0.38]
Arrhythmia	1 (0.1)	1	0.1	0			1 (0.0)	1	0.1	0.13 [-0.12; 0.37]
Atrial fibrillation	1 (0.1)	1	0.2	0			1 (0.0)	1	0.1	0.16 [-0.16; 0.48]
Bradycardia	1 (0.1)	1	0.1	0			1 (0.0)	1	0.1	0.13 [-0.12; 0.37]
Bundle branch block bilateral	1 (0.1)	1	0.2	0			1 (0.0)	1	0.1	0.16 [-0.15; 0.47]
Bundle branch block right	1 (0.1)	1	0.2	0			1 (0.0)	1	0.1	0.16 [-0.16; 0.48]
Sinus tachycardia	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.16 [-0.46; 0.15]
Supraventricular tachycardia	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.16 [-0.46; 0.15]
Tachycardia	1 (0.1)	1	0.1	0			1 (0.0)	1	0.1	0.13 [-0.12; 0.37]
Investigations	3 (0.2)	5	0.7	5 (0.6)	5	0.9	8 (0.4)	10	0.8	
Platelet count decreased	1 (0.1)	1	0.2	1 (0.1)	1	0.2	2 (0.1)	2	0.2	-0.03 [-0.51; 0.45]

%: Percentage of subjects, CI: Confidence interval, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, RD: Rate difference, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

Rare events adverse events by system organ class and preferred term - Cochran-Mantel Haenszel adjusted - treatment emergent - summary - overseas pooled data - safety analysis set

	Faster aspart N (%)	E	R	Comparator N (%)	E	R	Total N (%)	E	R	RD [95% CI]
Electrocardiogram P wave abnormal	1 (0.1)	1	0.1	0			1 (0.0)	1	0.1	0.13 [-0.12; 0.37]
Electrocardiogram PR prolongation	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.19 [-0.56; 0.18]
Electrocardiogram PR shortened	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.19 [-0.56; 0.18]
Eosinophil count abnormal	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.16 [-0.46; 0.15]
Heart rate increased	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.16 [-0.46; 0.15]
Lymphocyte count decreased	1 (0.1)	1	0.1	0			1 (0.0)	1	0.1	0.13 [-0.12; 0.37]
Neutrophil count decreased	1 (0.1)	1	0.1	0			1 (0.0)	1	0.1	0.13 [-0.12; 0.37]
White blood cell count abnormal	1 (0.1)	1	0.1	0			1 (0.0)	1	0.1	0.13 [-0.12; 0.37]
Hepatobiliary disorders	2 (0.2)	2	0.3	3 (0.4)	3	0.5	5 (0.2)	5	0.4	
Hepatic steatosis	2 (0.1)	2	0.3	2 (0.2)	2	0.3	4 (0.2)	4	0.3	-0.05 [-0.60; 0.50]
Hepatic calcification	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.16 [-0.46; 0.15]
Renal and urinary disorders	1 (0.1)	1	0.1	4 (0.5)	4	0.7	5 (0.2)	5	0.4	
Renal failure	1 (0.1)	1	0.2	2 (0.2)	2	0.3	3 (0.1)	3	0.2	-0.15 [-0.68; 0.38]
Nephrotic syndrome	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.15 [-0.45; 0.15]
Renal failure acute	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.16 [-0.46; 0.15]
Blood and lymphatic system disorders	1 (0.1)	1	0.1	2 (0.2)	3	0.5	3 (0.1)	4	0.3	
Leukopenia	1 (0.1)	1	0.1	2 (0.2)	2	0.3	3 (0.1)	3	0.2	-0.22 [-0.76; 0.32]
Neutropenia	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.16 [-0.46; 0.15]

%: Percentage of subjects, CI: Confidence interval, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, RD: Rate difference, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

Rare events adverse events by system organ class and preferred term - Cochran-Mantel Haenszel adjusted - treatment emergent - summary - overseas pooled data - safety analysis set

	Faster aspart N (%)	E	R	Comparator N (%)	E	R	Total N (%)	E	R	RD [95% CI]
Congenital, familial and genetic disorders	1 (0.1)	1	0.1	1 (0.1)	1	0.2	2 (0.1)	2	0.2	
Colour blindness	1 (0.1)	1	0.2	0			1 (0.0)	1	0.1	0.16 [-0.15; 0.47]
Phimosis	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1	-0.19 [-0.56; 0.18]
Gastrointestinal disorders	1 (0.1)	1	0.1	1 (0.1)	1	0.2	2 (0.1)	2	0.2	
Pancreatitis	1 (0.1)	1	0.1	1 (0.1)	1	0.2	2 (0.1)	2	0.2	-0.06 [-0.51; 0.38]

%: Percentage of subjects, CI: Confidence interval, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, RD: Rate difference, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart: combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 17.0.
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.
Comparator' consists of NovoRapid plus basal insulin.

2.7.4.7.2.2.15. 治験薬投与下で発現した稀な事象に関連する有害事象の一覧 - 海外併合データ - 安全性解析対象集団

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 105002/ Faster aspart (postmeal)/ 61/M/31.4	3	Hepatobiliary disorders/ Hepatic steatosis/ Liversteatosis	04MAR2014
NN1218-3852/ 212006/ Faster aspart (mealtime)/ 62/F/25.4	5	Cardiac disorders/ Palpitations/ Palpitations	22OCT2014
NN1218-3852/ 212010/ Faster aspart (postmeal)/ 23/F/29.7	10	Investigations/ Electrocardiogram P wave abnormal/ Ectopic P-Waves On Ecg	13AUG2014
NN1218-3852/ 219014/ Faster aspart (mealtime)/ 39/F/26.7	11	Cardiac disorders/ Palpitations/ Intermitant Heart Palpatations	06FEB2015
NN1218-3852/ 303006/ Faster aspart (mealtime)/ 82/M/22.9	2	Cardiac disorders/ Bradycardia/ Bradycardia	26MAY2014
NN1218-3852/ 405009/ NovoRapid/ 25/F/21.1	7	Blood and lymphatic system disorders/ Leukopenia/ Leukocytopenia	27NOV2014
NN1218-3852/ 506003/ Faster aspart (mealtime)/ 25/M/21.6	3	Cardiac disorders/ Tachycardia/ Tachycardia	14NOV2013

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0 .
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:20 - l_ae_over.sas/l_rare_ae_sas.txt

Rare events adverse events - treatment emergent - listing - overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 604004/ Faster aspart (postmeal)/ 41/M/28.8	10	Investigations/ White blood cell count abnormal/ Abnormal White Blood Count	07FEB2014
	11	Investigations/ Neutrophil count decreased/ Low Neutrophils	07FEB2014
	12	Investigations/ Lymphocyte count decreased/ Low Lymphocytes	07FEB2014
NN1218-3852/ 704006/ Faster aspart (postmeal)/ 39/M/32.3	4	Cardiac disorders/ Arrhythmia/ Cardiac Arrhythmia	28FEB2014
NN1218-3852/ 705001/ Faster aspart (postmeal)/ 28/M/30.2	3	Cardiac disorders/ Sinus bradycardia/ Sinus Bradycardia	21NOV2013
NN1218-3852/ 705006/ NovoRapid/ 46/F/22.9	12	Investigations/ Electrocardiogram PR shortened/ Short Pr Interval On Ekg	13JAN2014
NN1218-3852/ 705014/ NovoRapid/ 37/M/26.5	4	Cardiac disorders/ Sinus bradycardia/ Sinus Bradycardia	29OCT2014
NN1218-3852/ 710010/ NovoRapid/ 23/F/25.6	4	Investigations/ Electrocardiogram PR prolongation/ Prolonged P-R Interval	20AUG2014
NN1218-3852/ 720005/ NovoRapid/ 55/M/21.6	5	Gastrointestinal disorders/ Pancreatitis/ Pancreatitis	25FEB2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:20 - l_ae_over.sas/l_rare_ae_sas.txt

Rare events adverse events - treatment emergent - listing - overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3852/ 727008/ Faster aspart (mealtime)/ 58/M/28.1	1	Gastrointestinal disorders/ Pancreatitis/ Pancreatitis	05APR2014
NN1218-3852/ 732011/ Faster aspart (postmeal)/ 53/F/30.0	6	Cardiac disorders/ Palpitations/ Palpitations	25APR2014
NN1218-3852/ 736005/ NovoRapid/ 23/M/20.7	4	Investigations/ Platelet count decreased/ Low Platelet Levels	01JUL2014
NN1218-3852/ 753014/ Faster aspart (mealtime)/ 63/F/33.7	2	Blood and lymphatic system disorders/ Leukopenia/ Leukopenia	25NOV2014
NN1218-3852/ 762006/ Faster aspart (mealtime)/ 43/M/34.4	1	Hepatobiliary disorders/ Hepatic steatosis/ Fatty Liver	13DEC2013
NN1218-3852/ 762011/ NovoRapid/ 60/M/27.7	2	Congenital, familial and genetic disorders/ Phimosis/ Phimosis	12JUL2014
NN1218-3852/ 769006/ NovoRapid/ 20/M/22.6	2	Cardiac disorders/ Palpitations/ Heart Palpitations	24APR2014
NN1218-3853/ 104004/ NovoRapid/ 67/M/29.8	2	Investigations/ Eosinophil count abnormal/ Abnormal Lab Results For Eosinophils	17FEB2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

Rare events adverse events - treatment emergent - listing - overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3853/ 121007/ NovoRapid/ 70/M/34.5	3	Cardiac disorders/ Sinus tachycardia/ Sinus Tachycardia	15SEP2014
NN1218-3853/ 126005/ Faster aspart (mealtime)/ 66/F/39.8	2	Congenital, familial and genetic disorders/ Colour blindness/ Visual Disturbance (Lost Color Vision)	09JUL2014
NN1218-3853/ 134003/ NovoRapid/ 61/F/31.1	6	Cardiac disorders/ Palpitations/ Racing Heart	24APR2014
NN1218-3853/ 143008/ Faster aspart (mealtime)/ 69/F/37.7	2	Cardiac disorders/ Bundle branch block bilateral/ Rbbb With Anterior Fascicluar Block	29OCT2014
NN1218-3853/ 148002/ NovoRapid/ 51/F/37.5	3	Investigations/ Heart rate increased/ Rapid Heart Beat	16JUN2014
NN1218-3853/ 171004/ Faster aspart (mealtime)/ 50/M/32.3	4	Investigations/ Platelet count decreased/ Decreased Platelets	04SEP2014
NN1218-3853/ 200003/ NovoRapid/ 79/M/25.4	6	Renal and urinary disorders/ Renal failure acute/ Acute Kidney Injury Secondary To Nephrotoxic Drugs	16JUL2014
NN1218-3853/ 303013/ NovoRapid/ 72/F/25.3	6	Hepatobiliary disorders/ Hepatic calcification/ Liver Calcification, Diverticulum, Bearing By Ct Scan	01APR2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0 .
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:20 - l_ae_over.sas/l_rare_ae_sas.txt

Rare events adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-3853/ 504004/ NovoRapid/ 59/F/35.7	1	Blood and lymphatic system disorders/ Leukopenia/ Leukopenia	02APR2014
	2	Blood and lymphatic system disorders/ Neutropenia/ Neutropenia	02APR2014
	4	Cardiac disorders/ Supraventricular tachycardia/ Paroxysm Of Supraventricular Tachycardia	18JUN2014
NN1218-3853/ 510006/ Faster aspart (mealtime)/ 63/F/34.9	2	Investigations/ Heart rate increased/ Rapid Heartbeat	06APR2014
NN1218-3853/ 606004/ NovoRapid/ 79/F/31.2	4	Renal and urinary disorders/ Renal failure/ Renal Failure Worsening	21AUG2014
NN1218-3853/ 706021/ Faster aspart (mealtime)/ 70/M/22.6	1	Renal and urinary disorders/ Renal failure/ Renal Insufficency	28APR2014
NN1218-4049/ 102019/ Basal/ 58/F/32.7	1	Hepatobiliary disorders/ Hepatic steatosis/ Steatohepatitis	05MAR2014
NN1218-4049/ 210012/ Basal/ 65/M/24.6	1	Renal and urinary disorders/ Renal failure/ Renal Insufficiency.	07APR2014
NN1218-4049/ 402017/ Faster aspart (mealtime)/ 76/M/29.8	1	Cardiac disorders/ Atrial fibrillation/ Atrial Fibrillation	19MAY2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:20 - l_ae_over.sas/l_rare_ae_sas.txt

Rare events adverse events - treatment emergent – listing – overseas pooled data - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date
NN1218-4049/ 402017/ Faster aspart (mealtime)/ 76/M/29.8	2	Cardiac disorders/ Bundle branch block right/ Right Minor Bundle Branch Block	19MAY2014
NN1218-4049/ 405001/ Basal/ 67/M/37.7	9	Hepatobiliary disorders/ Hepatic steatosis/ Liver Steatosis	05FEB2014
	20	Renal and urinary disorders/ Nephrotic syndrome/ Nephrotic Syndrome	27JAN2014
NN1218-4049/ 405007/ Basal/ 64/M/23.7	1	Cardiac disorders/ Atrioventricular block first degree/ First Degree Atrio-Ventricular Block	21MAY2014
NN1218-4049/ 600009/ Faster aspart (mealtime)/ 67/F/32.1	1	Cardiac disorders/ Atrioventricular block first degree/ First Degree Av Block	07OCT2014

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0 .
Overseas pooled data consists of trials 3852(52w), 3853, 4049 and 3931.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:20 - l_ae_over.sas/l_rare_ae_sas.txt

2.7.4.7.2.2.16. 治験薬投与下で発現した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 - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

There are no data for this output.

2.7.4.7.2.2.17. 治験薬投与下で発現した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（器官別大分類別及び基本語別） - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:07:39 - t_ae_soc_sum_over.sas/t_sus_ae_soc_sum_sas.txt

2.7.4.7.2.2.18. 治験薬投与下で発現した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 - 海外併合データ - 安全性解析対象集団

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:21 - l_ae_over.sas/l_sus_ae_sas.txt

フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.4.7 付録
2 有害事象
3 海外併合データにおける
特に注目すべき安全性領域（120DSU）

ノボ ノルディスク ファーマ株式会社

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	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Number of subjects	1244				853				2097			
Total exposure (yrs)	741.21				566.26				1307.47			
Events	84	(6.4)	114	15.3	62	(7.4)	77	13.3	146	(7.0)	191	14.6
Severity												
Severe	56	(4.1)	74	9.7	36	(4.5)	42	7.5	92	(4.4)	116	8.9
Moderate	30	(2.4)	35	4.9	23	(2.6)	29	4.8	53	(2.5)	64	4.9
Mild	5	(0.4)	5	0.7	6	(0.6)	6	1.0	11	(0.5)	11	0.8
Related to investigational products												
Probable	17	(1.2)	24	3.2	8	(1.0)	10	1.8	25	(1.2)	34	2.6
Possible	10	(0.7)	12	1.7	7	(0.9)	7	1.3	17	(0.8)	19	1.5
Unlikely	59	(4.6)	77	10.4	44	(5.3)	53	9.1	103	(4.9)	130	9.9
Missing	1	(0.1)	1	0.2	5	(0.5)	7	1.1	6	(0.3)	8	0.6
Outcome												
Recovered/resolved	74	(5.6)	99	13.2	53	(6.4)	65	11.3	127	(6.1)	164	12.5
Recovering/resolving	6	(0.5)	6	0.8	3	(0.3)	3	0.5	9	(0.4)	9	0.7
Recovered/resolved with sequelae	1	(0.1)	1	0.2	1	(0.1)	1	0.2	2	(0.1)	2	0.2

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment. MedDRA version 17.0
The 'Diabetes pool' consists of trials 3852(52w), 3853, 4049 and 3931.
'Comparator' consists of NovoRapid plus basal insulin. Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.
NovoRapid is known as NovoLog in the U.S.

All serious adverse events - Cochran-Mantel-Haenszel adjusted - treatment emergent - summary - updated diabetes pool - safety analysis set

	Faster aspart			Comparator			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Not recovered/not resolved	6 (0.5)	6	0.8	6 (0.6)	6	1.0	12 (0.6)	12	0.9
Fatal	2 (0.2)	2	0.3	2 (0.2)	2	0.3	4 (0.2)	4	0.3
Unknown	0			0			0		

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment. MedDRA version 17.0
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NovoRapid is known as NovoLog in the U.S.

2.7.4.7.2.3.2. 治験薬投与下で発現した重篤な有害事象（いずれかの群で 1%以上の被験者で報告）の要約（器官別大分類、高位グループ語及び基本語別） - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart			Comparator			Total				
	N	(%)	E R	N	(%)	E R	N	(%)	E R	RD	[95% CI]
Number of subjects	1244			853			2097				
Total exposure (yrs)	741.21			566.26			1307.47				
Metabolism and nutrition disorders											
Glucose metabolism disorders (incl diabetes mellitus)											
Hypoglycaemia	27	(2.0)	33 4.4	13	(1.7)	15 2.7	40	(1.9)	48 3.7	1.70	[-0.32; 3.72]

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure, yrs: Years, RD: Rate difference, CI: Confidence interval
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
The 'Diabetes pool' consists of trials 3852(52w), 3853, 4049 and 3931. 'Comparator' consists of NovoRapid plus basal insulin.
Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.
NovoRapid is known as NovoLog in the U.S. MedDRA version 17.0

2.7.4.7.2.3.3. Faster aspart 又は対照薬との因果関係が「あり」又は「可能性あり」と判定された治験薬投与下で発現した重篤な有害事象（いずれかの群で 1%以上の被験者で報告）の要約（器官別大分類、高位グループ語及び基本語別） - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart			Comparator			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	1244			853			2097		
Total exposure (yrs)	741.21			566.26			1307.47		
Events	26 (1.9)	36	4.8	14 (1.8)	17	3.0	40 (1.9)	53	4.1
Metabolism and nutrition disorders	18 (1.3)	22	2.9	12 (1.5)	14	2.5	30 (1.4)	36	2.8
Glucose metabolism disorders (incl diabetes mellitus)	18 (1.3)	22	2.9	11 (1.4)	13	2.3	29 (1.4)	35	2.7
Hypoglycaemia	18 (1.3)	22	2.9	11 (1.4)	13	2.3	29 (1.4)	35	2.7
Diabetic complications	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1
Diabetic ketoacidosis	0			1 (0.1)	1	0.2	1 (0.0)	1	0.1
Nervous system disorders	7 (0.5)	10	1.3	2 (0.3)	3	0.6	9 (0.4)	13	1.0
Neurological disorders NEC	7 (0.5)	10	1.3	2 (0.3)	3	0.6	9 (0.4)	13	1.0
Hypoglycaemic unconsciousness	7 (0.5)	10	1.3	2 (0.3)	3	0.6	9 (0.4)	13	1.0
Injury, poisoning and procedural complications	2 (0.2)	2	0.3	0			2 (0.1)	2	0.2
Medication errors	2 (0.2)	2	0.3	0			2 (0.1)	2	0.2

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment.
The 'Diabetes pool' consists of trials 3852(52w), 3853, 4049 and 3931. 'Comparator' consists of NovoRapid plus basal insulin.
Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.
NovoRapid is known as NovoLog in the U.S. MedDRA version 17.0

Serious adverse events possibly or probably related to faster aspart or comparator by system organ class, higher level group term and preferred term - Cochran-Mantel-Haenszel adjusted - treatment emergent - summary - updated diabetes pool - safety analysis set

	Faster aspart			Comparator			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Wrong drug administered	2 (0.2)	2	0.3	0			2 (0.1)	2	0.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1)	1	0.2	0			1 (0.0)	1	0.1
Miscellaneous and site unspecified neoplasms benign	1 (0.1)	1	0.2	0			1 (0.0)	1	0.1
Cardiac myxoma	1 (0.1)	1	0.2	0			1 (0.0)	1	0.1
Respiratory, thoracic and mediastinal disorders	1 (0.1)	1	0.2	0			1 (0.0)	1	0.1
Pulmonary vascular disorders	1 (0.1)	1	0.2	0			1 (0.0)	1	0.1
Pulmonary embolism	1 (0.1)	1	0.2	0			1 (0.0)	1	0.1

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment.
The 'Diabetes pool' consists of trials 3852(52w), 3853, 4049 and 3931. 'Comparator' consists of NovoRapid plus basal insulin.
Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.
NovoRapid is known as NovoLog in the U.S. MedDRA version 17.0

2.7.4.7.2.3.4. イベント判定委員会により確定された心血管事象の要約 - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Number of subjects	1244				853				2097			
Total observation time (yrs)	855.87				642.97				1498.83			
Events sent for adjudication	18	(1.5)	33	4.0	14	(1.5)	17	2.4	32	(1.5)	50	3.3
Events positively adjudicated	9	(0.7)	12	1.5	9	(1.0)	9	1.3	18	(0.9)	21	1.4
MACE	4	(0.3)	4	0.5	6	(0.7)	6	0.9	10	(0.5)	10	0.7
Cardiovascular death	2	(0.2)	2	0.2	3	(0.3)	3	0.4	5	(0.2)	5	0.3
NSTEMI	2	(0.2)	2	0.2	1	(0.1)	1	0.1	3	(0.1)	3	0.2
Stroke	0				2	(0.2)	2	0.3	2	(0.1)	2	0.1
non-MACE	5	(0.4)	8	1.0	3	(0.3)	3	0.4	8	(0.4)	11	0.7
Heart failure	2	(0.2)	2	0.2	0				2	(0.1)	2	0.1
Percutaneous revascularization	3	(0.2)	4	0.5	2	(0.2)	2	0.3	5	(0.2)	6	0.4
Surgical revascularization	0				1	(0.1)	1	0.1	1	(0.0)	1	0.1
Unstable angina pectoris	2	(0.2)	2	0.2	0				2	(0.1)	2	0.1

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure from treatment start to follow up, yrs: Years,
MACE: Major adverse cardiovascular event, NSTEMI: Non-ST elevation myocardial infarction
MACE is defined as events positively adjudicated to cardiovascular-related death, nonfatal stroke or nonfatal myocardial infarction. Cardiovascular events were not sent for adjudication during the run-in period.
The 'Diabetes pool' consists of trials 3852(52w), 3853, 4049 and 3931. 'Comparator' consists of NovoRapid plus basal insulin.
NovoRapid is known as NovoLog in the U.S. MedDRA version 17.0.

2.7.4.7.2.3.5. 投薬過誤に関連する有害事象の要約 - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart			Comparator			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	1244			853			2097		
Total exposure (yrs)	741.21			566.26			1307.47		
Events	59 (4.2)	72	9.3	31 (4.1)	39	7.2	90 (4.3)	111	8.5
Serious									
Yes	4 (0.3)	4	0.5	1 (0.1)	1	0.2	5 (0.2)	5	0.4
No	55 (3.9)	68	8.7	30 (4.0)	38	7.1	85 (4.1)	106	8.1
Severity									
Severe	4 (0.3)	4	0.5	0			4 (0.2)	4	0.3
Moderate	12 (0.8)	13	1.6	13 (1.7)	13	2.4	25 (1.2)	26	2.0
Mild	43 (3.0)	55	7.1	22 (2.9)	26	4.8	65 (3.1)	81	6.2
Related to investigational products									
Probable	27 (1.9)	29	3.8	18 (2.4)	19	3.5	45 (2.1)	48	3.7
Possible	4 (0.3)	4	0.5	0			4 (0.2)	4	0.3
Unlikely	30 (2.1)	39	5.0	16 (2.1)	20	3.7	46 (2.2)	59	4.5
Outcome									
Recovered/resolved	59 (4.2)	72	9.3	31 (4.1)	39	7.2	90 (4.3)	111	8.5
Recovering/resolving	0			0			0		

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment. MedDRA version 17.0
The 'Diabetes pool' consists of trials 3852(52w), 3853, 4049 and 3931.
'Comparator' consists of NovoRapid plus basal insulin. Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.
NovoRapid is known as NovoLog in the U.S.

Medication errors adverse events - Cochran-Mantel-Haenszel adjusted - treatment emergent - summary - updated diabetes pool - safety analysis set

	Faster aspart			Comparator			Total		
	N	(%)	E R	N	(%)	E R	N	(%)	E R
Recovered/resolved with sequelae	0			0			0		
Not recovered/not resolved	0			0			0		
Fatal	0			0			0		
Unknown	0			0			0		

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment. MedDRA version 17.0
The 'Diabetes pool' consists of trials 3852(52w), 3853, 4049 and 3931.
'Comparator' consists of NovoRapid plus basal insulin. Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.
NovoRapid is known as NovoLog in the U.S.

2.7.4.7.2.3.6. 全身性アレルギー反応に関連する有害事象の要約 - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Number of subjects	1244				853				2097			
Total exposure (yrs)	741.21				566.26				1307.47			
Events	39	(2.9)	46	6.1	30	(3.8)	34	6.2	69	(3.3)	80	6.1
Serious												
Yes	0				0				0			
No	39	(2.9)	46	6.1	30	(3.8)	34	6.2	69	(3.3)	80	6.1
Severity												
Severe	1	(0.1)	1	0.1	0				1	(0.0)	1	0.1
Moderate	8	(0.6)	9	1.2	5	(0.6)	5	0.9	13	(0.6)	14	1.1
Mild	30	(2.2)	36	4.7	27	(3.4)	29	5.3	57	(2.7)	65	5.0
Related to investigational products												
Probable	0				0				0			
Possible	1	(0.1)	2	0.3	1	(0.1)	1	0.2	2	(0.1)	3	0.2
Unlikely	37	(2.7)	43	5.6	26	(3.3)	30	5.5	63	(3.0)	73	5.6
Missing	1	(0.1)	1	0.1	3	(0.3)	3	0.5	4	(0.2)	4	0.3
Outcome												
Recovered/resolved	28	(2.1)	34	4.5	25	(3.2)	29	5.3	53	(2.5)	63	4.8

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment. MedDRA version 17.0
The 'Diabetes pool' consists of trials 3852(52w), 3853, 4049 and 3931.
'Comparator' consists of NovoRapid plus basal insulin. Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.
NovoRapid is known as NovoLog in the U.S.

Systemic allergic reactions adverse events - Cochran-Mantel-Haenszel adjusted - treatment emergent - summary - updated diabetes pool - safety analysis set

	Faster aspart			Comparator			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Recovering/resolving	1 (0.1)	1	0.2	2 (0.2)	2	0.4	3 (0.1)	3	0.2
Recovered/resolved with sequelae	1 (0.1)	1	0.1	0			1 (0.0)	1	0.1
Not recovered/not resolved	10 (0.7)	10	1.3	3 (0.4)	3	0.5	13 (0.6)	13	1.0
Fatal	0			0			0		
Unknown	0			0			0		

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment. MedDRA version 17.0
The 'Diabetes pool' consists of trials 3852(52w), 3853, 4049 and 3931.
'Comparator' consists of NovoRapid plus basal insulin. Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.
NovoRapid is known as NovoLog in the U.S.

2.7.4.7.2.3.7. 注射部位反応に関連する有害事象の要約 - Cochran-Mantel-Haenszel 法を用いた調整 - 3582 試験（52 週）、3853 試験及び 4049 試験 - 安全性解析対象集団

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Number of subjects	1219				841				2060			
Total exposure (yrs)	738.30				564.85				1303.15			
Events	21	(1.6)	29	3.8	8	(1.0)	12	2.0	29	(1.4)	41	3.1
Serious												
Yes	0				0				0			
No	21	(1.6)	29	3.8	8	(1.0)	12	2.0	29	(1.4)	41	3.1
Severity												
Severe	0				0				0			
Moderate	2	(0.1)	2	0.3	0				2	(0.1)	2	0.2
Mild	20	(1.5)	27	3.6	8	(1.0)	12	2.0	28	(1.4)	39	3.0
Related to investigational products												
Probable	6	(0.4)	6	0.8	0				6	(0.3)	6	0.5
Possible	1	(0.1)	1	0.1	1	(0.1)	2	0.3	2	(0.1)	3	0.2
Unlikely	15	(1.2)	22	2.9	7	(0.9)	7	1.3	22	(1.1)	29	2.2
Missing	0				1	(0.1)	3	0.5	1	(0.0)	3	0.2
Outcome												
Recovered/resolved	17	(1.3)	24	3.2	8	(1.0)	12	2.0	25	(1.2)	36	2.8
Recovering/resolving	0				0				0			

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment. MedDRA version 17.0
'Comparator' consists of NovoRapid plus basal insulin. Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.
NovoRapid is known as NovoLog in the U.S.

Injection site reaction adverse events - Cochran-Mantel-Haenszel adjusted - treatment emergent - summary - trials 3852 52 weeks, 3853, 4049 - safety analysis set

	Faster aspart			Comparator			Total		
	N	(%)	E R	N	(%)	E R	N	(%)	E R
Recovered/resolved with sequelae	0			0			0		
Not recovered/not resolved	5	(0.3)	5 0.6	0			5	(0.2)	5 0.4
Fatal	0			0			0		
Unknown	0			0			0		

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment. MedDRA version 17.0
'Comparator' consists of NovoRapid plus basal insulin. Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.
NovoRapid is known as NovoLog in the U.S.

2.7.4.7.2.3.8. リポジストロフィーに関連する有害事象の要約 - Cochran-Mantel-Haenszel 法を用いた調整 - 海外併合データ - 安全性解析対象集団

	Faster aspart N	(%)	E	R	Comparator N	(%)	E	R	Total N	(%)	E	R
Number of subjects	1244				853				2097			
Total exposure (yrs)	741.21				566.26				1307.47			
Events	6	(0.4)	6	0.8	3	(0.4)	3	0.6	9	(0.4)	9	0.7
Serious												
Yes	0				0				0			
No	6	(0.4)	6	0.8	3	(0.4)	3	0.6	9	(0.4)	9	0.7
Severity												
Severe	0				0				0			
Moderate	1	(0.1)	1	0.1	0				1	(0.0)	1	0.1
Mild	5	(0.3)	5	0.6	3	(0.4)	3	0.6	8	(0.4)	8	0.6
Related to investigational products												
Probable	2	(0.1)	2	0.3	1	(0.1)	1	0.2	3	(0.1)	3	0.2
Possible	1	(0.1)	1	0.1	1	(0.1)	1	0.2	2	(0.1)	2	0.2
Unlikely	3	(0.2)	3	0.4	1	(0.1)	1	0.2	4	(0.2)	4	0.3
Outcome												
Recovered/resolved	3	(0.2)	3	0.4	2	(0.3)	2	0.4	5	(0.2)	5	0.4
Recovering/resolving	0				0				0			

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment. MedDRA version 17.0
The 'Diabetes pool' consists of trials 3852(52w), 3853, 4049 and 3931.
'Comparator' consists of NovoRapid plus basal insulin. Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.
NovoRapid is known as NovoLog in the U.S.

Lipodystrophy adverse events - Cochran-Mantel-Haenszel adjusted - treatment emergent - summary - updated diabetes pool - safety analysis set

	Faster aspart N (%)	E	R	Comparator N (%)	E	R	Total N (%)	E	R
Recovered/resolved with sequelae	0			0			0		
Not recovered/not resolved	3 (0.2)	3	0.4	1 (0.1)	1	0.2	4 (0.2)	4	0.3
Fatal	0			0			0		
Unknown	0			0			0		

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigator's assessment. MedDRA version 17.0
The 'Diabetes pool' consists of trials 3852(52w), 3853, 4049 and 3931.
'Comparator' consists of NovoRapid plus basal insulin. Proportions and event rates were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.
NovoRapid is known as NovoLog in the U.S.

フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.4.7. 付録
3. 内因性及び外因性民族的要因
1. 4131 試験における低血糖

ノボ ノルディスク ファーマ株式会社

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	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	322			319			323			964		
Total exposure (yrs)	161.4			159.5			160.6			481.6		
Total events	312 (96.9)	14675	9090	303 (95.0)	15579	9765	310 (96.0)	15722	9789	925 (96.0)	45976	9547
BG confirmed	284 (88.2)	5467	3386	272 (85.3)	6337	3972	281 (87.0)	6485	4038	837 (86.8)	18289	3798
Severe or BG confirmed symptomatic	265 (82.3)	3793	2349	250 (78.4)	4623	2898	254 (78.6)	4681	2915	769 (79.8)	13097	2720
Severe or BG confirmed	285 (88.5)	5510	3413	275 (86.2)	6366	3990	284 (87.9)	6530	4066	844 (87.6)	18406	3822
NN unclassifiable	309 (96.0)	9164	5676	298 (93.4)	9213	5775	307 (95.0)	9190	5722	914 (94.8)	27567	5724
ADA												
Severe	29 (9.0)	43	27	19 (6.0)	29	18	29 (9.0)	45	28	77 (8.0)	117	24
Documented symptomatic	289 (89.8)	8744	5416	269 (84.3)	9836	6165	273 (84.5)	9764	6080	831 (86.2)	28344	5886
Asymptomatic	250 (77.6)	5639	3493	243 (76.2)	5428	3402	246 (76.2)	5669	3530	739 (76.7)	16736	3475
Probable symptomatic	47 (14.6)	108	67	39 (12.2)	204	128	53 (16.4)	165	103	139 (14.4)	477	99
Pseudo-hypoglycaemia	9 (2.8)	14	9	13 (4.1)	48	30	11 (3.4)	24	15	33 (3.4)	86	18
ADA unclassifiable	20 (6.2)	126	78	21 (6.6)	34	21	22 (6.8)	53	33	63 (6.5)	213	44
Not able to selftreat - unclassifiable	1 (0.3)	1	1	0			2 (0.6)	2	1	3 (0.3)	3	1

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.2. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインの年齢が 65 歳以上の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	20			22			19			61		
Total exposure (yrs)	9.8			10.7			9.6			30.1		
Total events	20 (100.0)	1085	11030	21 (95.5)	1000	9370	19 (100.0)	798	8344	60 (98.4)	2883	9587
BG confirmed	19 (95.0)	326	3314	20 (90.9)	341	3195	18 (94.7)	288	3012	57 (93.4)	955	3176
Severe or BG confirmed symptomatic	17 (85.0)	213	2165	20 (90.9)	267	2502	15 (78.9)	177	1851	52 (85.2)	657	2185
Severe or BG confirmed	19 (95.0)	329	3344	20 (90.9)	341	3195	18 (94.7)	290	3032	57 (93.4)	960	3192
NN unclassifiable	20 (100.0)	755	7675	21 (95.5)	659	6175	19 (100.0)	508	5312	60 (98.4)	1922	6391
ADA												
Severe	3 (15.0)	3	30	0			2 (10.5)	2	21	5 (8.2)	5	17
Documented symptomatic	19 (95.0)	604	6140	20 (90.9)	593	5557	15 (78.9)	319	3336	54 (88.5)	1516	5041
Asymptomatic	18 (90.0)	463	4707	16 (72.7)	392	3673	18 (94.7)	445	4653	52 (85.2)	1300	4323
Probable symptomatic	3 (15.0)	13	132	3 (13.6)	7	66	3 (15.8)	19	199	9 (14.8)	39	130
Pseudo-hypoglycaemia	1 (5.0)	1	10	2 (9.1)	4	37	0			3 (4.9)	5	17
ADA unclassifiable	0			2 (9.1)	4	37	1 (5.3)	13	136	3 (4.9)	17	57
Not able to selftreat - unclassifiable	1 (5.0)	1	10	0			0			1 (1.6)	1	3

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.3. 治験薬投与下で発現した低血糖の要約（分類別）- 女性被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	158			155			163			476		
Total exposure (yrs)	78.7			77.5			80.1			236.3		
Total events	152 (96.2)	7746	9837	151 (97.4)	8475	10934	160 (98.2)	8852	11054	463 (97.3)	25073	10609
BG confirmed	146 (92.4)	2802	3558	136 (87.7)	3210	4141	150 (92.0)	3529	4407	432 (90.8)	9541	4037
Severe or BG confirmed symptomatic	137 (86.7)	2147	2727	128 (82.6)	2342	3021	137 (84.0)	2652	3312	402 (84.5)	7141	3022
Severe or BG confirmed	146 (92.4)	2822	3584	137 (88.4)	3222	4157	152 (93.3)	3547	4429	435 (91.4)	9591	4058
NN unclassifiable	152 (96.2)	4924	6253	149 (96.1)	5253	6777	158 (96.9)	5303	6622	459 (96.4)	15480	6550
ADA												
Severe	14 (8.9)	20	25	10 (6.5)	12	15	13 (8.0)	18	22	37 (7.8)	50	21
Documented symptomatic	146 (92.4)	5245	6661	137 (88.4)	5299	6836	143 (87.7)	5701	7119	426 (89.5)	16245	6874
Asymptomatic	117 (74.1)	2306	2929	125 (80.6)	3007	3879	137 (84.0)	2968	3706	379 (79.6)	8281	3504
Probable symptomatic	19 (12.0)	52	66	21 (13.5)	105	135	27 (16.6)	110	137	67 (14.1)	267	113
Pseudo-hypoglycaemia	6 (3.8)	7	9	7 (4.5)	36	46	6 (3.7)	14	17	19 (4.0)	57	24
ADA unclassifiable	12 (7.6)	116	147	9 (5.8)	16	21	7 (4.3)	39	49	28 (5.9)	171	72
Not able to selftreat - unclassifiable	0			0			2 (1.2)	2	2	2 (0.4)	2	1

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.4. 治験薬投与下で発現した低血糖の要約（分類別）- 男性被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	184			186			179			549		
Total exposure (yrs)	92.5			92.7			90.1			275.3		
Total events	180 (97.8)	8014	8661	173 (93.0)	8104	8742	169 (94.4)	7668	8512	522 (95.1)	23786	8640
BG confirmed	157 (85.3)	2991	3232	156 (83.9)	3468	3741	149 (83.2)	3244	3601	462 (84.2)	9703	3524
Severe or BG confirmed symptomatic	145 (78.8)	1859	2009	142 (76.3)	2548	2749	132 (73.7)	2206	2449	419 (76.3)	6613	2402
Severe or BG confirmed	158 (85.9)	3017	3260	158 (84.9)	3485	3760	150 (83.8)	3273	3633	466 (84.9)	9775	3550
NN unclassifiable	177 (96.2)	4995	5398	170 (91.4)	4619	4983	168 (93.9)	4395	4879	515 (93.8)	14009	5088
ADA												
Severe	18 (9.8)	26	28	9 (4.8)	17	18	18 (10.1)	29	32	45 (8.2)	72	26
Documented symptomatic	162 (88.0)	4103	4434	152 (81.7)	5130	5534	145 (81.0)	4382	4864	459 (83.6)	13615	4945
Asymptomatic	151 (82.1)	3796	4102	134 (72.0)	2813	3035	127 (70.9)	3146	3492	412 (75.0)	9755	3543
Probable symptomatic	31 (16.8)	69	75	21 (11.3)	106	114	29 (16.2)	74	82	81 (14.8)	249	90
Pseudo-hypoglycaemia	4 (2.2)	8	9	8 (4.3)	16	17	5 (2.8)	10	11	17 (3.1)	34	12
ADA unclassifiable	8 (4.3)	10	11	14 (7.5)	22	24	16 (8.9)	27	30	38 (6.9)	59	21
Not able to selftreat - unclassifiable	2 (1.1)	2	2	0			0			2 (0.4)	2	1

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.5. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインの BMI（kg/m^2）が 25 未満の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	190			185			194			569		
Total exposure (yrs)	95.1			92.7			95.6			283.4		
Total events	184 (96.8)	9489	9975	182 (98.4)	9052	9770	187 (96.4)	10333	10806	553 (97.2)	28874	10188
BG confirmed	170 (89.5)	3470	3648	166 (89.7)	3651	3940	174 (89.7)	4248	4442	510 (89.6)	11369	4012
Severe or BG confirmed symptomatic	163 (85.8)	2471	2598	149 (80.5)	2666	2877	159 (82.0)	3110	3252	471 (82.8)	8247	2910
Severe or BG confirmed	170 (89.5)	3499	3678	167 (90.3)	3670	3961	176 (90.7)	4284	4480	513 (90.2)	11453	4041
NN unclassifiable	182 (95.8)	5990	6297	179 (96.8)	5382	5809	185 (95.4)	6049	6326	546 (96.0)	17421	6147
ADA												
Severe	18 (9.5)	29	30	13 (7.0)	19	21	20 (10.3)	36	38	51 (9.0)	84	30
Documented symptomatic	178 (93.7)	5833	6132	161 (87.0)	5740	6195	167 (86.1)	6355	6646	506 (88.9)	17928	6326
Asymptomatic	142 (74.7)	3504	3683	139 (75.1)	3107	3353	148 (76.3)	3816	3991	429 (75.4)	10427	3679
Probable symptomatic	30 (15.8)	66	69	24 (13.0)	120	130	31 (16.0)	87	91	85 (14.9)	273	96
Pseudo-hypoglycaemia	6 (3.2)	11	12	11 (5.9)	39	42	6 (3.1)	13	14	23 (4.0)	63	22
ADA unclassifiable	7 (3.7)	46	48	17 (9.2)	27	29	11 (5.7)	26	27	35 (6.2)	99	35
Not able to selftreat - unclassifiable	0			0			0			0		

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.6. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインの BMI（kg/m^2）が 25 以上 30 未満の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	105			104			99			308		
Total exposure (yrs)	52.7			51.3			50.2			154.2		
Total events	104 (99.0)	4313	8179	96 (92.3)	5100	9951	94 (94.9)	4265	8500	294 (95.5)	13678	8873
BG confirmed	93 (88.6)	1573	2983	86 (82.7)	2011	3924	80 (80.8)	1668	3324	259 (84.1)	5252	3407
Severe or BG confirmed symptomatic	84 (80.0)	1071	2031	81 (77.9)	1451	2831	71 (71.7)	1169	2330	236 (76.6)	3691	2394
Severe or BG confirmed	94 (89.5)	1584	3004	88 (84.6)	2020	3941	80 (80.8)	1674	3336	262 (85.1)	5278	3424
NN unclassifiable	103 (98.1)	2728	5173	94 (90.4)	3080	6009	93 (93.9)	2589	5160	290 (94.2)	8397	5447
ADA												
Severe	10 (9.5)	11	21	5 (4.8)	9	18	6 (6.1)	6	12	21 (6.8)	26	17
Documented symptomatic	92 (87.6)	2501	4743	86 (82.7)	3129	6105	81 (81.8)	2539	5060	259 (84.1)	8169	5299
Asymptomatic	88 (83.8)	1673	3173	82 (78.8)	1908	3723	74 (74.7)	1591	3171	244 (79.2)	5172	3355
Probable symptomatic	16 (15.2)	47	89	12 (11.5)	35	68	18 (18.2)	88	175	46 (14.9)	170	110
Pseudo-hypoglycaemia	4 (3.8)	4	8	2 (1.9)	11	21	4 (4.0)	7	14	10 (3.2)	22	14
ADA unclassifiable	10 (9.5)	76	144	3 (2.9)	8	16	9 (9.1)	32	64	22 (7.1)	116	75
Not able to selftreat - unclassifiable	1 (1.0)	1	2	0			2 (2.0)	2	4	3 (1.0)	3	2

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.7. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインの BMI（kg/m^2）が 30 以上の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	47			52			49			148		
Total exposure (yrs)	23.4			26.3			24.4			74.1		
Total events	44 (93.6)	1958	8362	46 (88.5)	2427	9227	48 (98.0)	1922	7888	138 (93.2)	6307	8513
BG confirmed	40 (85.1)	750	3203	40 (76.9)	1016	3863	45 (91.8)	857	3517	125 (84.5)	2623	3541
Severe or BG confirmed symptomatic	35 (74.5)	464	1982	40 (76.9)	773	2939	39 (79.6)	579	2376	114 (77.0)	1816	2451
Severe or BG confirmed	40 (85.1)	756	3229	40 (76.9)	1017	3867	46 (93.9)	862	3538	126 (85.1)	2635	3557
NN unclassifiable	44 (93.6)	1201	5129	46 (88.5)	1410	5361	48 (98.0)	1060	4350	138 (93.2)	3671	4955
ADA												
Severe	4 (8.5)	6	26	1 (1.9)	1	4	5 (10.2)	5	21	10 (6.8)	12	16
Documented symptomatic	38 (80.9)	1014	4331	42 (80.8)	1560	5931	40 (81.6)	1189	4880	120 (81.1)	3763	5079
Asymptomatic	38 (80.9)	925	3951	38 (73.1)	805	3061	42 (85.7)	707	2901	118 (79.7)	2437	3290
Probable symptomatic	4 (8.5)	8	34	6 (11.5)	56	213	7 (14.3)	9	37	17 (11.5)	73	99
Pseudo-hypoglycaemia	0			2 (3.8)	2	8	1 (2.0)	4	16	3 (2.0)	6	8
ADA unclassifiable	3 (6.4)	4	17	3 (5.8)	3	11	3 (6.1)	8	33	9 (6.1)	15	20
Not able to selftreat - unclassifiable	1 (2.1)	1	4	0			0			1 (0.7)	1	1

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.8. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインの HbA1c が 8%未満の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	265			280			276			821		
Total exposure (yrs)	132.7			139.7			137.1			409.4		
Total events	256 (96.6)	12773	9626	268 (95.7)	13971	10002	266 (96.4)	13888	10132	790 (96.2)	40632	9924
BG confirmed	231 (87.2)	4657	3510	239 (85.4)	5541	3967	244 (88.4)	5675	4140	714 (87.0)	15873	3877
Severe or BG confirmed symptomatic	215 (81.1)	3210	2419	222 (79.3)	4069	2913	218 (79.0)	4058	2960	655 (79.8)	11337	2769
Severe or BG confirmed	232 (87.5)	4691	3535	242 (86.4)	5561	3981	245 (88.8)	5707	4163	719 (87.6)	15959	3898
NN unclassifiable	253 (95.5)	8080	6089	263 (93.9)	8410	6021	263 (95.3)	8179	5967	779 (94.9)	24669	6025
ADA												
Severe	21 (7.9)	34	26	16 (5.7)	20	14	23 (8.3)	32	23	60 (7.3)	86	21
Documented symptomatic	235 (88.7)	7395	5573	237 (84.6)	8767	6277	233 (84.4)	8385	6117	705 (85.9)	24547	5995
Asymptomatic	209 (78.9)	5120	3858	211 (75.4)	4934	3532	216 (78.3)	5231	3816	636 (77.5)	15285	3733
Probable symptomatic	38 (14.3)	94	71	31 (11.1)	172	123	46 (16.7)	164	120	115 (14.0)	430	105
Pseudo-hypoglycaemia	10 (3.8)	15	11	15 (5.4)	52	37	7 (2.5)	17	12	32 (3.9)	84	21
ADA unclassifiable	11 (4.2)	113	85	19 (6.8)	26	19	18 (6.5)	57	42	48 (5.8)	196	48
Not able to selftreat - unclassifiable	2 (0.8)	2	2	0			2 (0.7)	2	1	4 (0.5)	4	1

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.9. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインの HbA1c が 8%以上の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	77			61			66			204		
Total exposure (yrs)	38.6			30.5			33.1			102.2		
Total events	76 (98.7)	2987	7742	56 (91.8)	2608	8542	63 (95.5)	2632	7953	195 (95.6)	8227	8050
BG confirmed	72 (93.5)	1136	2944	53 (86.9)	1137	3724	55 (83.3)	1098	3318	180 (88.2)	3371	3298
Severe or BG confirmed symptomatic	67 (87.0)	796	2063	48 (78.7)	821	2689	51 (77.3)	800	2417	166 (81.4)	2417	2365
Severe or BG confirmed	72 (93.5)	1148	2975	53 (86.9)	1146	3754	57 (86.4)	1113	3363	182 (89.2)	3407	3334
NN unclassifiable	76 (98.7)	1839	4766	56 (91.8)	1462	4789	63 (95.5)	1519	4590	195 (95.6)	4820	4716
ADA												
Severe	11 (14.3)	12	31	3 (4.9)	9	29	8 (12.1)	15	45	22 (10.8)	36	35
Documented symptomatic	73 (94.8)	1953	5062	52 (85.2)	1662	5444	55 (83.3)	1698	5131	180 (88.2)	5313	5198
Asymptomatic	59 (76.6)	982	2545	48 (78.7)	886	2902	48 (72.7)	883	2668	155 (76.0)	2751	2692
Probable symptomatic	12 (15.6)	27	70	11 (18.0)	39	128	10 (15.2)	20	60	33 (16.2)	86	84
Pseudo-hypoglycaemia	0			0			4 (6.1)	7	21	4 (2.0)	7	7
ADA unclassifiable	9 (11.7)	13	34	4 (6.6)	12	39	5 (7.6)	9	27	18 (8.8)	34	33
Not able to selftreat - unclassifiable	0			0			0			0		

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.10. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインの糖尿病罹病期間が 15 年未満の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	177			190			175			542		
Total exposure (yrs)	88.6			93.9			86.8			269.2		
Total events	172 (97.2)	7524	8491	180 (94.7)	8014	8538	164 (93.7)	7578	8733	516 (95.2)	23116	8585
BG confirmed	156 (88.1)	2682	3027	157 (82.6)	3015	3212	143 (81.7)	3000	3457	456 (84.1)	8697	3230
Severe or BG confirmed symptomatic	144 (81.4)	1782	2011	145 (76.3)	2304	2455	125 (71.4)	2040	2351	414 (76.4)	6126	2275
Severe or BG confirmed	156 (88.1)	2705	3053	160 (84.2)	3029	3227	145 (82.9)	3029	3491	461 (85.1)	8763	3255
NN unclassifiable	170 (96.0)	4819	5438	176 (92.6)	4985	5311	162 (92.6)	4549	5242	508 (93.7)	14353	5331
ADA												
Severe	14 (7.9)	23	26	9 (4.7)	14	15	16 (9.1)	29	33	39 (7.2)	66	25
Documented symptomatic	159 (89.8)	4206	4747	157 (82.6)	5175	5513	138 (78.9)	4307	4963	454 (83.8)	13688	5084
Asymptomatic	138 (78.0)	3168	3575	139 (73.2)	2625	2797	130 (74.3)	3114	3589	407 (75.1)	8907	3308
Probable symptomatic	28 (15.8)	53	60	25 (13.2)	134	143	27 (15.4)	67	77	80 (14.8)	254	94
Pseudo-hypoglycaemia	5 (2.8)	6	7	7 (3.7)	36	38	6 (3.4)	16	18	18 (3.3)	58	22
ADA unclassifiable	11 (6.2)	68	77	16 (8.4)	30	32	11 (6.3)	45	52	38 (7.0)	143	53
Not able to selftreat - unclassifiable	0			0			0			0		

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.11. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインの糖尿病罹病期間が 15 年以上の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	165			151			167			483		
Total exposure (yrs)	82.7			76.3			83.4			242.4		
Total events	160 (97.0)	8236	9963	144 (95.4)	8565	11218	165 (98.8)	8942	10723	469 (97.1)	25743	10620
BG confirmed	147 (89.1)	3111	3763	135 (89.4)	3663	4798	156 (93.4)	3773	4525	438 (90.7)	10547	4351
Severe or BG confirmed symptomatic	138 (83.6)	2224	2690	125 (82.8)	2586	3387	144 (86.2)	2818	3379	407 (84.3)	7628	3147
Severe or BG confirmed	148 (89.7)	3134	3791	135 (89.4)	3678	4817	157 (94.0)	3791	4546	440 (91.1)	10603	4374
NN unclassifiable	159 (96.4)	5100	6169	143 (94.7)	4887	6401	164 (98.2)	5149	6175	466 (96.5)	15136	6244
ADA												
Severe	18 (10.9)	23	28	10 (6.6)	15	20	15 (9.0)	18	22	43 (8.9)	56	23
Documented symptomatic	149 (90.3)	5142	6220	132 (87.4)	5254	6882	150 (89.8)	5776	6927	431 (89.2)	16172	6672
Asymptomatic	130 (78.8)	2934	3549	120 (79.5)	3195	4185	134 (80.2)	3000	3598	384 (79.5)	9129	3766
Probable symptomatic	22 (13.3)	68	82	17 (11.3)	77	101	29 (17.4)	117	140	68 (14.1)	262	108
Pseudo-hypoglycaemia	5 (3.0)	9	11	8 (5.3)	16	21	5 (3.0)	8	10	18 (3.7)	33	14
ADA unclassifiable	9 (5.5)	58	70	7 (4.6)	8	10	12 (7.2)	21	25	28 (5.8)	87	36
Not able to selftreat - unclassifiable	2 (1.2)	2	2	0			2 (1.2)	2	2	4 (0.8)	4	2

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.12. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインで正常肝機能を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	318			320			318			956		
Total exposure (yrs)	159.0			159.6			158.1			476.7		
Total events	308 (96.9)	14571	9164	305 (95.3)	16119	10101	306 (96.2)	15379	9728	919 (96.1)	46069	9665
BG confirmed	281 (88.4)	5339	3358	279 (87.2)	6483	4063	277 (87.1)	6329	4004	837 (87.6)	18151	3808
Severe or BG confirmed symptomatic	262 (82.4)	3751	2359	258 (80.6)	4792	3003	249 (78.3)	4506	2850	769 (80.4)	13049	2738
Severe or BG confirmed	282 (88.7)	5374	3380	282 (88.1)	6507	4078	280 (88.1)	6371	4030	844 (88.3)	18252	3829
NN unclassifiable	305 (95.9)	9195	5783	301 (94.1)	9612	6023	303 (95.3)	9006	5697	909 (95.1)	27813	5835
ADA												
Severe	26 (8.2)	35	22	16 (5.0)	24	15	27 (8.5)	42	27	69 (7.2)	101	21
Documented symptomatic	285 (89.6)	8747	5501	275 (85.9)	10240	6417	267 (84.0)	9312	5891	827 (86.5)	28299	5937
Asymptomatic	247 (77.7)	5531	3479	244 (76.3)	5555	3481	244 (76.7)	5758	3642	735 (76.9)	16844	3534
Probable symptomatic	48 (15.1)	119	75	42 (13.1)	211	132	52 (16.4)	175	111	142 (14.9)	505	106
Pseudo-hypoglycaemia	7 (2.2)	11	7	14 (4.4)	51	32	11 (3.5)	24	15	32 (3.3)	86	18
ADA unclassifiable	20 (6.3)	126	79	23 (7.2)	38	24	23 (7.2)	66	42	66 (6.9)	230	48
Not able to selftreat - unclassifiable	2 (0.6)	2	1	0			2 (0.6)	2	1	4 (0.4)	4	1

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.13. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインで肝機能障害を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	24			21			24			69		
Total exposure (yrs)	12.3			10.6			12.1			35.0		
Total events	24 (100.0)	1189	9681	19 (90.5)	460	4326	23 (95.8)	1141	9444	66 (95.7)	2790	7972
BG confirmed	22 (91.7)	454	3696	13 (61.9)	195	1834	22 (91.7)	444	3675	57 (82.6)	1093	3123
Severe or BG confirmed symptomatic	20 (83.3)	255	2076	12 (57.1)	98	922	20 (83.3)	352	2913	52 (75.4)	705	2014
Severe or BG confirmed	22 (91.7)	465	3786	13 (61.9)	200	1881	22 (91.7)	449	3716	57 (82.6)	1114	3183
NN unclassifiable	24 (100.0)	724	5895	18 (85.7)	260	2445	23 (95.8)	692	5727	65 (94.2)	1676	4789
ADA												
Severe	6 (25.0)	11	90	3 (14.3)	5	47	4 (16.7)	5	41	13 (18.8)	21	60
Documented symptomatic	23 (95.8)	601	4893	14 (66.7)	189	1777	21 (87.5)	771	6381	58 (84.1)	1561	4460
Asymptomatic	21 (87.5)	571	4649	15 (71.4)	265	2492	20 (83.3)	356	2946	56 (81.2)	1192	3406
Probable symptomatic	2 (8.3)	2	16	0			4 (16.7)	9	74	6 (8.7)	11	31
Pseudo-hypoglycaemia	3 (12.5)	4	33	1 (4.8)	1	9	0			4 (5.8)	5	14
ADA unclassifiable	0			0			0			0		
Not able to selftreat - unclassifiable	0			0			0			0		

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.14. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインで正常腎機能を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	272			263			277			812		
Total exposure (yrs)	136.2			131.5			138.1			405.8		
Total events	262 (96.3)	12072	8863	249 (94.7)	12866	9785	264 (95.3)	13118	9496	775 (95.4)	38056	9377
BG confirmed	238 (87.5)	4513	3313	224 (85.2)	5379	4091	240 (86.6)	5496	3979	702 (86.5)	15388	3792
Severe or BG confirmed symptomatic	220 (80.9)	3042	2233	207 (78.7)	3979	3026	213 (76.9)	3841	2781	640 (78.8)	10862	2676
Severe or BG confirmed	239 (87.9)	4550	3340	226 (85.9)	5402	4108	242 (87.4)	5536	4008	707 (87.1)	15488	3816
NN unclassifiable	259 (95.2)	7521	5521	246 (93.5)	7464	5677	261 (94.2)	7581	5488	766 (94.3)	22566	5560
ADA												
Severe	25 (9.2)	37	27	15 (5.7)	23	17	25 (9.0)	40	29	65 (8.0)	100	25
Documented symptomatic	241 (88.6)	6877	5049	221 (84.0)	8236	6264	230 (83.0)	7885	5708	692 (85.2)	22998	5667
Asymptomatic	211 (77.6)	4936	3624	203 (77.2)	4390	3339	208 (75.1)	4980	3605	622 (76.6)	14306	3525
Probable symptomatic	42 (15.4)	93	68	30 (11.4)	148	113	43 (15.5)	139	101	115 (14.2)	380	94
Pseudo-hypoglycaemia	6 (2.2)	7	5	8 (3.0)	37	28	7 (2.5)	16	12	21 (2.6)	60	15
ADA unclassifiable	19 (7.0)	121	89	19 (7.2)	32	24	20 (7.2)	57	41	58 (7.1)	210	52
Not able to selftreat - unclassifiable	1 (0.4)	1	1	0			1 (0.4)	1	1	2 (0.2)	2	0

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.15. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインで軽度腎機能障害を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	69			68			58			195		
Total exposure (yrs)	34.6			34.1			28.5			97.2		
Total events	69 (100.0)	3645	10547	66 (97.1)	3100	9081	58 (100.0)	3046	10686	193 (99.0)	9791	10073
BG confirmed	64 (92.8)	1267	3666	60 (88.2)	1080	3164	54 (93.1)	1144	4014	178 (91.3)	3491	3591
Severe or BG confirmed symptomatic	61 (88.4)	952	2755	55 (80.9)	764	2238	50 (86.2)	889	3119	166 (85.1)	2605	2680
Severe or BG confirmed	64 (92.8)	1276	3692	61 (89.7)	1086	3181	54 (93.1)	1150	4035	179 (91.8)	3512	3613
NN unclassifiable	69 (100.0)	2368	6852	64 (94.1)	2014	5900	58 (100.0)	1895	6648	191 (97.9)	6277	6458
ADA												
Severe	7 (10.1)	9	26	4 (5.9)	6	18	5 (8.6)	6	21	16 (8.2)	21	22
Documented symptomatic	66 (95.7)	2438	7054	60 (88.2)	1853	5428	52 (89.7)	1908	6694	178 (91.3)	6199	6377
Asymptomatic	56 (81.2)	1156	3345	50 (73.5)	1195	3500	49 (84.5)	1085	3807	155 (79.5)	3436	3535
Probable symptomatic	8 (11.6)	28	81	10 (14.7)	29	85	11 (19.0)	29	102	29 (14.9)	86	88
Pseudo-hypoglycaemia	4 (5.8)	8	23	6 (8.8)	13	38	4 (6.9)	8	28	14 (7.2)	29	30
ADA unclassifiable	1 (1.4)	5	14	3 (4.4)	4	12	3 (5.2)	9	32	7 (3.6)	18	19
Not able to selftreat - unclassifiable	1 (1.4)	1	3	0			1 (1.7)	1	4	2 (1.0)	2	2

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.16. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインで中等度腎機能障害を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	1			10			7			18		
Total exposure (yrs)	0.5			4.6			3.5			8.6		
Total events	1 (100.0)	43	8536	9 (90.0)	613	13375	7 (100.0)	356	10103	17 (94.4)	1012	11753
BG confirmed	1 (100.0)	13	2581	8 (80.0)	219	4778	5 (71.4)	133	3775	14 (77.8)	365	4239
Severe or BG confirmed symptomatic	1 (100.0)	12	2382	8 (80.0)	147	3207	6 (85.7)	128	3633	15 (83.3)	287	3333
Severe or BG confirmed	1 (100.0)	13	2581	8 (80.0)	219	4778	6 (85.7)	134	3803	15 (83.3)	366	4251
NN unclassifiable	1 (100.0)	30	5955	9 (90.0)	394	8597	7 (100.0)	222	6300	17 (94.4)	646	7502
ADA												
Severe	0			0			1 (14.3)	1	28	1 (5.6)	1	12
Documented symptomatic	1 (100.0)	33	6551	8 (80.0)	340	7418	6 (85.7)	290	8230	15 (83.3)	663	7700
Asymptomatic	1 (100.0)	10	1985	6 (60.0)	235	5127	7 (100.0)	49	1391	14 (77.8)	294	3414
Probable symptomatic	0			2 (20.0)	34	742	2 (28.6)	16	454	4 (22.2)	50	581
Pseudo-hypoglycaemia	0			1 (10.0)	2	44	0			1 (5.6)	2	23
ADA unclassifiable	0			1 (10.0)	2	44	0			1 (5.6)	2	23
Not able to selftreat - unclassifiable	0			0			0			0		

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.17. 治験薬投与下で発現した低血糖の要約（分類別）- ベースラインで重度腎機能障害を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

There are no data for this output.

2.7.4.7.3.1.18. 治験薬投与下で発現した低血糖の要約（分類別）- Bolus インスリン投与量調節アルゴリズムを用いた被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	200			191			206			597		
Total exposure (yrs)	100.7			95.0			102.4			298.1		
Total events	191 (95.5)	9257	9192	179 (93.7)	9551	10053	196 (95.1)	9549	9328	566 (94.8)	28357	9513
BG confirmed	172 (86.0)	3412	3388	158 (82.7)	3951	4159	173 (84.0)	3911	3821	503 (84.3)	11274	3782
Severe or BG confirmed symptomatic	157 (78.5)	2285	2269	146 (76.4)	2841	2990	154 (74.8)	2719	2656	457 (76.5)	7845	2632
Severe or BG confirmed	173 (86.5)	3445	3421	161 (84.3)	3976	4185	176 (85.4)	3951	3860	510 (85.4)	11372	3815
NN unclassifiable	188 (94.0)	5811	5770	176 (92.1)	5575	5868	194 (94.2)	5597	5468	558 (93.5)	16983	5698
ADA												
Severe	21 (10.5)	33	33	15 (7.9)	25	26	24 (11.7)	40	39	60 (10.1)	98	33
Documented symptomatic	174 (87.0)	5369	5331	156 (81.7)	5902	6212	168 (81.6)	5525	5397	498 (83.4)	16796	5635
Asymptomatic	150 (75.0)	3751	3725	142 (74.3)	3498	3682	159 (77.2)	3854	3765	451 (75.5)	11103	3725
Probable symptomatic	29 (14.5)	63	63	22 (11.5)	90	95	30 (14.6)	100	98	81 (13.6)	253	85
Pseudo-hypoglycaemia	6 (3.0)	10	10	9 (4.7)	21	22	6 (2.9)	14	14	21 (3.5)	45	15
ADA unclassifiable	13 (6.5)	30	30	11 (5.8)	15	16	9 (4.4)	15	15	33 (5.5)	60	20
Not able to selftreat - unclassifiable	1 (0.5)	1	1	0			1 (0.5)	1	1	2 (0.3)	2	1

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

2.7.4.7.3.1.19. 治験薬投与下で発現した低血糖の要約（分類別）- カーボカウントを用いた被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)				Faster aspart (post)				NovoRapid (meal)				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	142				150				136				428			
Total exposure (yrs)	70.6				75.2				67.8				213.6			
Total events	141	(99.3)	6503	9215	145	(96.7)	7028	9345	133	(97.8)	6971	10282	419	(97.9)	20502	9599
BG confirmed	131	(92.3)	2381	3374	134	(89.3)	2727	3626	126	(92.6)	2862	4221	391	(91.4)	7970	3732
Severe or BG confirmed symptomatic	125	(88.0)	1721	2439	124	(82.7)	2049	2725	115	(84.6)	2139	3155	364	(85.0)	5909	2767
Severe or BG confirmed	131	(92.3)	2394	3392	134	(89.3)	2731	3631	126	(92.6)	2869	4232	391	(91.4)	7994	3743
NN unclassifiable	141	(99.3)	4108	5821	143	(95.3)	4297	5714	132	(97.1)	4101	6049	416	(97.2)	12506	5855
ADA																
Severe	11	(7.7)	13	18	4	(2.7)	4	5	7	(5.1)	7	10	22	(5.1)	24	11
Documented symptomatic	134	(94.4)	3979	5638	133	(88.7)	4527	6019	120	(88.2)	4558	6723	387	(90.4)	13064	6117
Asymptomatic	118	(83.1)	2351	3331	117	(78.0)	2322	3088	105	(77.2)	2260	3333	340	(79.4)	6933	3246
Probable symptomatic	21	(14.8)	58	82	20	(13.3)	121	161	26	(19.1)	84	124	67	(15.7)	263	123
Pseudo-hypoglycaemia	4	(2.8)	5	7	6	(4.0)	31	41	5	(3.7)	10	15	15	(3.5)	46	22
ADA unclassifiable	7	(4.9)	96	136	12	(8.0)	23	31	14	(10.3)	51	75	33	(7.7)	170	80
Not able to selftreat - unclassifiable	1	(0.7)	1	1	0				1	(0.7)	1	1	2	(0.5)	2	1

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes episodes where subjects were able to selftreat and that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as episodes where subjects were able to selftreat but cannot be classified due to missing data.
Not able to selftreat - unclassifiable: Not able to selftreat but not classifiable as severe hypoglycaemia.

フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.4.7. 付録
3. 内因性及び外因性民族的要因
2. 4131 試験における有害事象

ノボ ノルディスク ファーマ株式会社

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	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	322			319			641			323		
Total exposure (yrs)	161.4			159.5			321.0			160.6		
Total events	222 (68.9)	595	368.6	223 (69.9)	616	386.1	445 (69.4)	1211	377.3	235 (72.8)	587	365.5
Infections and infestations	136 (42.2)	218	135.0	126 (39.5)	217	136.0	262 (40.9)	435	135.5	142 (44.0)	235	146.3
Viral upper respiratory tract infection	67 (20.8)	94	58.2	67 (21.0)	95	59.5	134 (20.9)	189	58.9	75 (23.2)	112	69.7
Upper respiratory tract infection	28 (8.7)	36	22.3	26 (8.2)	34	21.3	54 (8.4)	70	21.8	27 (8.4)	34	21.2
Influenza	21 (6.5)	22	13.6	14 (4.4)	14	8.8	35 (5.5)	36	11.2	9 (2.8)	9	5.6
Gastroenteritis	7 (2.2)	8	5.0	12 (3.8)	13	8.1	19 (3.0)	21	6.5	11 (3.4)	13	8.1
Urinary tract infection	4 (1.2)	5	3.1	7 (2.2)	9	5.6	11 (1.7)	14	4.4	7 (2.2)	7	4.4
Sinusitis	5 (1.6)	6	3.7	5 (1.6)	5	3.1	10 (1.6)	11	3.4	4 (1.2)	4	2.5
Viral infection	4 (1.2)	6	3.7	4 (1.3)	5	3.1	8 (1.2)	11	3.4	3 (0.9)	3	1.9
Pharyngitis	3 (0.9)	3	1.9	1 (0.3)	1	0.6	4 (0.6)	4	1.2	4 (1.2)	7	4.4
Gastroenteritis viral	3 (0.9)	3	1.9	0			3 (0.5)	3	0.9	7 (2.2)	7	4.4
Bronchitis	1 (0.3)	1	0.6	4 (1.3)	4	2.5	5 (0.8)	5	1.6	4 (1.2)	4	2.5
Cystitis	1 (0.3)	2	1.2	2 (0.6)	2	1.3	3 (0.5)	4	1.2	2 (0.6)	2	1.2
Rhinitis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	5 (1.5)	5	3.1
Otitis media	3 (0.9)	3	1.9	1 (0.3)	1	0.6	4 (0.6)	4	1.2	1 (0.3)	1	0.6
Respiratory tract infection viral	2 (0.6)	3	1.9	2 (0.6)	2	1.3	4 (0.6)	5	1.6	0		
Tonsillitis	2 (0.6)	4	2.5	1 (0.3)	1	0.6	3 (0.5)	5	1.6	0		
Cellulitis	2 (0.6)	2	1.2	1 (0.3)	1	0.6	3 (0.5)	3	0.9	1 (0.3)	1	0.6
Acute sinusitis	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	0		
Ear infection	1 (0.3)	2	1.2	1 (0.3)	1	0.6	2 (0.3)	3	0.9	0		
Fungal infection	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Herpes zoster	2 (0.6)	2	1.2	1 (0.3)	1	0.6	3 (0.5)	3	0.9	0		
Onychomycosis	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Otitis externa	2 (0.6)	2	1.2	1 (0.3)	1	0.6	3 (0.5)	3	0.9	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - 18 <= age at baseline < 65 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Periodontitis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	2 (0.6)	2	1.2
Tooth abscess	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Conjunctivitis	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Localised infection	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Respiratory tract infection	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Skin infection	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Subcutaneous abscess	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Varicella	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Vulvovaginal candidiasis	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Vulvovaginal mycotic infection	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Abscess limb	0			0			0			1 (0.3)	1	0.6
Adenoiditis	0			0			0			1 (0.3)	1	0.6
Angular cheilitis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Candida infection	0			0			0			1 (0.3)	1	0.6
Cytomegalovirus infection	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Diverticulitis	0			0			0			1 (0.3)	1	0.6
Epstein-Barr virus infection	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Folliculitis	0			0			0			1 (0.3)	1	0.6
Fungal skin infection	0			0			0			1 (0.3)	1	0.6
Furuncle	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Gastrointestinal viral infection	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Gingivitis	0			0			0			1 (0.3)	1	0.6
Herpes ophthalmic	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Impetigo	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Infectious mononucleosis	0			0			0			1 (0.3)	1	0.6
Labyrinthitis	0			0			0			1 (0.3)	1	0.6
Laryngitis	0			0			0			1 (0.3)	1	0.6
Lower respiratory tract infection bacterial	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Molluscum contagiosum	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		

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	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Nasopharyngitis	0				0				0				1	(0.3)	1	0.6
Oral herpes	0				0				0				1	(0.3)	1	0.6
Oral infection	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Otitis media acute	0				0				0				1	(0.3)	1	0.6
Paronychia	0				0				0				1	(0.3)	1	0.6
Pharyngitis streptococcal	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Pilonidal cyst	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Pneumonia	0				0				0				1	(0.3)	1	0.6
Pulpitis dental	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Pyelonephritis chronic	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Spermatic cord funiculitis	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Syphilis	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Tinea cruris	0				0				0				1	(0.3)	1	0.6
Urethritis	0				0				0				1	(0.3)	1	0.6
Urinary tract infection fungal	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Viral rhinitis	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Investigations	66	(20.5)	89	55.1	69	(21.6)	86	53.9	135	(21.1)	175	54.5	66	(20.4)	78	48.6
Blood glucose decreased	56	(17.4)	78	48.3	64	(20.1)	77	48.3	120	(18.7)	155	48.3	62	(19.2)	70	43.6
Blood creatinine increased	1	(0.3)	1	0.6	1	(0.3)	1	0.6	2	(0.3)	2	0.6	1	(0.3)	1	0.6
Hepatic enzyme increased	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	2	(0.6)	2	1.2
Weight increased	1	(0.3)	1	0.6	2	(0.6)	2	1.3	3	(0.5)	3	0.9	0			
Blood pressure increased	2	(0.6)	2	1.2	0				2	(0.3)	2	0.6	0			
Haemoglobin decreased	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	1	(0.3)	1	0.6
Urine albumin/creatinine ratio increased	1	(0.3)	1	0.6	1	(0.3)	1	0.6	2	(0.3)	2	0.6	0			
Alanine aminotransferase increased	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Aspartate aminotransferase increased	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Blood bilirubin increased	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Blood glucose fluctuation	0				0				0				1	(0.3)	1	0.6

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Blood potassium increased	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Blood thyroid stimulating hormone	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Blood thyroid stimulating hormone increased	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Electrocardiogram change	0			0			0			1 (0.3)	1	0.6
Haematocrit decreased	0			0			0			1 (0.3)	1	0.6
Heart rate increased	0			0			0			1 (0.3)	1	0.6
Lipids abnormal	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Protein urine present	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Transaminases increased	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Gastrointestinal disorders	33 (10.2)	48	29.7	30 (9.4)	45	28.2	63 (9.8)	93	29.0	37 (11.5)	46	28.6
Nausea	11 (3.4)	13	8.1	2 (0.6)	2	1.3	13 (2.0)	15	4.7	9 (2.8)	12	7.5
Diarrhoea	3 (0.9)	3	1.9	8 (2.5)	8	5.0	11 (1.7)	11	3.4	4 (1.2)	4	2.5
Gastritis	3 (0.9)	4	2.5	4 (1.3)	5	3.1	7 (1.1)	9	2.8	3 (0.9)	3	1.9
Vomiting	4 (1.2)	5	3.1	3 (0.9)	3	1.9	7 (1.1)	8	2.5	4 (1.2)	4	2.5
Toothache	2 (0.6)	2	1.2	4 (1.3)	4	2.5	6 (0.9)	6	1.9	2 (0.6)	2	1.2
Constipation	5 (1.6)	5	3.1	1 (0.3)	1	0.6	6 (0.9)	6	1.9	0		
Food poisoning	2 (0.6)	2	1.2	2 (0.6)	2	1.3	4 (0.6)	4	1.2	2 (0.6)	2	1.2
Gastrooesophageal reflux disease	3 (0.9)	3	1.9	0			3 (0.5)	3	0.9	3 (0.9)	3	1.9
Abdominal pain upper	1 (0.3)	1	0.6	3 (0.9)	3	1.9	4 (0.6)	4	1.2	1 (0.3)	1	0.6
Abdominal pain	0			0			0			4 (1.2)	4	2.5
Dental caries	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	1 (0.3)	1	0.6
Dyspepsia	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	1 (0.3)	1	0.6
Abdominal discomfort	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Aphthous ulcer	0			1 (0.3)	2	1.3	1 (0.2)	2	0.6	1 (0.3)	1	0.6
Hiatus hernia	0			3 (0.9)	3	1.9	3 (0.5)	3	0.9	0		
Enteritis	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Periodontal disease	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Stomatitis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Abdominal distension	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Apical granuloma	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Chronic gastritis	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Coeliac disease	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Colitis ulcerative	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Enterocolitis	0			0			0			1 (0.3)	1	0.6
Gastric polyps	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Gastric ulcer	0			0			0			1 (0.3)	1	0.6
Gastritis erosive	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Gastrointestinal disorder	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Haemorrhoids	0			0			0			1 (0.3)	1	0.6
Hyperchlorhydria	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Oral discomfort	0			0			0			1 (0.3)	1	0.6
Proctalgia	0			0			0			1 (0.3)	1	0.6
Retching	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Musculoskeletal and connective tissue disorders	28 (8.7)	35	21.7	28 (8.8)	32	20.1	56 (8.7)	67	20.9	26 (8.0)	33	20.5
Back pain	4 (1.2)	4	2.5	6 (1.9)	7	4.4	10 (1.6)	11	3.4	5 (1.5)	5	3.1
Pain in extremity	8 (2.5)	8	5.0	5 (1.6)	5	3.1	13 (2.0)	13	4.1	2 (0.6)	2	1.2
Arthralgia	2 (0.6)	2	1.2	4 (1.3)	4	2.5	6 (0.9)	6	1.9	2 (0.6)	2	1.2
Myalgia	3 (0.9)	4	2.5	1 (0.3)	1	0.6	4 (0.6)	5	1.6	2 (0.6)	2	1.2
Muscle spasms	2 (0.6)	2	1.2	1 (0.3)	1	0.6	3 (0.5)	3	0.9	3 (0.9)	3	1.9
Musculoskeletal pain	3 (0.9)	3	1.9	0			3 (0.5)	3	0.9	1 (0.3)	1	0.6
Tenosynovitis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	3 (0.9)	3	1.9
Trigger finger	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	2 (0.6)	3	1.9
Arthritis	2 (0.6)	2	1.2	0			2 (0.3)	2	0.6	1 (0.3)	1	0.6
Neck pain	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	0		
Plantar fasciitis	0			2 (0.6)	3	1.9	2 (0.3)	3	0.9	0		
Intervertebral disc disorder	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6

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Intervertebral disc protrusion	0				0				0				2	(0.6)	2	1.2
Musculoskeletal stiffness	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	1	(0.3)	1	0.6
Periarthritis	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	1	(0.3)	1	0.6
Rheumatoid arthritis	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	1	(0.3)	1	0.6
Arthropathy	0				0				0				1	(0.3)	1	0.6
Bursitis	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Collagen disorder	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Exostosis	0				0				0				1	(0.3)	1	0.6
Intervertebral disc degeneration	0				0				0				1	(0.3)	1	0.6
Joint contracture	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Joint effusion	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Joint swelling	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Muscular weakness	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Musculoskeletal chest pain	0				0				0				1	(0.3)	1	0.6
Osteoarthritis	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Osteoporotic fracture	0				0				0				1	(0.3)	1	0.6
Rheumatic disorder	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Rotator cuff syndrome	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Spinal osteoarthritis	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Spinal pain	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Tendonitis	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Nervous system disorders	20	(6.2)	20	12.4	27	(8.5)	38	23.8	47	(7.3)	58	18.1	16	(5.0)	28	17.4
Headache	3	(0.9)	3	1.9	12	(3.8)	19	11.9	15	(2.3)	22	6.9	5	(1.5)	15	9.3
Dizziness	2	(0.6)	2	1.2	4	(1.3)	5	3.1	6	(0.9)	7	2.2	3	(0.9)	4	2.5
Hypoglycaemic unconsciousness	2	(0.6)	2	1.2	3	(0.9)	3	1.9	5	(0.8)	5	1.6	2	(0.6)	2	1.2
Diabetic neuropathy	3	(0.9)	3	1.9	0				3	(0.5)	3	0.9	0			
Migraine	3	(0.9)	3	1.9	0				3	(0.5)	3	0.9	0			
Paraesthesia	1	(0.3)	1	0.6	1	(0.3)	1	0.6	2	(0.3)	2	0.6	1	(0.3)	1	0.6
Hypoglycaemic seizure	1	(0.3)	1	0.6	1	(0.3)	1	0.6	2	(0.3)	2	0.6	0			

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Lethargy	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Polyneuropathy	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Presyncope	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Syncope	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Tension headache	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Carpal tunnel syndrome	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Cerebrovascular accident	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Hypertonia	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Hypoaesthesia	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Hypoglycaemic coma	0			0			0			1 (0.3)	1	0.6
Hyporeflexia	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Neurodegenerative disorder	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Occipital neuralgia	0			0			0			1 (0.3)	1	0.6
Post herpetic neuralgia	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Tremor	0			0			0			1 (0.3)	1	0.6
Injury, poisoning and procedural complications	30 (9.3)	33	20.4	20 (6.3)	23	14.4	50 (7.8)	56	17.4	26 (8.0)	29	18.1
Wrong drug administered	7 (2.2)	8	5.0	8 (2.5)	8	5.0	15 (2.3)	16	5.0	6 (1.9)	6	3.7
Ligament sprain	3 (0.9)	3	1.9	3 (0.9)	3	1.9	6 (0.9)	6	1.9	3 (0.9)	3	1.9
Contusion	2 (0.6)	2	1.2	3 (0.9)	3	1.9	5 (0.8)	5	1.6	1 (0.3)	1	0.6
Limb injury	5 (1.6)	5	3.1	0			5 (0.8)	5	1.6	1 (0.3)	1	0.6
Fall	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	0		
Foot fracture	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	2 (0.6)	2	1.2
Muscle strain	3 (0.9)	3	1.9	0			3 (0.5)	3	0.9	0		
Skin abrasion	0			0			0			2 (0.6)	3	1.9
Hand fracture	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Laceration	2 (0.6)	2	1.2	0			2 (0.3)	2	0.6	0		
Road traffic accident	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Tendon rupture	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		

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	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Thermal burn	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Accidental underdose	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Animal bite	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Extradural haematoma	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Eyelid injury	0			0			0			1 (0.3)	1	0.6
Facial bones fracture	0			0			0			1 (0.3)	1	0.6
Femoral neck fracture	0			0			0			1 (0.3)	1	0.6
Forearm fracture	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Foreign body in eye	0			0			0			1 (0.3)	1	0.6
Heat illness	0			0			0			1 (0.3)	1	0.6
Joint dislocation	0			0			0			1 (0.3)	1	0.6
Joint injury	0			0			0			1 (0.3)	1	0.6
Ligament rupture	0			0			0			1 (0.3)	1	0.6
Post procedural discharge	0			0			0			1 (0.3)	1	0.6
Postoperative ileus	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Radius fracture	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Skull fractured base	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Tooth fracture	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Traumatic fracture	0			0			0			1 (0.3)	1	0.6
Wound	0			0			0			1 (0.3)	1	0.6
Wrist fracture	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
General disorders and administration site conditions	20 (6.2)	26	16.1	24 (7.5)	31	19.4	44 (6.9)	57	17.8	17 (5.3)	26	16.2
Influenza like illness	5 (1.6)	7	4.3	4 (1.3)	4	2.5	9 (1.4)	11	3.4	4 (1.2)	6	3.7
Pyrexia	6 (1.9)	6	3.7	7 (2.2)	7	4.4	13 (2.0)	13	4.1	2 (0.6)	2	1.2
Injection site haematoma	2 (0.6)	2	1.2	2 (0.6)	4	2.5	4 (0.6)	6	1.9	2 (0.6)	4	2.5
Injection site bruising	1 (0.3)	2	1.2	2 (0.6)	2	1.3	3 (0.5)	4	1.2	0		
Injection site pain	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	2 (0.6)	2	1.2
Injection site reaction	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	2 (0.6)	3	1.9

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Chest pain	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	2 (0.6)	2	1.2
Fatigue	0			2 (0.6)	3	1.9	2 (0.3)	3	0.9	0		
Injection site hypertrophy	2 (0.6)	2	1.2	1 (0.3)	1	0.6	3 (0.5)	3	0.9	0		
Oedema peripheral	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Chest discomfort	0			0			0			2 (0.6)	2	1.2
Malaise	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Administration site induration	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Asthenia	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Drug therapeutic incompatibility	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Feeling abnormal	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
General symptom	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Inflammation	0			0			0			1 (0.3)	1	0.6
Injection site haemorrhage	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Injection site hypersensitivity	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Injection site induration	0			0			0			1 (0.3)	1	0.6
Injection site rash	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Injection site swelling	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Pain	0			0			0			1 (0.3)	1	0.6
Peripheral swelling	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Metabolism and nutrition disorders	28 (8.7)	29	18.0	16 (5.0)	22	13.8	44 (6.9)	51	15.9	20 (6.2)	22	13.7
Hypoglycaemia	20 (6.2)	21	13.0	6 (1.9)	9	5.6	26 (4.1)	30	9.3	12 (3.7)	13	8.1
Hyperglycaemia	2 (0.6)	2	1.2	1 (0.3)	1	0.6	3 (0.5)	3	0.9	2 (0.6)	3	1.9
Diabetic metabolic decompensation	2 (0.6)	2	1.2	1 (0.3)	1	0.6	3 (0.5)	3	0.9	1 (0.3)	1	0.6
Hyperlipidaemia	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	1 (0.3)	1	0.6
Vitamin D deficiency	0			3 (0.9)	3	1.9	3 (0.5)	3	0.9	0		
Decreased appetite	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Dehydration	2 (0.6)	2	1.2	0			2 (0.3)	2	0.6	0		
Hypertriglyceridaemia	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Hypoglycaemia unawareness	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Hypokalaemia	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Fluid retention	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Gout	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Hypercholesterolaemia	0			0			0			1 (0.3)	1	0.6
Eye disorders	15 (4.7)	16	9.9	26 (8.2)	32	20.1	41 (6.4)	48	15.0	21 (6.5)	23	14.3
Diabetic retinopathy	5 (1.6)	5	3.1	12 (3.8)	12	7.5	17 (2.7)	17	5.3	7 (2.2)	7	4.4
Macular oedema	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	2 (0.6)	2	1.2
Retinopathy	2 (0.6)	2	1.2	0			2 (0.3)	2	0.6	2 (0.6)	2	1.2
Retinal tear	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	2 (0.6)	2	1.2
Retinopathy hypertensive	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Dry eye	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Retinal aneurysm	2 (0.6)	2	1.2	0			2 (0.3)	2	0.6	0		
Retinopathy proliferative	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Vitreous haemorrhage	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Astigmatism	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Blepharochalasis	0			0			0			1 (0.3)	1	0.6
Cataract	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Cataract nuclear	0			0			0			1 (0.3)	1	0.6
Chalazion	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Conjunctival haemorrhage	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Conjunctivitis allergic	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Cystoid macular oedema	0			0			0			1 (0.3)	1	0.6
Eye disorder	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Eye inflammation	0			0			0			1 (0.3)	1	0.6
Eye pruritus	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Eye ulcer	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Glaucoma	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Iritis	0			0			0			1 (0.3)	1	0.6
Maculopathy	0			0			0			1 (0.3)	1	0.6

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Myopia	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Normal tension glaucoma	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Ocular discomfort	0			0			0			1 (0.3)	1	0.6
Ocular hypertension	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Retinal exudates	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Retinal haemorrhage	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Retinal ischaemia	0			0			0			1 (0.3)	1	0.6
Visual acuity reduced transiently	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Visual impairment	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Vitreous detachment	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Skin and subcutaneous tissue disorders	16 (5.0)	20	12.4	22 (6.9)	24	15.0	38 (5.9)	44	13.7	17 (5.3)	18	11.2
Dermatitis	1 (0.3)	3	1.9	4 (1.3)	4	2.5	5 (0.8)	7	2.2	0		
Urticaria	2 (0.6)	2	1.2	3 (0.9)	3	1.9	5 (0.8)	5	1.6	2 (0.6)	2	1.2
Lipohypertrophy	2 (0.6)	2	1.2	3 (0.9)	3	1.9	5 (0.8)	5	1.6	0		
Dermatitis contact	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	2 (0.6)	2	1.2
Dry skin	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Eczema	2 (0.6)	2	1.2	0			2 (0.3)	2	0.6	1 (0.3)	1	0.6
Pruritus	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Ecchymosis	0			0			0			1 (0.3)	2	1.2
Rash	0			0			0			2 (0.6)	2	1.2
Skin ulcer	2 (0.6)	2	1.2	0			2 (0.3)	2	0.6	0		
Acne cystic	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Alopecia	0			0			0			1 (0.3)	1	0.6
Asteatosis	0			0			0			1 (0.3)	1	0.6
Blister	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Blood blister	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Dermal cyst	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Dermatitis atopic	0			0			0			1 (0.3)	1	0.6
Hidradenitis	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Lipodystrophy acquired	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Miliaria	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Nail bed inflammation	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Nail disorder	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Nail pigmentation	0			0			0			1 (0.3)	1	0.6
Onychomadesis	0			0			0			1 (0.3)	1	0.6
Papule	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Parapsoriasis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Rash erythematous	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Rash papular	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Rash pruritic	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Skin exfoliation	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Skin fissures	0			0			0			1 (0.3)	1	0.6
Skin lesion	0			0			0			1 (0.3)	1	0.6
Skin mass	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Skin reaction	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Xeroderma	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Respiratory, thoracic and mediastinal disorders	18 (5.6)	20	12.4	18 (5.6)	21	13.2	36 (5.6)	41	12.8	18 (5.6)	19	11.8
Oropharyngeal pain	3 (0.9)	3	1.9	3 (0.9)	3	1.9	6 (0.9)	6	1.9	6 (1.9)	7	4.4
Cough	1 (0.3)	1	0.6	5 (1.6)	5	3.1	6 (0.9)	6	1.9	1 (0.3)	1	0.6
Rhinorrhoea	2 (0.6)	2	1.2	1 (0.3)	1	0.6	3 (0.5)	3	0.9	2 (0.6)	2	1.2
Sinus congestion	3 (0.9)	3	1.9	2 (0.6)	2	1.3	5 (0.8)	5	1.6	0		
Asthma	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	2 (0.6)	2	1.2
Nasal congestion	3 (0.9)	3	1.9	1 (0.3)	1	0.6	4 (0.6)	4	1.2	0		
Rhinitis allergic	2 (0.6)	2	1.2	1 (0.3)	1	0.6	3 (0.5)	3	0.9	1 (0.3)	1	0.6
Upper respiratory tract inflammation	0			2 (0.6)	3	1.9	2 (0.3)	3	0.9	1 (0.3)	1	0.6
Epistaxis	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Respiratory disorder	2 (0.6)	2	1.2	1 (0.3)	1	0.6	3 (0.5)	3	0.9	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - 18 <= age at baseline < 65 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Dyspnoea	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Throat irritation	0			0			0			2 (0.6)	2	1.2
Chronic obstructive pulmonary disease	0			0			0			1 (0.3)	1	0.6
Paranasal sinus discomfort	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Tonsillar hypertrophy	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Upper respiratory tract congestion	0			0			0			1 (0.3)	1	0.6
Psychiatric disorders	6 (1.9)	7	4.3	8 (2.5)	9	5.6	14 (2.2)	16	5.0	1 (0.3)	1	0.6
Depression	4 (1.2)	4	2.5	3 (0.9)	3	1.9	7 (1.1)	7	2.2	0		
Insomnia	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Stress	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	0		
Anxiety	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Affective disorder	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Sleep disorder	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Renal and urinary disorders	4 (1.2)	4	2.5	7 (2.2)	7	4.4	11 (1.7)	11	3.4	4 (1.2)	6	3.7
Haematuria	1 (0.3)	1	0.6	3 (0.9)	3	1.9	4 (0.6)	4	1.2	1 (0.3)	1	0.6
Microalbuminuria	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	3 (0.9)	4	2.5
Acute kidney injury	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Bladder pain	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Crystalluria	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Dysuria	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Nephrolithiasis	0			0			0			1 (0.3)	1	0.6
Renal cyst	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Renal failure	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Vascular disorders	6 (1.9)	6	3.7	4 (1.3)	4	2.5	10 (1.6)	10	3.1	4 (1.2)	4	2.5
Hypertension	3 (0.9)	3	1.9	3 (0.9)	3	1.9	6 (0.9)	6	1.9	1 (0.3)	1	0.6
Hypotension	0			0			0			2 (0.6)	2	1.2
Orthostatic hypotension	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - 18 <= age at baseline < 65 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Arteriosclerosis	0			0			0			1 (0.3)	1	0.6
Peripheral arterial occlusive disease	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Thrombophlebitis superficial	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Blood and lymphatic system disorders	7 (2.2)	7	4.3	0			7 (1.1)	7	2.2	5 (1.5)	5	3.1
Anaemia	3 (0.9)	3	1.9	0			3 (0.5)	3	0.9	4 (1.2)	4	2.5
Iron deficiency anaemia	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Lymphadenopathy	2 (0.6)	2	1.2	0			2 (0.3)	2	0.6	0		
Leukopenia	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Reproductive system and breast disorders	3 (0.9)	3	1.9	3 (0.9)	5	3.1	6 (0.9)	8	2.5	2 (0.6)	2	1.2
Dysmenorrhoea	0			1 (0.3)	2	1.3	1 (0.2)	2	0.6	0		
Priapism	0			1 (0.3)	2	1.3	1 (0.2)	2	0.6	0		
Breast tenderness	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Endometriosis	0			0			0			1 (0.3)	1	0.6
Genital haemorrhage	0			0			0			1 (0.3)	1	0.6
Gynaecomastia	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Testicular swelling	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Vulvovaginal inflammation	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Ear and labyrinth disorders	3 (0.9)	3	1.9	3 (0.9)	4	2.5	6 (0.9)	7	2.2	2 (0.6)	2	1.2
Ear discomfort	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Ear pain	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Tinnitus	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Sudden hearing loss	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Tympanic membrane perforation	0			0			0			1 (0.3)	1	0.6
Vertigo	0			0			0			1 (0.3)	1	0.6
Immune system disorders	1 (0.3)	1	0.6	4 (1.3)	6	3.8	5 (0.8)	7	2.2	2 (0.6)	2	1.2
Seasonal allergy	0			3 (0.9)	3	1.9	3 (0.5)	3	0.9	1 (0.3)	1	0.6

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Hypersensitivity	0			1 (0.3)	3	1.9	1 (0.2)	3	0.9	0		
Multiple allergies	0			0			0			1 (0.3)	1	0.6
Mycotic allergy	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Cardiac disorders	3 (0.9)	3	1.9	3 (0.9)	3	1.9	6 (0.9)	6	1.9	1 (0.3)	1	0.6
Palpitations	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Coronary artery disease	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Extrasystoles	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Myocardial ischaemia	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Sinus bradycardia	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Ventricular extrasystoles	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Endocrine disorders	1 (0.3)	1	0.6	3 (0.9)	4	2.5	4 (0.6)	5	1.6	2 (0.6)	2	1.2
Goitre	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	2 (0.6)	2	1.2
Hypothyroidism	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Hyperadrenalism	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Thyroid cyst	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Hepatobiliary disorders	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	2 (0.6)	2	1.2
Hepatic steatosis	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Cholecystitis	0			0			0			1 (0.3)	1	0.6
Gallbladder polyp	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	1 (0.3)	1	0.6
Haemangioma of liver	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Conjunctival neoplasm	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Skin papilloma	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Surgical and medical procedures	2 (0.6)	2	1.2	0			2 (0.3)	2	0.6	2 (0.6)	2	1.2

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Cataract operation	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Endodontic procedure	0			0			0			1 (0.3)	1	0.6
Haemorrhoid operation	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Tooth extraction	0			0			0			1 (0.3)	1	0.6
Congenital, familial and genetic disorders	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Accessory spleen	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Pregnancy, puerperium and perinatal conditions	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Subchorionic haemorrhage	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		

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2.7.4.7.3.2.2. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインの年齢が 65 歳以上の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	20			22			42			19		
Total exposure (yrs)	9.8			10.7			20.5			9.6		
Total events	18 (90.0)	54	548.9	14 (63.6)	40	374.8	32 (76.2)	94	458.3	13 (68.4)	40	418.3
Infections and infestations	10 (50.0)	15	152.5	4 (18.2)	7	65.6	14 (33.3)	22	107.3	7 (36.8)	9	94.1
Viral upper respiratory tract infection	6 (30.0)	7	71.2	3 (13.6)	5	46.9	9 (21.4)	12	58.5	5 (26.3)	6	62.7
Rhinitis	2 (10.0)	2	20.3	0			2 (4.8)	2	9.8	0		
Upper respiratory tract infection	2 (10.0)	2	20.3	0			2 (4.8)	2	9.8	0		
Urinary tract infection	2 (10.0)	2	20.3	0			2 (4.8)	2	9.8	0		
Empyema	0			1 (4.5)	1	9.4	1 (2.4)	1	4.9	0		
Gastroenteritis	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Influenza	0			0			0			1 (5.3)	1	10.5
Lower respiratory tract infection	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Otitis externa	0			1 (4.5)	1	9.4	1 (2.4)	1	4.9	0		
Pharyngitis	0			0			0			1 (5.3)	1	10.5
Pneumonia	0			0			0			1 (5.3)	1	10.5
Investigations	3 (15.0)	4	40.7	4 (18.2)	8	75.0	7 (16.7)	12	58.5	7 (36.8)	13	135.9
Blood glucose decreased	2 (10.0)	3	30.5	3 (13.6)	6	56.2	5 (11.9)	9	43.9	6 (31.6)	12	125.5
Blood 1,5-anhydroglucitol decreased	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Blood pressure increased	0			0			0			1 (5.3)	1	10.5
Blood urine present	0			1 (4.5)	1	9.4	1 (2.4)	1	4.9	0		
Helicobacter test positive	0			1 (4.5)	1	9.4	1 (2.4)	1	4.9	0		
Injury, poisoning and procedural complications	4 (20.0)	7	71.2	5 (22.7)	9	84.3	9 (21.4)	16	78.0	2 (10.5)	2	20.9
Wrong drug administered	1 (5.0)	1	10.2	3 (13.6)	6	56.2	4 (9.5)	7	34.1	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - age at baseline >= 65 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Tooth fracture	2 (10.0)	2	20.3	0			2 (4.8)	2	9.8	1 (5.3)	1	10.5
Fall	1 (5.0)	1	10.2	1 (4.5)	1	9.4	2 (4.8)	2	9.8	0		
Accidental overdose	0			1 (4.5)	1	9.4	1 (2.4)	1	4.9	0		
Buttock injury	0			1 (4.5)	1	9.4	1 (2.4)	1	4.9	0		
Laceration	0			0			0			1 (5.3)	1	10.5
Muscle strain	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Radius fracture	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Ulna fracture	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Musculoskeletal and connective tissue disorders	3 (15.0)	3	30.5	3 (13.6)	3	28.1	6 (14.3)	6	29.3	4 (21.1)	6	62.7
Back pain	0			1 (4.5)	1	9.4	1 (2.4)	1	4.9	1 (5.3)	1	10.5
Muscle spasms	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	1 (5.3)	1	10.5
Myalgia	0			0			0			1 (5.3)	2	20.9
Arthralgia	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Flank pain	0			1 (4.5)	1	9.4	1 (2.4)	1	4.9	0		
Lumbar spinal stenosis	0			1 (4.5)	1	9.4	1 (2.4)	1	4.9	0		
Musculoskeletal pain	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Myositis	0			0			0			1 (5.3)	1	10.5
Pain in extremity	0			0			0			1 (5.3)	1	10.5
General disorders and administration site conditions	5 (25.0)	5	50.8	1 (4.5)	4	37.5	6 (14.3)	9	43.9	1 (5.3)	1	10.5
Oedema peripheral	0			1 (4.5)	1	9.4	1 (2.4)	1	4.9	1 (5.3)	1	10.5
Pyrexia	2 (10.0)	2	20.3	0			2 (4.8)	2	9.8	0		
Asthenia	0			1 (4.5)	1	9.4	1 (2.4)	1	4.9	0		
Fatigue	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Malaise	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Oedema	0			1 (4.5)	1	9.4	1 (2.4)	1	4.9	0		
Pain	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - age at baseline >= 65 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Peripheral swelling	0				1	(4.5)	1	9.4	1	(2.4)	1	4.9	0			
Gastrointestinal disorders	3	(15.0)	4	40.7	3	(13.6)	3	28.1	6	(14.3)	7	34.1	2	(10.5)	2	20.9
Diarrhoea	0				1	(4.5)	1	9.4	1	(2.4)	1	4.9	1	(5.3)	1	10.5
Nausea	1	(5.0)	1	10.2	1	(4.5)	1	9.4	2	(4.8)	2	9.8	0			
Abdominal discomfort	0				0				0				1	(5.3)	1	10.5
Abdominal distension	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Chronic gastritis	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Gastritis	0				1	(4.5)	1	9.4	1	(2.4)	1	4.9	0			
Toothache	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Nervous system disorders	2	(10.0)	6	61.0	1	(4.5)	1	9.4	3	(7.1)	7	34.1	2	(10.5)	2	20.9
Headache	1	(5.0)	3	30.5	0				1	(2.4)	3	14.6	0			
Hypoaesthesia	0				1	(4.5)	1	9.4	1	(2.4)	1	4.9	1	(5.3)	1	10.5
Carotid arteriosclerosis	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Hypoglycaemic seizure	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Lumbar radiculopathy	0				0				0				1	(5.3)	1	10.5
Memory impairment	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Eye disorders	2	(10.0)	2	20.3	2	(9.1)	2	18.7	4	(9.5)	4	19.5	0			
Diabetic retinopathy	2	(10.0)	2	20.3	0				2	(4.8)	2	9.8	0			
Eyelid oedema	0				1	(4.5)	1	9.4	1	(2.4)	1	4.9	0			
Lacrimation increased	0				1	(4.5)	1	9.4	1	(2.4)	1	4.9	0			
Skin and subcutaneous tissue disorders	2	(10.0)	3	30.5	0				2	(4.8)	3	14.6	1	(5.3)	1	10.5
Actinic keratosis	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Dermatitis atopic	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Eczema asteatotic	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Skin ulcer	0				0				0				1	(5.3)	1	10.5

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - age at baseline >= 65 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Respiratory, thoracic and mediastinal disorders	1	(5.0)	1	10.2	1	(4.5)	1	9.4	2	(4.8)	2	9.8	1	(5.3)	1	10.5
Oropharyngeal pain	0				1	(4.5)	1	9.4	1	(2.4)	1	4.9	0			
Pleurisy	0				0				0				1	(5.3)	1	10.5
Sinus congestion	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Metabolism and nutrition disorders	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	1	(5.3)	1	10.5
Hyperlipidaemia	0				0				0				1	(5.3)	1	10.5
Hypoglycaemia	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Ear and labyrinth disorders	0				1	(4.5)	1	9.4	1	(2.4)	1	4.9	0			
Vertigo	0				1	(4.5)	1	9.4	1	(2.4)	1	4.9	0			
Immune system disorders	0				0				0				1	(5.3)	1	10.5
Hypersensitivity	0				0				0				1	(5.3)	1	10.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Bladder transitional cell carcinoma	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Psychiatric disorders	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Insomnia	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Reproductive system and breast disorders	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Benign prostatic hyperplasia	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9	0			
Surgical and medical procedures	0				0				0				1	(5.3)	1	10.5
Inguinal hernia repair	0				0				0				1	(5.3)	1	10.5
Vascular disorders	0				1	(4.5)	1	9.4	1	(2.4)	1	4.9	0			

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Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - age at baseline >= 65 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hypertension	0				1	(4.5)	1	9.4	1	(2.4)	1	4.9	0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
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2.7.4.7.3.2.3. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- 女性被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	158			155			313			163		
Total exposure (yrs)	78.7			77.5			156.3			80.1		
Total events	110 (69.6)	298	378.4	110 (71.0)	345	445.1	220 (70.3)	643	411.5	117 (71.8)	333	415.8
Infections and infestations	63 (39.9)	105	133.3	61 (39.4)	111	143.2	124 (39.6)	216	138.2	73 (44.8)	126	157.3
Viral upper respiratory tract infection	33 (20.9)	49	62.2	30 (19.4)	45	58.1	63 (20.1)	94	60.2	43 (26.4)	61	76.2
Upper respiratory tract infection	9 (5.7)	11	14.0	12 (7.7)	13	16.8	21 (6.7)	24	15.4	12 (7.4)	18	22.5
Urinary tract infection	5 (3.2)	6	7.6	7 (4.5)	9	11.6	12 (3.8)	15	9.6	6 (3.7)	6	7.5
Influenza	8 (5.1)	9	11.4	6 (3.9)	6	7.7	14 (4.5)	15	9.6	3 (1.8)	3	3.7
Gastroenteritis	2 (1.3)	2	2.5	7 (4.5)	8	10.3	9 (2.9)	10	6.4	7 (4.3)	7	8.7
Pharyngitis	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	2 (1.2)	5	6.2
Sinusitis	3 (1.9)	4	5.1	3 (1.9)	3	3.9	6 (1.9)	7	4.5	0		
Cystitis	1 (0.6)	2	2.5	2 (1.3)	2	2.6	3 (1.0)	4	2.6	2 (1.2)	2	2.5
Viral infection	2 (1.3)	3	3.8	2 (1.3)	2	2.6	4 (1.3)	5	3.2	1 (0.6)	1	1.2
Bronchitis	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	3 (1.8)	3	3.7
Rhinitis	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	3 (1.8)	3	3.7
Tonsillitis	1 (0.6)	3	3.8	1 (0.6)	1	1.3	2 (0.6)	4	2.6	0		
Gastroenteritis viral	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	2 (1.2)	2	2.5
Otitis externa	1 (0.6)	1	1.3	2 (1.3)	2	2.6	3 (1.0)	3	1.9	0		
Otitis media	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	1 (0.6)	1	1.2
Respiratory tract infection viral	1 (0.6)	1	1.3	2 (1.3)	2	2.6	3 (1.0)	3	1.9	0		
Acute sinusitis	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Ear infection	1 (0.6)	2	2.5	0			1 (0.3)	2	1.3	0		
Fungal infection	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Herpes zoster	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	0		
Periodontitis	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Pneumonia	0			0			0			2 (1.2)	2	2.5

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Adverse events by system organ class and preferred term - treatment emergent - summary - female - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Vulvovaginal candidiasis	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Vulvovaginal mycotic infection	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Abscess limb	0			0			0			1 (0.6)	1	1.2
Adenoiditis	0			0			0			1 (0.6)	1	1.2
Angular cheilitis	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Candida infection	0			0			0			1 (0.6)	1	1.2
Conjunctivitis	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Empyema	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Folliculitis	0			0			0			1 (0.6)	1	1.2
Furuncle	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Gastrointestinal viral infection	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Herpes ophthalmic	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Laryngitis	0			0			0			1 (0.6)	1	1.2
Molluscum contagiosum	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Nasopharyngitis	0			0			0			1 (0.6)	1	1.2
Paronychia	0			0			0			1 (0.6)	1	1.2
Pharyngitis streptococcal	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Pulpitis dental	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Pyelonephritis chronic	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Respiratory tract infection	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Subcutaneous abscess	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Tooth abscess	0			0			0			1 (0.6)	1	1.2
Varicella	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Viral rhinitis	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Investigations	31 (19.6)	46	58.4	39 (25.2)	52	67.1	70 (22.4)	98	62.7	34 (20.9)	42	52.4
Blood glucose decreased	28 (17.7)	42	53.3	36 (23.2)	48	61.9	64 (20.4)	90	57.6	32 (19.6)	40	49.9
Blood pressure increased	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Weight increased	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	0		
Blood glucose fluctuation	0			0			0			1 (0.6)	1	1.2

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Blood urine present	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Haemoglobin decreased	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Helicobacter test positive	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Hepatic enzyme increased	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Urine albumin/creatinine ratio increased	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Gastrointestinal disorders	20 (12.7)	32	40.6	20 (12.9)	26	33.5	40 (12.8)	58	37.1	21 (12.9)	28	35.0
Nausea	8 (5.1)	10	12.7	2 (1.3)	2	2.6	10 (3.2)	12	7.7	6 (3.7)	9	11.2
Diarrhoea	2 (1.3)	2	2.5	6 (3.9)	6	7.7	8 (2.6)	8	5.1	3 (1.8)	3	3.7
Gastritis	2 (1.3)	3	3.8	3 (1.9)	3	3.9	5 (1.6)	6	3.8	3 (1.8)	3	3.7
Vomiting	1 (0.6)	1	1.3	3 (1.9)	3	3.9	4 (1.3)	4	2.6	3 (1.8)	3	3.7
Constipation	3 (1.9)	3	3.8	1 (0.6)	1	1.3	4 (1.3)	4	2.6	0		
Abdominal pain upper	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	1 (0.6)	1	1.2
Aphthous ulcer	0			1 (0.6)	2	2.6	1 (0.3)	2	1.3	1 (0.6)	1	1.2
Dental caries	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	1 (0.6)	1	1.2
Food poisoning	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	1 (0.6)	1	1.2
Abdominal discomfort	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Chronic gastritis	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	0		
Gastrooesophageal reflux disease	2 (1.3)	2	2.5	0			2 (0.6)	2	1.3	0		
Hiatus hernia	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Toothache	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Abdominal distension	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Abdominal pain	0			0			0			1 (0.6)	1	1.2
Coeliac disease	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Colitis ulcerative	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Dyspepsia	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Enteritis	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Enterocolitis	0			0			0			1 (0.6)	1	1.2
Gastric polyps	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - female - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Gastrointestinal disorder	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Oral discomfort	0			0			0			1 (0.6)	1	1.2
Periodontal disease	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Stomatitis	0			0			0			1 (0.6)	1	1.2
Musculoskeletal and connective tissue disorders	17 (10.8)	19	24.1	16 (10.3)	19	24.5	33 (10.5)	38	24.3	18 (11.0)	26	32.5
Back pain	2 (1.3)	2	2.5	5 (3.2)	6	7.7	7 (2.2)	8	5.1	2 (1.2)	2	2.5
Pain in extremity	6 (3.8)	6	7.6	1 (0.6)	1	1.3	7 (2.2)	7	4.5	1 (0.6)	1	1.2
Arthralgia	3 (1.9)	3	3.8	2 (1.3)	2	2.6	5 (1.6)	5	3.2	1 (0.6)	1	1.2
Muscle spasms	0			0			0			4 (2.5)	4	5.0
Myalgia	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	2 (1.2)	3	3.7
Tenosynovitis	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	2 (1.2)	2	2.5
Arthritis	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Intervertebral disc protrusion	0			0			0			2 (1.2)	2	2.5
Neck pain	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Periarthritis	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Rheumatoid arthritis	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Trigger finger	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Arthropathy	0			0			0			1 (0.6)	1	1.2
Collagen disorder	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Exostosis	0			0			0			1 (0.6)	1	1.2
Flank pain	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Intervertebral disc disorder	0			0			0			1 (0.6)	1	1.2
Joint contracture	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Joint effusion	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Joint swelling	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Lumbar spinal stenosis	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Musculoskeletal chest pain	0			0			0			1 (0.6)	1	1.2
Musculoskeletal pain	0			0			0			1 (0.6)	1	1.2

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Musculoskeletal stiffness	0			0			0			1 (0.6)	1	1.2
Myositis	0			0			0			1 (0.6)	1	1.2
Osteoarthritis	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Plantar fasciitis	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Rheumatic disorder	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Spinal pain	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Nervous system disorders	11 (7.0)	11	14.0	15 (9.7)	23	29.7	26 (8.3)	34	21.8	13 (8.0)	25	31.2
Headache	2 (1.3)	2	2.5	5 (3.2)	11	14.2	7 (2.2)	13	8.3	5 (3.1)	15	18.7
Dizziness	1 (0.6)	1	1.3	3 (1.9)	4	5.2	4 (1.3)	5	3.2	2 (1.2)	3	3.7
Hypoglycaemic unconsciousness	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	2 (1.2)	2	2.5
Hypoaesthesia	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	1 (0.6)	1	1.2
Migraine	3 (1.9)	3	3.8	0			3 (1.0)	3	1.9	0		
Diabetic neuropathy	2 (1.3)	2	2.5	0			2 (0.6)	2	1.3	0		
Carotid arteriosclerosis	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Carpal tunnel syndrome	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Cerebrovascular accident	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Hypoglycaemic coma	0			0			0			1 (0.6)	1	1.2
Lethargy	0			0			0			1 (0.6)	1	1.2
Neurodegenerative disorder	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Occipital neuralgia	0			0			0			1 (0.6)	1	1.2
Paraesthesia	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Polyneuropathy	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Post herpetic neuralgia	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Syncope	0			0			0			1 (0.6)	1	1.2
General disorders and administration site conditions	10 (6.3)	11	14.0	12 (7.7)	19	24.5	22 (7.0)	30	19.2	11 (6.7)	19	23.7
Influenza like illness	2 (1.3)	2	2.5	2 (1.3)	2	2.6	4 (1.3)	4	2.6	4 (2.5)	6	7.5
Pyrexia	5 (3.2)	5	6.3	3 (1.9)	3	3.9	8 (2.6)	8	5.1	2 (1.2)	2	2.5

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Adverse events by system organ class and preferred term - treatment emergent - summary - female - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Injection site haematoma	0			2 (1.3)	4	5.2	2 (0.6)	4	2.6	1 (0.6)	3	3.7
Injection site reaction	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	2	2.5
Oedema peripheral	1 (0.6)	1	1.3	2 (1.3)	2	2.6	3 (1.0)	3	1.9	0		
Asthenia	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Administration site induration	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Chest discomfort	0			0			0			1 (0.6)	1	1.2
Chest pain	0			0			0			1 (0.6)	1	1.2
General symptom	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Injection site hypersensitivity	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Injection site hypertrophy	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Injection site induration	0			0			0			1 (0.6)	1	1.2
Injection site pain	0			0			0			1 (0.6)	1	1.2
Injection site rash	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Injection site swelling	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Malaise	0			0			0			1 (0.6)	1	1.2
Oedema	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Pain	0			0			0			1 (0.6)	1	1.2
Peripheral swelling	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Injury, poisoning and procedural complications	16 (10.1)	19	24.1	12 (7.7)	15	19.4	28 (8.9)	34	21.8	12 (7.4)	14	17.5
Wrong drug administered	3 (1.9)	3	3.8	5 (3.2)	6	7.7	8 (2.6)	9	5.8	2 (1.2)	2	2.5
Fall	2 (1.3)	2	2.5	2 (1.3)	2	2.6	4 (1.3)	4	2.6	0		
Ligament sprain	2 (1.3)	2	2.5	1 (0.6)	1	1.3	3 (1.0)	3	1.9	1 (0.6)	1	1.2
Limb injury	4 (2.5)	4	5.1	0			4 (1.3)	4	2.6	0		
Contusion	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	1 (0.6)	1	1.2
Skin abrasion	0			0			0			2 (1.2)	3	3.7
Foot fracture	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Hand fracture	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Radius fracture	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Tooth fracture	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Accidental underdose	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Femoral neck fracture	0			0			0			1 (0.6)	1	1.2
Joint dislocation	0			0			0			1 (0.6)	1	1.2
Laceration	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Post procedural discharge	0			0			0			1 (0.6)	1	1.2
Postoperative ileus	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Tendon rupture	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Thermal burn	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Ulna fracture	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Wound	0			0			0			1 (0.6)	1	1.2
Wrist fracture	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Eye disorders	10 (6.3)	11	14.0	14 (9.0)	15	19.4	24 (7.7)	26	16.6	10 (6.1)	11	13.7
Diabetic retinopathy	5 (3.2)	5	6.3	7 (4.5)	7	9.0	12 (3.8)	12	7.7	4 (2.5)	4	5.0
Dry eye	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Macular oedema	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Retinopathy	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Retinopathy proliferative	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Cataract nuclear	0			0			0			1 (0.6)	1	1.2
Chalazion	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Conjunctival haemorrhage	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Cystoid macular oedema	0			0			0			1 (0.6)	1	1.2
Eye inflammation	0			0			0			1 (0.6)	1	1.2
Eyelid oedema	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Glaucoma	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Lacrimation increased	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Ocular hypertension	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Retinal ischaemia	0			0			0			1 (0.6)	1	1.2
Retinal tear	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Visual acuity reduced transiently	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Vitreous haemorrhage	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Respiratory, thoracic and mediastinal disorders	6 (3.8)	7	8.9	13 (8.4)	16	20.6	19 (6.1)	23	14.7	10 (6.1)	10	12.5
Oropharyngeal pain	2 (1.3)	2	2.5	3 (1.9)	3	3.9	5 (1.6)	5	3.2	4 (2.5)	4	5.0
Cough	0			4 (2.6)	4	5.2	4 (1.3)	4	2.6	1 (0.6)	1	1.2
Asthma	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	2 (1.2)	2	2.5
Rhinitis allergic	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	1 (0.6)	1	1.2
Nasal congestion	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	0		
Respiratory disorder	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	0		
Sinus congestion	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	0		
Upper respiratory tract inflammation	0			1 (0.6)	2	2.6	1 (0.3)	2	1.3	0		
Epistaxis	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Paranasal sinus discomfort	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Pleurisy	0			0			0			1 (0.6)	1	1.2
Rhinorrhoea	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Throat irritation	0			0			0			1 (0.6)	1	1.2
Metabolism and nutrition disorders	10 (6.3)	10	12.7	7 (4.5)	10	12.9	17 (5.4)	20	12.8	8 (4.9)	9	11.2
Hypoglycaemia	7 (4.4)	7	8.9	1 (0.6)	1	1.3	8 (2.6)	8	5.1	4 (2.5)	4	5.0
Hyperglycaemia	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	1 (0.6)	2	2.5
Dehydration	2 (1.3)	2	2.5	0			2 (0.6)	2	1.3	0		
Hyperlipidaemia	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Hypoglycaemia unawareness	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Vitamin D deficiency	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Decreased appetite	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Diabetic metabolic decompensation	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Fluid retention	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Hypercholesterolaemia	0			0			0			1 (0.6)	1	1.2

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Hypertriglyceridaemia	0			0			0			1 (0.6)	1	1.2
Skin and subcutaneous tissue disorders	6 (3.8)	7	8.9	9 (5.8)	11	14.2	15 (4.8)	18	11.5	9 (5.5)	9	11.2
Urticaria	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	2 (1.2)	2	2.5
Dermatitis atopic	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Dermatitis contact	0			0			0			2 (1.2)	2	2.5
Lipohypertrophy	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Pruritus	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Skin ulcer	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Alopecia	0			0			0			1 (0.6)	1	1.2
Blister	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Dermal cyst	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Dermatitis	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Dry skin	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Eczema	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Miliaria	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Rash erythematous	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Rash papular	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Skin fissures	0			0			0			1 (0.6)	1	1.2
Skin lesion	0			0			0			1 (0.6)	1	1.2
Skin mass	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Xeroderma	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Blood and lymphatic system disorders	5 (3.2)	5	6.3	0			5 (1.6)	5	3.2	3 (1.8)	3	3.7
Anaemia	2 (1.3)	2	2.5	0			2 (0.6)	2	1.3	2 (1.2)	2	2.5
Iron deficiency anaemia	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Leukopenia	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Lymphadenopathy	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Immune system disorders	1 (0.6)	1	1.3	2 (1.3)	4	5.2	3 (1.0)	5	3.2	3 (1.8)	3	3.7

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Hypersensitivity	0			1 (0.6)	3	3.9	1 (0.3)	3	1.9	1 (0.6)	1	1.2
Seasonal allergy	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Multiple allergies	0			0			0			1 (0.6)	1	1.2
Mycotic allergy	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Psychiatric disorders	3 (1.9)	4	5.1	3 (1.9)	3	3.9	6 (1.9)	7	4.5	1 (0.6)	1	1.2
Depression	3 (1.9)	3	3.8	1 (0.6)	1	1.3	4 (1.3)	4	2.6	0		
Insomnia	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Affective disorder	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Anxiety	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Ear and labyrinth disorders	2 (1.3)	2	2.5	4 (2.6)	5	6.5	6 (1.9)	7	4.5	0		
Ear discomfort	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	0		
Ear pain	1 (0.6)	1	1.3	1 (0.6)	1	1.3	2 (0.6)	2	1.3	0		
Sudden hearing loss	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Tinnitus	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Vertigo	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Endocrine disorders	0			3 (1.9)	4	5.2	3 (1.0)	4	2.6	2 (1.2)	2	2.5
Goitre	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	2 (1.2)	2	2.5
Hyperadrenalism	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Hypothyroidism	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Thyroid cyst	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Reproductive system and breast disorders	1 (0.6)	1	1.3	2 (1.3)	3	3.9	3 (1.0)	4	2.6	2 (1.2)	2	2.5
Dysmenorrhoea	0			1 (0.6)	2	2.6	1 (0.3)	2	1.3	0		
Breast tenderness	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Endometriosis	0			0			0			1 (0.6)	1	1.2
Genital haemorrhage	0			0			0			1 (0.6)	1	1.2
Vulvovaginal inflammation	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Vascular disorders	3 (1.9)	3	3.8	2 (1.3)	2	2.6	5 (1.6)	5	3.2	1 (0.6)	1	1.2
Hypertension	2 (1.3)	2	2.5	2 (1.3)	2	2.6	4 (1.3)	4	2.6	0		
Hypotension	0			0			0			1 (0.6)	1	1.2
Peripheral arterial occlusive disease	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Cardiac disorders	1 (0.6)	1	1.3	2 (1.3)	2	2.6	3 (1.0)	3	1.9	1 (0.6)	1	1.2
Palpitations	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Sinus bradycardia	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Ventricular extrasystoles	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Renal and urinary disorders	2 (1.3)	2	2.5	2 (1.3)	2	2.6	4 (1.3)	4	2.6	0		
Crystalluria	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Dysuria	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Haematuria	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Renal cyst	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Hepatobiliary disorders	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Cholecystitis	0			0			0			1 (0.6)	1	1.2
Hepatic steatosis	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Conjunctival neoplasm	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Skin papilloma	0			1 (0.6)	1	1.3	1 (0.3)	1	0.6	0		
Pregnancy, puerperium and perinatal conditions	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Subchorionic haemorrhage	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		

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2.7.4.7.3.2.4. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- 男性被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	184			186			370			179		
Total exposure (yrs)	92.5			92.7			185.2			90.1		
Total events	130 (70.7)	351	379.3	127 (68.3)	311	335.5	257 (69.5)	662	357.4	131 (73.2)	294	326.4
Infections and infestations	83 (45.1)	128	138.3	69 (37.1)	113	121.9	152 (41.1)	241	130.1	76 (42.5)	118	131.0
Viral upper respiratory tract infection	40 (21.7)	52	56.2	40 (21.5)	55	59.3	80 (21.6)	107	57.8	37 (20.7)	57	63.3
Upper respiratory tract infection	21 (11.4)	27	29.2	14 (7.5)	21	22.7	35 (9.5)	48	25.9	15 (8.4)	16	17.8
Influenza	13 (7.1)	13	14.0	8 (4.3)	8	8.6	21 (5.7)	21	11.3	7 (3.9)	7	7.8
Gastroenteritis	6 (3.3)	7	7.6	5 (2.7)	5	5.4	11 (3.0)	12	6.5	4 (2.2)	6	6.7
Sinusitis	2 (1.1)	2	2.2	2 (1.1)	2	2.2	4 (1.1)	4	2.2	4 (2.2)	4	4.4
Viral infection	2 (1.1)	3	3.2	2 (1.1)	3	3.2	4 (1.1)	6	3.2	2 (1.1)	2	2.2
Gastroenteritis viral	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	5 (2.8)	5	5.6
Pharyngitis	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	3 (1.7)	3	3.3
Bronchitis	1 (0.5)	1	1.1	2 (1.1)	2	2.2	3 (0.8)	3	1.6	1 (0.6)	1	1.1
Cellulitis	2 (1.1)	2	2.2	1 (0.5)	1	1.1	3 (0.8)	3	1.6	1 (0.6)	1	1.1
Rhinitis	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	2 (1.1)	2	2.2
Onychomycosis	0			2 (1.1)	2	2.2	2 (0.5)	2	1.1	1 (0.6)	1	1.1
Localised infection	0			2 (1.1)	2	2.2	2 (0.5)	2	1.1	0		
Otitis media	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	0		
Respiratory tract infection viral	1 (0.5)	2	2.2	0			1 (0.3)	2	1.1	0		
Skin infection	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.1
Tooth abscess	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Urinary tract infection	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.1
Acute sinusitis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Conjunctivitis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Cytomegalovirus infection	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Diverticulitis	0			0			0			1 (0.6)	1	1.1

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - male - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Ear infection	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Epstein-Barr virus infection	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Fungal infection	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Fungal skin infection	0				0				0				1	(0.6)	1	1.1
Gingivitis	0				0				0				1	(0.6)	1	1.1
Herpes zoster	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Impetigo	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Infectious mononucleosis	0				0				0				1	(0.6)	1	1.1
Labyrinthitis	0				0				0				1	(0.6)	1	1.1
Lower respiratory tract infection	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Lower respiratory tract infection bacterial	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Oral herpes	0				0				0				1	(0.6)	1	1.1
Oral infection	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Otitis externa	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Otitis media acute	0				0				0				1	(0.6)	1	1.1
Periodontitis	0				0				0				1	(0.6)	1	1.1
Pilonidal cyst	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Respiratory tract infection	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Spermatic cord funiculitis	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Subcutaneous abscess	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Syphilis	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Tinea cruris	0				0				0				1	(0.6)	1	1.1
Tonsillitis	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Urethritis	0				0				0				1	(0.6)	1	1.1
Urinary tract infection fungal	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Varicella	0				0				0				1	(0.6)	1	1.1
Investigations	38	(20.7)	47	50.8	34	(18.3)	42	45.3	72	(19.5)	89	48.0	39	(21.8)	49	54.4
Blood glucose decreased	30	(16.3)	39	42.1	31	(16.7)	35	37.8	61	(16.5)	74	39.9	36	(20.1)	42	46.6

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Adverse events by system organ class and preferred term - treatment emergent - summary - male - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Blood creatinine increased	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	1 (0.6)	1	1.1
Hepatic enzyme increased	0			0			0			2 (1.1)	2	2.2
Alanine aminotransferase increased	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Aspartate aminotransferase increased	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Blood 1,5-anhydroglucitol decreased	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Blood bilirubin increased	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Blood potassium increased	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Blood pressure increased	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Blood thyroid stimulating hormone	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Blood thyroid stimulating hormone increased	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Electrocardiogram change	0			0			0			1 (0.6)	1	1.1
Haematocrit decreased	0			0			0			1 (0.6)	1	1.1
Haemoglobin decreased	0			0			0			1 (0.6)	1	1.1
Heart rate increased	0			0			0			1 (0.6)	1	1.1
Lipids abnormal	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Protein urine present	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Transaminases increased	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Urine albumin/creatinine ratio increased	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Weight increased	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Gastrointestinal disorders	16 (8.7)	20	21.6	13 (7.0)	22	23.7	29 (7.8)	42	22.7	18 (10.1)	20	22.2
Nausea	4 (2.2)	4	4.3	1 (0.5)	1	1.1	5 (1.4)	5	2.7	3 (1.7)	3	3.3
Toothache	2 (1.1)	2	2.2	4 (2.2)	4	4.3	6 (1.6)	6	3.2	1 (0.6)	1	1.1
Diarrhoea	1 (0.5)	1	1.1	3 (1.6)	3	3.2	4 (1.1)	4	2.2	2 (1.1)	2	2.2
Vomiting	3 (1.6)	4	4.3	0			3 (0.8)	4	2.2	1 (0.6)	1	1.1
Gastritis	1 (0.5)	1	1.1	2 (1.1)	3	3.2	3 (0.8)	4	2.2	0		
Gastrooesophageal reflux disease	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	3 (1.7)	3	3.3
Abdominal pain	0			0			0			3 (1.7)	3	3.3

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Adverse events by system organ class and preferred term - treatment emergent - summary - male - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Dyspepsia	0			2 (1.1)	2	2.2	2 (0.5)	2	1.1	1 (0.6)	1	1.1
Food poisoning	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	1 (0.6)	1	1.1
Abdominal discomfort	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.1
Abdominal pain upper	0			2 (1.1)	2	2.2	2 (0.5)	2	1.1	0		
Constipation	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	0		
Abdominal distension	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Apical granuloma	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Dental caries	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Enteritis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Gastric ulcer	0			0			0			1 (0.6)	1	1.1
Gastritis erosive	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Haemorrhoids	0			0			0			1 (0.6)	1	1.1
Hiatus hernia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Hyperchlorhydria	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Periodontal disease	0			0			0			1 (0.6)	1	1.1
Proctalgia	0			0			0			1 (0.6)	1	1.1
Retching	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Stomatitis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Injury, poisoning and procedural complications	18 (9.8)	21	22.7	13 (7.0)	17	18.3	31 (8.4)	38	20.5	16 (8.9)	17	18.9
Wrong drug administered	5 (2.7)	6	6.5	6 (3.2)	8	8.6	11 (3.0)	14	7.6	4 (2.2)	4	4.4
Ligament sprain	1 (0.5)	1	1.1	2 (1.1)	2	2.2	3 (0.8)	3	1.6	2 (1.1)	2	2.2
Muscle strain	4 (2.2)	4	4.3	0			4 (1.1)	4	2.2	0		
Contusion	2 (1.1)	2	2.2	1 (0.5)	1	1.1	3 (0.8)	3	1.6	0		
Laceration	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.1
Limb injury	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.1
Road traffic accident	0			2 (1.1)	2	2.2	2 (0.5)	2	1.1	0		
Tooth fracture	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	0		
Accidental overdose	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - male - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Animal bite	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Buttock injury	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Extradural haematoma	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Eyelid injury	0			0			0			1 (0.6)	1	1.1
Facial bones fracture	0			0			0			1 (0.6)	1	1.1
Fall	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Foot fracture	0			0			0			1 (0.6)	1	1.1
Forearm fracture	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Foreign body in eye	0			0			0			1 (0.6)	1	1.1
Heat illness	0			0			0			1 (0.6)	1	1.1
Joint injury	0			0			0			1 (0.6)	1	1.1
Ligament rupture	0			0			0			1 (0.6)	1	1.1
Skull fractured base	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Tendon rupture	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Thermal burn	0			0			0			1 (0.6)	1	1.1
Traumatic fracture	0			0			0			1 (0.6)	1	1.1
Musculoskeletal and connective tissue disorders	14 (7.6)	19	20.5	15 (8.1)	16	17.3	29 (7.8)	35	18.9	12 (6.7)	13	14.4
Back pain	2 (1.1)	2	2.2	2 (1.1)	2	2.2	4 (1.1)	4	2.2	4 (2.2)	4	4.4
Pain in extremity	2 (1.1)	2	2.2	4 (2.2)	4	4.3	6 (1.6)	6	3.2	2 (1.1)	2	2.2
Myalgia	2 (1.1)	3	3.2	1 (0.5)	1	1.1	3 (0.8)	4	2.2	1 (0.6)	1	1.1
Muscle spasms	3 (1.6)	3	3.2	1 (0.5)	1	1.1	4 (1.1)	4	2.2	0		
Musculoskeletal pain	4 (2.2)	4	4.3	0			4 (1.1)	4	2.2	0		
Arthralgia	0			2 (1.1)	2	2.2	2 (0.5)	2	1.1	1 (0.6)	1	1.1
Plantar fasciitis	0			1 (0.5)	2	2.2	1 (0.3)	2	1.1	0		
Trigger finger	0			0			0			1 (0.6)	2	2.2
Arthritis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Bursitis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Intervertebral disc degeneration	0			0			0			1 (0.6)	1	1.1

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Intervertebral disc disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Muscular weakness	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Musculoskeletal stiffness	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Neck pain	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Osteoporotic fracture	0			0			0			1 (0.6)	1	1.1
Rotator cuff syndrome	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Spinal osteoarthritis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Tendonitis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Tenosynovitis	0			0			0			1 (0.6)	1	1.1
Metabolism and nutrition disorders	19 (10.3)	20	21.6	9 (4.8)	12	12.9	28 (7.6)	32	17.3	13 (7.3)	14	15.5
Hypoglycaemia	14 (7.6)	15	16.2	5 (2.7)	8	8.6	19 (5.1)	23	12.4	8 (4.5)	9	10.0
Diabetic metabolic decompensation	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	1 (0.6)	1	1.1
Hyperlipidaemia	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	1 (0.6)	1	1.1
Hyperglycaemia	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.1
Hypokalaemia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.1
Decreased appetite	0			0			0			1 (0.6)	1	1.1
Gout	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Hypertriglyceridaemia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Vitamin D deficiency	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
General disorders and administration site conditions	15 (8.2)	20	21.6	13 (7.0)	16	17.3	28 (7.6)	36	19.4	7 (3.9)	8	8.9
Influenza like illness	3 (1.6)	5	5.4	2 (1.1)	2	2.2	5 (1.4)	7	3.8	0		
Pyrexia	3 (1.6)	3	3.2	4 (2.2)	4	4.3	7 (1.9)	7	3.8	0		
Fatigue	1 (0.5)	1	1.1	2 (1.1)	3	3.2	3 (0.8)	4	2.2	0		
Injection site bruising	1 (0.5)	2	2.2	2 (1.1)	2	2.2	3 (0.8)	4	2.2	0		
Injection site haematoma	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	1 (0.6)	1	1.1
Injection site pain	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	1 (0.6)	1	1.1
Chest pain	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.1

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Injection site hypertrophy	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Malaise	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	0		
Oedema peripheral	0			0			0			2 (1.1)	2	2.2
Chest discomfort	0			0			0			1 (0.6)	1	1.1
Drug therapeutic incompatibility	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Feeling abnormal	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Inflammation	0			0			0			1 (0.6)	1	1.1
Injection site haemorrhage	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Injection site reaction	0			0			0			1 (0.6)	1	1.1
Pain	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Peripheral swelling	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Skin and subcutaneous tissue disorders	12 (6.5)	16	17.3	13 (7.0)	13	14.0	25 (6.8)	29	15.7	9 (5.0)	10	11.1
Dermatitis	1 (0.5)	3	3.2	3 (1.6)	3	3.2	4 (1.1)	6	3.2	0		
Lipohypertrophy	2 (1.1)	2	2.2	1 (0.5)	1	1.1	3 (0.8)	3	1.6	0		
Urticaria	2 (1.1)	2	2.2	1 (0.5)	1	1.1	3 (0.8)	3	1.6	0		
Dry skin	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.1
Ecchymosis	0			0			0			1 (0.6)	2	2.2
Eczema	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.1
Rash	0			0			0			2 (1.1)	2	2.2
Acne cystic	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Actinic keratosis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Asteatosis	0			0			0			1 (0.6)	1	1.1
Blood blister	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Dermatitis contact	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Eczema asteatotic	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Hidradenitis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Lipodystrophy acquired	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Nail bed inflammation	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Nail disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - male - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Nail pigmentation	0			0			0			1 (0.6)	1	1.1
Onychomadesis	0			0			0			1 (0.6)	1	1.1
Papule	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Parapsoriasis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Pruritus	0			0			0			1 (0.6)	1	1.1
Rash pruritic	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Skin exfoliation	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Skin reaction	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Skin ulcer	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Eye disorders	7 (3.8)	7	7.6	14 (7.5)	19	20.5	21 (5.7)	26	14.0	11 (6.1)	12	13.3
Diabetic retinopathy	2 (1.1)	2	2.2	5 (2.7)	5	5.4	7 (1.9)	7	3.8	3 (1.7)	3	3.3
Retinopathy hypertensive	0			2 (1.1)	2	2.2	2 (0.5)	2	1.1	1 (0.6)	1	1.1
Macular oedema	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.1
Retinal aneurysm	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	0		
Retinal tear	0			0			0			2 (1.1)	2	2.2
Retinopathy	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.1
Astigmatism	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Blepharochalasis	0			0			0			1 (0.6)	1	1.1
Cataract	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Conjunctivitis allergic	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Eye disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Eye pruritus	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Eye ulcer	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Iritis	0			0			0			1 (0.6)	1	1.1
Maculopathy	0			0			0			1 (0.6)	1	1.1
Myopia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Normal tension glaucoma	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Ocular discomfort	0			0			0			1 (0.6)	1	1.1
Retinal exudates	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - male - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Retinal haemorrhage	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Visual impairment	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Vitreous detachment	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Vitreous haemorrhage	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Nervous system disorders	11 (6.0)	15	16.2	13 (7.0)	16	17.3	24 (6.5)	31	16.7	5 (2.8)	5	5.6
Headache	2 (1.1)	4	4.3	7 (3.8)	8	8.6	9 (2.4)	12	6.5	0		
Dizziness	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	1 (0.6)	1	1.1
Hypoglycaemic seizure	2 (1.1)	2	2.2	1 (0.5)	1	1.1	3 (0.8)	3	1.6	0		
Hypoglycaemic unconsciousness	2 (1.1)	2	2.2	1 (0.5)	1	1.1	3 (0.8)	3	1.6	0		
Paraesthesia	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.1
Presyncope	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.1
Tension headache	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Diabetic neuropathy	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Hypertonia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Hyporeflexia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Lethargy	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Lumbar radiculopathy	0			0			0			1 (0.6)	1	1.1
Memory impairment	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Polyneuropathy	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Syncope	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Tremor	0			0			0			1 (0.6)	1	1.1
Respiratory, thoracic and mediastinal disorders	13 (7.1)	14	15.1	6 (3.2)	6	6.5	19 (5.1)	20	10.8	9 (5.0)	10	11.1
Oropharyngeal pain	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	2 (1.1)	3	3.3
Rhinorrhoea	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	2 (1.1)	2	2.2
Sinus congestion	3 (1.6)	3	3.2	1 (0.5)	1	1.1	4 (1.1)	4	2.2	0		
Cough	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Dyspnoea	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - male - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Epistaxis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.1
Nasal congestion	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	0		
Upper respiratory tract inflammation	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.1
Asthma	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Chronic obstructive pulmonary disease	0			0			0			1 (0.6)	1	1.1
Respiratory disorder	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Rhinitis allergic	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Throat irritation	0			0			0			1 (0.6)	1	1.1
Tonsillar hypertrophy	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Upper respiratory tract congestion	0			0			0			1 (0.6)	1	1.1
Renal and urinary disorders	2 (1.1)	2	2.2	5 (2.7)	5	5.4	7 (1.9)	7	3.8	4 (2.2)	6	6.7
Microalbuminuria	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	3 (1.7)	4	4.4
Haematuria	0			3 (1.6)	3	3.2	3 (0.8)	3	1.6	1 (0.6)	1	1.1
Acute kidney injury	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Bladder pain	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Nephrolithiasis	0			0			0			1 (0.6)	1	1.1
Renal failure	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Psychiatric disorders	4 (2.2)	4	4.3	5 (2.7)	6	6.5	9 (2.4)	10	5.4	0		
Depression	1 (0.5)	1	1.1	2 (1.1)	2	2.2	3 (0.8)	3	1.6	0		
Stress	1 (0.5)	1	1.1	2 (1.1)	2	2.2	3 (0.8)	3	1.6	0		
Insomnia	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	0		
Anxiety	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Sleep disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Vascular disorders	3 (1.6)	3	3.2	3 (1.6)	3	3.2	6 (1.6)	6	3.2	3 (1.7)	3	3.3
Hypertension	1 (0.5)	1	1.1	2 (1.1)	2	2.2	3 (0.8)	3	1.6	1 (0.6)	1	1.1
Orthostatic hypotension	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Arteriosclerosis	0			0			0			1 (0.6)	1	1.1

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - male - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Hypotension	0			0			0			1 (0.6)	1	1.1
Thrombophlebitis superficial	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Reproductive system and breast disorders	3 (1.6)	3	3.2	1 (0.5)	2	2.2	4 (1.1)	5	2.7	0		
Priapism	0			1 (0.5)	2	2.2	1 (0.3)	2	1.1	0		
Benign prostatic hyperplasia	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Gynaecomastia	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Testicular swelling	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Surgical and medical procedures	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	3 (1.7)	3	3.3
Cataract operation	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Endodontic procedure	0			0			0			1 (0.6)	1	1.1
Haemorrhoid operation	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Inguinal hernia repair	0			0			0			1 (0.6)	1	1.1
Tooth extraction	0			0			0			1 (0.6)	1	1.1
Blood and lymphatic system disorders	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	2 (1.1)	2	2.2
Anaemia	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	2 (1.1)	2	2.2
Lymphadenopathy	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Cardiac disorders	2 (1.1)	2	2.2	1 (0.5)	1	1.1	3 (0.8)	3	1.6	0		
Coronary artery disease	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Extrasystoles	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Myocardial ischaemia	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Ear and labyrinth disorders	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	2 (1.1)	2	2.2
Tinnitus	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Tympanic membrane perforation	0			0			0			1 (0.6)	1	1.1
Vertigo	0			0			0			1 (0.6)	1	1.1

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Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - male - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	1 (0.6)	1	1.1
Haemangioma of liver	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.1
Bladder transitional cell carcinoma	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Hepatobiliary disorders	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.1
Gallbladder polyp	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Hepatic steatosis	0			0			0			1 (0.6)	1	1.1
Immune system disorders	0			2 (1.1)	2	2.2	2 (0.5)	2	1.1	0		
Seasonal allergy	0			2 (1.1)	2	2.2	2 (0.5)	2	1.1	0		
Congenital, familial and genetic disorders	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Accessory spleen	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Endocrine disorders	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Hypothyroidism	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		

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2.7.4.7.3.2.5. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインの BMI（kg/m^2）が 25 未満の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N	(%)	E R	N	(%)	E R	N	(%)	E R	N	(%)	E R
Number of subjects	190			185			375			194		
Total exposure (yrs)	95.1			92.7			187.8			95.6		
Total events	123	(64.7)	328 344.8	123	(66.5)	307 331.3	246	(65.6)	635 338.2	135	(69.6)	333 348.2
Infections and infestations	73	(38.4)	113 118.8	67	(36.2)	103 111.2	140	(37.3)	216 115.0	74	(38.1)	121 126.5
Viral upper respiratory tract infection	35	(18.4)	48 50.5	33	(17.8)	42 45.3	68	(18.1)	90 47.9	44	(22.7)	64 66.9
Upper respiratory tract infection	14	(7.4)	18 18.9	16	(8.6)	21 22.7	30	(8.0)	39 20.8	10	(5.2)	13 13.6
Influenza	10	(5.3)	11 11.6	4	(2.2)	4 4.3	14	(3.7)	15 8.0	7	(3.6)	7 7.3
Gastroenteritis	5	(2.6)	5 5.3	4	(2.2)	4 4.3	9	(2.4)	9 4.8	7	(3.6)	7 7.3
Urinary tract infection	4	(2.1)	5 5.3	3	(1.6)	3 3.2	7	(1.9)	8 4.3	4	(2.1)	4 4.2
Viral infection	2	(1.1)	3 3.2	3	(1.6)	4 4.3	5	(1.3)	7 3.7	1	(0.5)	1 1.0
Cystitis	1	(0.5)	2 2.1	1	(0.5)	1 1.1	2	(0.5)	3 1.6	2	(1.0)	2 2.1
Pharyngitis	2	(1.1)	2 2.1	1	(0.5)	1 1.1	3	(0.8)	3 1.6	2	(1.0)	2 2.1
Gastroenteritis viral	0			0			0			4	(2.1)	4 4.2
Respiratory tract infection viral	1	(0.5)	2 2.1	2	(1.1)	2 2.2	3	(0.8)	4 2.1	0		
Sinusitis	3	(1.6)	4 4.2	0			3	(0.8)	4 2.1	0		
Bronchitis	1	(0.5)	1 1.1	1	(0.5)	1 1.1	2	(0.5)	2 1.1	1	(0.5)	1 1.0
Ear infection	1	(0.5)	2 2.1	1	(0.5)	1 1.1	2	(0.5)	3 1.6	0		
Otitis externa	1	(0.5)	1 1.1	2	(1.1)	2 2.2	3	(0.8)	3 1.6	0		
Periodontitis	1	(0.5)	1 1.1	0			1	(0.3)	1 0.5	2	(1.0)	2 2.1
Rhinitis	2	(1.1)	2 2.1	0			2	(0.5)	2 1.1	1	(0.5)	1 1.0
Otitis media	1	(0.5)	1 1.1	0			1	(0.3)	1 0.5	1	(0.5)	1 1.0
Pneumonia	0			0			0			2	(1.0)	2 2.1
Respiratory tract infection	1	(0.5)	1 1.1	1	(0.5)	1 1.1	2	(0.5)	2 1.1	0		
Subcutaneous abscess	0			2	(1.1)	2 2.2	2	(0.5)	2 1.1	0		
Abscess limb	0			0			0			1	(0.5)	1 1.0
Acute sinusitis	0			1	(0.5)	1 1.1	1	(0.3)	1 0.5	0		

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - BMI at baseline < 25 kg/m^2 - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Adenoiditis	0				0				0				1	(0.5)	1	1.1
Angular cheilitis	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Candida infection	0				0				0				1	(0.5)	1	1.1
Cellulitis	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Conjunctivitis	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Cytomegalovirus infection	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Empyema	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Epstein-Barr virus infection	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Folliculitis	0				0				0				1	(0.5)	1	1.1
Fungal infection	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Furuncle	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Gastrointestinal viral infection	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Gingivitis	0				0				0				1	(0.5)	1	1.1
Labyrinthitis	0				0				0				1	(0.5)	1	1.1
Laryngitis	0				0				0				1	(0.5)	1	1.1
Localised infection	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Lower respiratory tract infection bacterial	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Nasopharyngitis	0				0				0				1	(0.5)	1	1.1
Onychomycosis	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Paronychia	0				0				0				1	(0.5)	1	1.1
Pyelonephritis chronic	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Spermatic cord funiculitis	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Syphilis	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Tooth abscess	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Vulvovaginal candidiasis	0				0				0				1	(0.5)	1	1.1
Vulvovaginal mycotic infection	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Investigations	39	(20.5)	53	55.7	39	(21.1)	49	52.9	78	(20.8)	102	54.3	49	(25.3)	60	62.7
Blood glucose decreased	35	(18.4)	48	50.5	35	(18.9)	44	47.5	70	(18.7)	92	49.0	46	(23.7)	57	59.6

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	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Blood pressure increased	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	1	(0.5)	1	1.0
Hepatic enzyme increased	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	1	(0.5)	1	1.0
Blood 1,5-anhydroglucitol decreased	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Blood bilirubin increased	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Blood creatinine increased	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Blood glucose fluctuation	0				0				0				1	(0.5)	1	1.0
Blood urine present	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Haemoglobin decreased	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Helicobacter test positive	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Urine albumin/creatinine ratio increased	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Weight increased	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Gastrointestinal disorders	25	(13.2)	40	42.0	17	(9.2)	25	27.0	42	(11.2)	65	34.6	21	(10.8)	25	26.1
Nausea	9	(4.7)	11	11.6	1	(0.5)	1	1.1	10	(2.7)	12	6.4	5	(2.6)	6	6.3
Gastritis	3	(1.6)	4	4.2	5	(2.7)	6	6.5	8	(2.1)	10	5.3	3	(1.5)	3	3.1
Diarrhoea	1	(0.5)	1	1.1	5	(2.7)	5	5.4	6	(1.6)	6	3.2	4	(2.1)	4	4.2
Vomiting	3	(1.6)	4	4.2	3	(1.6)	3	3.2	6	(1.6)	7	3.7	1	(0.5)	1	1.0
Abdominal pain upper	1	(0.5)	1	1.1	2	(1.1)	2	2.2	3	(0.8)	3	1.6	1	(0.5)	1	1.0
Constipation	4	(2.1)	4	4.2	0				4	(1.1)	4	2.1	0			
Food poisoning	2	(1.1)	2	2.1	1	(0.5)	1	1.1	3	(0.8)	3	1.6	1	(0.5)	1	1.0
Toothache	1	(0.5)	1	1.1	2	(1.1)	2	2.2	3	(0.8)	3	1.6	1	(0.5)	1	1.0
Abdominal discomfort	1	(0.5)	1	1.1	1	(0.5)	1	1.1	2	(0.5)	2	1.1	1	(0.5)	1	1.0
Dyspepsia	1	(0.5)	1	1.1	1	(0.5)	1	1.1	2	(0.5)	2	1.1	1	(0.5)	1	1.0
Abdominal pain	0				0				0				2	(1.0)	2	2.1
Enteritis	0				2	(1.1)	2	2.2	2	(0.5)	2	1.1	0			
Gastrooesophageal reflux disease	2	(1.1)	2	2.1	0				2	(0.5)	2	1.1	0			
Stomatitis	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	1	(0.5)	1	1.0
Abdominal distension	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Aphthous ulcer	0				0				0				1	(0.5)	1	1.0

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Apical granuloma	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Dental caries	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Enterocolitis	0			0			0			1 (0.5)	1	1.0
Gastric polyps	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Gastric ulcer	0			0			0			1 (0.5)	1	1.0
Gastritis erosive	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Gastrointestinal disorder	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Hyperchlorhydria	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Retching	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Musculoskeletal and connective tissue disorders	15 (7.9)	17	17.9	12 (6.5)	13	14.0	27 (7.2)	30	16.0	15 (7.7)	22	23.0
Back pain	2 (1.1)	2	2.1	4 (2.2)	4	4.3	6 (1.6)	6	3.2	2 (1.0)	2	2.1
Arthralgia	2 (1.1)	2	2.1	1 (0.5)	1	1.1	3 (0.8)	3	1.6	2 (1.0)	2	2.1
Myalgia	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	2 (1.0)	3	3.1
Pain in extremity	2 (1.1)	2	2.1	1 (0.5)	1	1.1	3 (0.8)	3	1.6	1 (0.5)	1	1.0
Muscle spasms	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	1 (0.5)	1	1.0
Musculoskeletal pain	3 (1.6)	3	3.2	0			3 (0.8)	3	1.6	0		
Tenosynovitis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	2 (1.0)	2	2.1
Intervertebral disc protrusion	0			0			0			2 (1.0)	2	2.1
Plantar fasciitis	0			1 (0.5)	2	2.2	1 (0.3)	2	1.1	0		
Rheumatoid arthritis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Trigger finger	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Arthritis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Arthropathy	0			0			0			1 (0.5)	1	1.0
Collagen disorder	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Exostosis	0			0			0			1 (0.5)	1	1.0
Flank pain	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Intervertebral disc disorder	0			0			0			1 (0.5)	1	1.0
Joint contracture	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Musculoskeletal chest pain	0			0			0			1 (0.5)	1	1.0
Musculoskeletal stiffness	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Myositis	0			0			0			1 (0.5)	1	1.0
Osteoarthritis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Osteoporotic fracture	0			0			0			1 (0.5)	1	1.0
Periarthritis	0			0			0			1 (0.5)	1	1.0
Spinal pain	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
General disorders and administration site conditions	9 (4.7)	10	10.5	17 (9.2)	21	22.7	26 (6.9)	31	16.5	10 (5.2)	17	17.8
Pyrexia	3 (1.6)	3	3.2	7 (3.8)	7	7.6	10 (2.7)	10	5.3	2 (1.0)	2	2.1
Influenza like illness	1 (0.5)	1	1.1	2 (1.1)	2	2.2	3 (0.8)	3	1.6	3 (1.5)	4	4.2
Injection site haematoma	0			2 (1.1)	4	4.3	2 (0.5)	4	2.1	1 (0.5)	3	3.1
Injection site hypertrophy	2 (1.1)	2	2.1	1 (0.5)	1	1.1	3 (0.8)	3	1.6	0		
Injection site reaction	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	2	2.1
Chest pain	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Pain	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Administration site induration	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Asthenia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Chest discomfort	0			0			0			1 (0.5)	1	1.0
Drug therapeutic incompatibility	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Feeling abnormal	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Injection site bruising	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Injection site hypersensitivity	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Injection site induration	0			0			0			1 (0.5)	1	1.0
Injection site pain	0			0			0			1 (0.5)	1	1.0
Injection site swelling	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Malaise	0			0			0			1 (0.5)	1	1.0
Oedema peripheral	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		

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	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Injury, poisoning and procedural complications	17	(8.9)	19	20.0	11	(5.9)	14	15.1	28	(7.5)	33	17.6	12	(6.2)	12	12.5
Wrong drug administered	4	(2.1)	4	4.2	6	(3.2)	7	7.6	10	(2.7)	11	5.9	1	(0.5)	1	1.0
Ligament sprain	1	(0.5)	1	1.1	1	(0.5)	1	1.1	2	(0.5)	2	1.1	2	(1.0)	2	2.1
Tooth fracture	2	(1.1)	2	2.1	0				2	(0.5)	2	1.1	1	(0.5)	1	1.0
Laceration	2	(1.1)	2	2.1	0				2	(0.5)	2	1.1	0			
Limb injury	2	(1.1)	2	2.1	0				2	(0.5)	2	1.1	0			
Road traffic accident	0				2	(1.1)	2	2.2	2	(0.5)	2	1.1	0			
Thermal burn	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	1	(0.5)	1	1.0
Animal bite	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Buttock injury	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Contusion	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Extradural haematoma	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Facial bones fracture	0				0				0				1	(0.5)	1	1.0
Femoral neck fracture	0				0				0				1	(0.5)	1	1.0
Forearm fracture	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Hand fracture	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Heat illness	0				0				0				1	(0.5)	1	1.0
Joint injury	0				0				0				1	(0.5)	1	1.0
Muscle strain	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Post procedural discharge	0				0				0				1	(0.5)	1	1.0
Radius fracture	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Skin abrasion	0				0				0				1	(0.5)	1	1.0
Skull fractured base	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Tendon rupture	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Wound	0				0				0				1	(0.5)	1	1.0
Wrist fracture	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Eye disorders	10	(5.3)	11	11.6	14	(7.6)	17	18.3	24	(6.4)	28	14.9	9	(4.6)	11	11.5
Diabetic retinopathy	4	(2.1)	4	4.2	9	(4.9)	9	9.7	13	(3.5)	13	6.9	4	(2.1)	4	4.2

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Retinopathy	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	2 (1.0)	2	2.1
Retinal tear	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Cataract	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Cataract nuclear	0			0			0			1 (0.5)	1	1.0
Conjunctival haemorrhage	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Conjunctivitis allergic	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Eye disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Eyelid oedema	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Glaucoma	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Lacrimation increased	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Macular oedema	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Maculopathy	0			0			0			1 (0.5)	1	1.0
Ocular discomfort	0			0			0			1 (0.5)	1	1.0
Ocular hypertension	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Retinal aneurysm	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Retinopathy hypertensive	0			0			0			1 (0.5)	1	1.0
Visual acuity reduced transiently	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Visual impairment	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Vitreous haemorrhage	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Skin and subcutaneous tissue disorders	10 (5.3)	12	12.6	13 (7.0)	13	14.0	23 (6.1)	25	13.3	10 (5.2)	11	11.5
Lipohypertrophy	1 (0.5)	1	1.1	3 (1.6)	3	3.2	4 (1.1)	4	2.1	0		
Urticaria	2 (1.1)	2	2.1	1 (0.5)	1	1.1	3 (0.8)	3	1.6	1 (0.5)	1	1.0
Dry skin	0			2 (1.1)	2	2.2	2 (0.5)	2	1.1	1 (0.5)	1	1.0
Eczema	2 (1.1)	2	2.1	0			2 (0.5)	2	1.1	1 (0.5)	1	1.0
Dermatitis	0			2 (1.1)	2	2.2	2 (0.5)	2	1.1	0		
Dermatitis atopic	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Dermatitis contact	0			0			0			2 (1.0)	2	2.1
Ecchymosis	0			0			0			1 (0.5)	2	2.1
Skin ulcer	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - BMI at baseline < 25 kg/m^2 - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Acne cystic	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Asteatosis	0			0			0			1 (0.5)	1	1.0
Dermal cyst	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Hidradenitis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Lipodystrophy acquired	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Miliaria	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Nail bed inflammation	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Nail disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Pruritus	0			0			0			1 (0.5)	1	1.0
Rash erythematous	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Rash papular	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Xeroderma	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Respiratory, thoracic and mediastinal disorders	10 (5.3)	11	11.6	13 (7.0)	16	17.3	23 (6.1)	27	14.4	8 (4.1)	8	8.4
Oropharyngeal pain	2 (1.1)	2	2.1	3 (1.6)	3	3.2	5 (1.3)	5	2.7	3 (1.5)	3	3.1
Cough	0			5 (2.7)	5	5.4	5 (1.3)	5	2.7	0		
Rhinitis allergic	2 (1.1)	2	2.1	1 (0.5)	1	1.1	3 (0.8)	3	1.6	1 (0.5)	1	1.0
Respiratory disorder	2 (1.1)	2	2.1	1 (0.5)	1	1.1	3 (0.8)	3	1.6	0		
Upper respiratory tract inflammation	0			2 (1.1)	3	3.2	2 (0.5)	3	1.6	0		
Asthma	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Nasal congestion	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Rhinorrhoea	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Sinus congestion	2 (1.1)	2	2.1	0			2 (0.5)	2	1.1	0		
Paranasal sinus discomfort	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Pleurisy	0			0			0			1 (0.5)	1	1.0
Throat irritation	0			0			0			1 (0.5)	1	1.0
Tonsillar hypertrophy	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Metabolism and nutrition disorders	11 (5.8)	11	11.6	6 (3.2)	7	7.6	17 (4.5)	18	9.6	12 (6.2)	13	13.6

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Adverse events by system organ class and preferred term - treatment emergent - summary - BMI at baseline < 25 kg/m^2 - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Hypoglycaemia	7 (3.7)	7	7.4	1 (0.5)	1	1.1	8 (2.1)	8	4.3	5 (2.6)	5	5.2
Hyperglycaemia	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	2 (1.0)	3	3.1
Dehydration	2 (1.1)	2	2.1	0			2 (0.5)	2	1.1	0		
Diabetic metabolic decompensation	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Hyperlipidaemia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Hypertriglyceridaemia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Hypokalaemia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Decreased appetite	0			0			0			1 (0.5)	1	1.0
Hypercholesterolaemia	0			0			0			1 (0.5)	1	1.0
Hypoglycaemia unawareness	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Vitamin D deficiency	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Nervous system disorders	5 (2.6)	5	5.3	9 (4.9)	11	11.9	14 (3.7)	16	8.5	9 (4.6)	13	13.6
Headache	0			3 (1.6)	3	3.2	3 (0.8)	3	1.6	4 (2.1)	7	7.3
Dizziness	0			2 (1.1)	3	3.2	2 (0.5)	3	1.6	1 (0.5)	1	1.0
Hypoglycaemic unconsciousness	0			2 (1.1)	2	2.2	2 (0.5)	2	1.1	2 (1.0)	2	2.1
Diabetic neuropathy	2 (1.1)	2	2.1	0			2 (0.5)	2	1.1	0		
Hypoaesthesia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Migraine	2 (1.1)	2	2.1	0			2 (0.5)	2	1.1	0		
Carotid arteriosclerosis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Hypoglycaemic seizure	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Lethargy	0			0			0			1 (0.5)	1	1.0
Lumbar radiculopathy	0			0			0			1 (0.5)	1	1.0
Polyneuropathy	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Psychiatric disorders	3 (1.6)	4	4.2	5 (2.7)	6	6.5	8 (2.1)	10	5.3	0		
Depression	2 (1.1)	2	2.1	3 (1.6)	3	3.2	5 (1.3)	5	2.7	0		
Anxiety	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Affective disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Insomnia	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - BMI at baseline < 25 kg/m^2 - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Stress	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Renal and urinary disorders	2 (1.1)	2	2.1	4 (2.2)	4	4.3	6 (1.6)	6	3.2	3 (1.5)	4	4.2
Microalbuminuria	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	2 (1.0)	3	3.1
Haematuria	0			3 (1.6)	3	3.2	3 (0.8)	3	1.6	0		
Crystalluria	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Nephrolithiasis	0			0			0			1 (0.5)	1	1.0
Renal cyst	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Blood and lymphatic system disorders	6 (3.2)	6	6.3	0			6 (1.6)	6	3.2	2 (1.0)	2	2.1
Anaemia	2 (1.1)	2	2.1	0			2 (0.5)	2	1.1	2 (1.0)	2	2.1
Lymphadenopathy	2 (1.1)	2	2.1	0			2 (0.5)	2	1.1	0		
Iron deficiency anaemia	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Leukopenia	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Vascular disorders	3 (1.6)	3	3.2	3 (1.6)	3	3.2	6 (1.6)	6	3.2	2 (1.0)	2	2.1
Hypertension	2 (1.1)	2	2.1	2 (1.1)	2	2.2	4 (1.1)	4	2.1	0		
Hypotension	0			0			0			2 (1.0)	2	2.1
Orthostatic hypotension	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Thrombophlebitis superficial	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Reproductive system and breast disorders	2 (1.1)	2	2.1	1 (0.5)	2	2.2	3 (0.8)	4	2.1	2 (1.0)	2	2.1
Dysmenorrhoea	0			1 (0.5)	2	2.2	1 (0.3)	2	1.1	0		
Breast tenderness	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Endometriosis	0			0			0			1 (0.5)	1	1.0
Genital haemorrhage	0			0			0			1 (0.5)	1	1.0
Testicular swelling	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Cardiac disorders	2 (1.1)	2	2.1	1 (0.5)	1	1.1	3 (0.8)	3	1.6	1 (0.5)	1	1.0
Coronary artery disease	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - BMI at baseline < 25 kg/m^2 - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Extrasystoles	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Palpitations	0			0			0			1 (0.5)	1	1.0
Sinus bradycardia	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Ear and labyrinth disorders	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	2 (1.0)	2	2.1
Vertigo	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Ear discomfort	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Tympanic membrane perforation	0			0			0			1 (0.5)	1	1.0
Immune system disorders	1 (0.5)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	2 (1.0)	2	2.1
Seasonal allergy	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Hypersensitivity	0			0			0			1 (0.5)	1	1.0
Mycotic allergy	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Endocrine disorders	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Goitre	0			0			0			1 (0.5)	1	1.0
Hypothyroidism	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Hepatobiliary disorders	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Cholecystitis	0			0			0			1 (0.5)	1	1.0
Gallbladder polyp	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Haemangioma of liver	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Surgical and medical procedures	0			0			0			2 (1.0)	2	2.1
Inguinal hernia repair	0			0			0			1 (0.5)	1	1.0
Tooth extraction	0			0			0			1 (0.5)	1	1.0

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Adverse events by system organ class and preferred term - treatment emergent - summary - BMI at baseline < 25 kg/m^2 - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Congenital, familial and genetic disorders	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Accessory spleen	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Pregnancy, puerperium and perinatal conditions	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Subchorionic haemorrhage	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		

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2.7.4.7.3.2.6. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインの BMI（kg/m^2）が 25 以上 30 未満の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	105				104				209				99			
Total exposure (yrs)	52.7				51.3				104.0				50.2			
Total events	81	(77.1)	217	411.5	75	(72.1)	224	437.1	156	(74.6)	441	424.1	73	(73.7)	182	362.7
Infections and infestations	49	(46.7)	81	153.6	37	(35.6)	64	124.9	86	(41.1)	145	139.4	48	(48.5)	76	151.5
Viral upper respiratory tract infection	28	(26.7)	40	75.9	22	(21.2)	35	68.3	50	(23.9)	75	72.1	23	(23.2)	33	65.8
Upper respiratory tract infection	11	(10.5)	13	24.7	6	(5.8)	8	15.6	17	(8.1)	21	20.2	9	(9.1)	12	23.9
Influenza	6	(5.7)	6	11.4	4	(3.8)	4	7.8	10	(4.8)	10	9.6	2	(2.0)	2	4.0
Gastroenteritis	1	(1.0)	1	1.9	5	(4.8)	5	9.8	6	(2.9)	6	5.8	3	(3.0)	3	6.0
Pharyngitis	0				0				0				3	(3.0)	6	12.0
Viral infection	2	(1.9)	3	5.7	0				2	(1.0)	3	2.9	2	(2.0)	2	4.0
Sinusitis	1	(1.0)	1	1.9	2	(1.9)	2	3.9	3	(1.4)	3	2.9	1	(1.0)	1	2.0
Bronchitis	0				2	(1.9)	2	3.9	2	(1.0)	2	1.9	1	(1.0)	1	2.0
Cellulitis	1	(1.0)	1	1.9	1	(1.0)	1	2.0	2	(1.0)	2	1.9	1	(1.0)	1	2.0
Gastroenteritis viral	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	2	(2.0)	2	4.0
Herpes zoster	2	(1.9)	2	3.8	1	(1.0)	1	2.0	3	(1.4)	3	2.9	0			
Rhinitis	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	2	(2.0)	2	4.0
Urinary tract infection	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	2	(2.0)	2	4.0
Fungal infection	0				1	(1.0)	1	2.0	1	(0.5)	1	1.0	1	(1.0)	1	2.0
Otitis media	2	(1.9)	2	3.8	0				2	(1.0)	2	1.9	0			
Tooth abscess	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	1	(1.0)	1	2.0
Varicella	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	1	(1.0)	1	2.0
Diverticulitis	0				0				0				1	(1.0)	1	2.0
Fungal skin infection	0				0				0				1	(1.0)	1	2.0
Impetigo	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	0			
Localised infection	0				1	(1.0)	1	2.0	1	(0.5)	1	1.0	0			
Lower respiratory tract infection	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	0			

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Adverse events by system organ class and preferred term - treatment emergent - summary - 25 <= BMI at baseline < 30 kg/m^2 - trial 4131 - on -treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Molluscum contagiosum	0				1	(1.0)	1	2.0	1	(0.5)	1	1.0	0			
Oral herpes	0				0				0				1	(1.0)	1	2.0
Oral infection	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	0			
Otitis externa	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	0			
Pilonidal cyst	0				1	(1.0)	1	2.0	1	(0.5)	1	1.0	0			
Pulpitis dental	0				1	(1.0)	1	2.0	1	(0.5)	1	1.0	0			
Respiratory tract infection viral	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	0			
Skin infection	0				0				0				1	(1.0)	1	2.0
Tinea cruris	0				0				0				1	(1.0)	1	2.0
Tonsillitis	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	0			
Urinary tract infection fungal	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	0			
Vulvovaginal candidiasis	0				1	(1.0)	1	2.0	1	(0.5)	1	1.0	0			
Vulvovaginal mycotic infection	0				0				0				1	(1.0)	1	2.0
Investigations	23	(21.9)	30	56.9	18	(17.3)	27	52.7	41	(19.6)	57	54.8	16	(16.2)	19	37.9
Blood glucose decreased	17	(16.2)	24	45.5	17	(16.3)	22	42.9	34	(16.3)	46	44.2	16	(16.2)	19	37.9
Alanine aminotransferase increased	0				1	(1.0)	1	2.0	1	(0.5)	1	1.0	0			
Aspartate aminotransferase increased	0				1	(1.0)	1	2.0	1	(0.5)	1	1.0	0			
Blood creatinine increased	0				1	(1.0)	1	2.0	1	(0.5)	1	1.0	0			
Blood potassium increased	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	0			
Blood pressure increased	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	0			
Blood thyroid stimulating hormone increased	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	0			
Lipids abnormal	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	0			
Protein urine present	0				1	(1.0)	1	2.0	1	(0.5)	1	1.0	0			
Transaminases increased	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	0			
Urine albumin/creatinine ratio increased	0				1	(1.0)	1	2.0	1	(0.5)	1	1.0	0			
Weight increased	1	(1.0)	1	1.9	0				1	(0.5)	1	1.0	0			

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - 25 <= BMI at baseline < 30 kg/m^2 - trial 4131 - on -treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Nervous system disorders	11 (10.5)	15	28.4	17 (16.3)	26	50.7	28 (13.4)	41	39.4	6 (6.1)	7	14.0
Headache	4 (3.8)	6	11.4	8 (7.7)	15	29.3	12 (5.7)	21	20.2	0		
Dizziness	2 (1.9)	2	3.8	2 (1.9)	2	3.9	4 (1.9)	4	3.8	2 (2.0)	3	6.0
Hypoglycaemic seizure	2 (1.9)	2	3.8	0			2 (1.0)	2	1.9	0		
Paraesthesia	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	1 (1.0)	1	2.0
Presyncope	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	1 (1.0)	1	2.0
Cerebrovascular accident	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Diabetic neuropathy	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Hypertonia	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Hypoglycaemic coma	0			0			0			1 (1.0)	1	2.0
Hypoglycaemic unconsciousness	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Hyporeflexia	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Memory impairment	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Migraine	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Neurodegenerative disorder	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Occipital neuralgia	0			0			0			1 (1.0)	1	2.0
Polyneuropathy	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Post herpetic neuralgia	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Syncope	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Tension headache	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Gastrointestinal disorders	8 (7.6)	9	17.1	11 (10.6)	16	31.2	19 (9.1)	25	24.0	11 (11.1)	16	31.9
Nausea	2 (1.9)	2	3.8	1 (1.0)	1	2.0	3 (1.4)	3	2.9	3 (3.0)	5	10.0
Diarrhoea	2 (1.9)	2	3.8	4 (3.8)	4	7.8	6 (2.9)	6	5.8	0		
Gastrooesophageal reflux disease	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	2 (2.0)	2	4.0
Vomiting	0			0			0			3 (3.0)	3	6.0
Aphthous ulcer	0			1 (1.0)	2	3.9	1 (0.5)	2	1.9	0		
Chronic gastritis	1 (1.0)	1	1.9	1 (1.0)	1	2.0	2 (1.0)	2	1.9	0		
Constipation	1 (1.0)	1	1.9	1 (1.0)	1	2.0	2 (1.0)	2	1.9	0		
Dental caries	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	1 (1.0)	1	2.0

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Adverse events by system organ class and preferred term - treatment emergent - summary - 25 <= BMI at baseline < 30 kg/m^2 - trial 4131 - on -treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Food poisoning	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	1 (1.0)	1	2.0
Periodontal disease	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	1 (1.0)	1	2.0
Toothache	2 (1.9)	2	3.8	0			2 (1.0)	2	1.9	0		
Abdominal distension	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Abdominal pain upper	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Dyspepsia	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Haemorrhoids	0			0			0			1 (1.0)	1	2.0
Hiatus hernia	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Oral discomfort	0			0			0			1 (1.0)	1	2.0
Proctalgia	0			0			0			1 (1.0)	1	2.0
Injury, poisoning and procedural complications	12 (11.4)	16	30.3	6 (5.8)	9	17.6	18 (8.6)	25	24.0	11 (11.1)	14	27.9
Wrong drug administered	3 (2.9)	4	7.6	3 (2.9)	5	9.8	6 (2.9)	9	8.7	3 (3.0)	3	6.0
Limb injury	3 (2.9)	3	5.7	0			3 (1.4)	3	2.9	1 (1.0)	1	2.0
Contusion	2 (1.9)	2	3.8	1 (1.0)	1	2.0	3 (1.4)	3	2.9	0		
Fall	1 (1.0)	1	1.9	1 (1.0)	1	2.0	2 (1.0)	2	1.9	0		
Foot fracture	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	1 (1.0)	1	2.0
Ligament sprain	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	1 (1.0)	1	2.0
Skin abrasion	0			0			0			1 (1.0)	2	4.0
Accidental overdose	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Foreign body in eye	0			0			0			1 (1.0)	1	2.0
Hand fracture	0			0			0			1 (1.0)	1	2.0
Joint dislocation	0			0			0			1 (1.0)	1	2.0
Laceration	0			0			0			1 (1.0)	1	2.0
Ligament rupture	0			0			0			1 (1.0)	1	2.0
Muscle strain	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Postoperative ileus	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Radius fracture	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Tooth fracture	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Traumatic fracture	0			0			0			1 (1.0)	1	2.0
Ulna fracture	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
General disorders and administration site conditions	10 (9.5)	15	28.4	7 (6.7)	13	25.4	17 (8.1)	28	26.9	6 (6.1)	8	15.9
Influenza like illness	3 (2.9)	5	9.5	2 (1.9)	2	3.9	5 (2.4)	7	6.7	1 (1.0)	2	4.0
Fatigue	0			2 (1.9)	3	5.9	2 (1.0)	3	2.9	0		
Injection site bruising	1 (1.0)	2	3.8	1 (1.0)	1	2.0	2 (1.0)	3	2.9	0		
Pyrexia	3 (2.9)	3	5.7	0			3 (1.4)	3	2.9	0		
Injection site haematoma	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	1 (1.0)	1	2.0
Injection site pain	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	1 (1.0)	1	2.0
Malaise	2 (1.9)	2	3.8	0			2 (1.0)	2	1.9	0		
Oedema peripheral	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	1 (1.0)	1	2.0
Peripheral swelling	0			2 (1.9)	2	3.9	2 (1.0)	2	1.9	0		
Asthenia	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Chest discomfort	0			0			0			1 (1.0)	1	2.0
Chest pain	0			0			0			1 (1.0)	1	2.0
General symptom	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Injection site haemorrhage	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Injection site rash	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Injection site reaction	0			0			0			1 (1.0)	1	2.0
Oedema	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Musculoskeletal and connective tissue disorders	5 (4.8)	5	9.5	12 (11.5)	14	27.3	17 (8.1)	19	18.3	10 (10.1)	12	23.9
Pain in extremity	2 (1.9)	2	3.8	4 (3.8)	4	7.8	6 (2.9)	6	5.8	1 (1.0)	1	2.0
Back pain	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	3 (3.0)	3	6.0
Arthralgia	0			2 (1.9)	2	3.9	2 (1.0)	2	1.9	0		
Muscle spasms	0			0			0			2 (2.0)	2	4.0
Musculoskeletal pain	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	1 (1.0)	1	2.0

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	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Myalgia	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	1 (1.0)	1	2.0
Neck pain	0			2 (1.9)	2	3.9	2 (1.0)	2	1.9	0		
Trigger finger	0			0			0			1 (1.0)	2	4.0
Arthritis	0			0			0			1 (1.0)	1	2.0
Bursitis	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Lumbar spinal stenosis	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Muscular weakness	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Musculoskeletal stiffness	0			0			0			1 (1.0)	1	2.0
Periarthritis	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Rheumatic disorder	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Tendonitis	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Metabolism and nutrition disorders	11 (10.5)	12	22.8	5 (4.8)	9	17.6	16 (7.7)	21	20.2	5 (5.1)	5	10.0
Hypoglycaemia	9 (8.6)	10	19.0	2 (1.9)	5	9.8	11 (5.3)	15	14.4	5 (5.1)	5	10.0
Hyperglycaemia	1 (1.0)	1	1.9	1 (1.0)	1	2.0	2 (1.0)	2	1.9	0		
Decreased appetite	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Diabetic metabolic decompensation	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Hypoglycaemia unawareness	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Vitamin D deficiency	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Eye disorders	3 (2.9)	3	5.7	10 (9.6)	12	23.4	13 (6.2)	15	14.4	8 (8.1)	8	15.9
Diabetic retinopathy	1 (1.0)	1	1.9	2 (1.9)	2	3.9	3 (1.4)	3	2.9	2 (2.0)	2	4.0
Macular oedema	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	2 (2.0)	2	4.0
Dry eye	0			2 (1.9)	2	3.9	2 (1.0)	2	1.9	0		
Retinopathy hypertensive	0			2 (1.9)	2	3.9	2 (1.0)	2	1.9	0		
Astigmatism	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Cystoid macular oedema	0			0			0			1 (1.0)	1	2.0
Eye inflammation	0			0			0			1 (1.0)	1	2.0
Eye pruritus	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Eye ulcer	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Myopia	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Retinal aneurysm	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Retinal exudates	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Retinal ischaemia	0			0			0			1 (1.0)	1	2.0
Retinal tear	0			0			0			1 (1.0)	1	2.0
Vitreous detachment	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Skin and subcutaneous tissue disorders	6 (5.7)	8	15.2	5 (4.8)	7	13.7	11 (5.3)	15	14.4	3 (3.0)	3	6.0
Dermatitis	1 (1.0)	3	5.7	0			1 (0.5)	3	2.9	0		
Alopecia	0			0			0			1 (1.0)	1	2.0
Blister	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Blood blister	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Dermatitis contact	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Lipohypertrophy	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Papule	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Parapsoriasis	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Pruritus	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Rash	0			0			0			1 (1.0)	1	2.0
Skin exfoliation	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Skin fissures	0			0			0			1 (1.0)	1	2.0
Skin mass	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Skin reaction	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Skin ulcer	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Urticaria	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Respiratory, thoracic and mediastinal disorders	5 (4.8)	6	11.4	4 (3.8)	4	7.8	9 (4.3)	10	9.6	6 (6.1)	6	12.0
Oropharyngeal pain	1 (1.0)	1	1.9	1 (1.0)	1	2.0	2 (1.0)	2	1.9	1 (1.0)	1	2.0
Sinus congestion	1 (1.0)	1	1.9	2 (1.9)	2	3.9	3 (1.4)	3	2.9	0		
Cough	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	1 (1.0)	1	2.0

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Nasal congestion	2 (1.9)	2	3.8	0			2 (1.0)	2	1.9	0		
Asthma	0			0			0			1 (1.0)	1	2.0
Dyspnoea	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Epistaxis	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Rhinorrhoea	0			0			0			1 (1.0)	1	2.0
Upper respiratory tract congestion	0			0			0			1 (1.0)	1	2.0
Upper respiratory tract inflammation	0			0			0			1 (1.0)	1	2.0
Immune system disorders	0			3 (2.9)	5	9.8	3 (1.4)	5	4.8	1 (1.0)	1	2.0
Hypersensitivity	0			1 (1.0)	3	5.9	1 (0.5)	3	2.9	0		
Seasonal allergy	0			2 (1.9)	2	3.9	2 (1.0)	2	1.9	0		
Multiple allergies	0			0			0			1 (1.0)	1	2.0
Psychiatric disorders	3 (2.9)	3	5.7	2 (1.9)	2	3.9	5 (2.4)	5	4.8	1 (1.0)	1	2.0
Insomnia	1 (1.0)	1	1.9	1 (1.0)	1	2.0	2 (1.0)	2	1.9	1 (1.0)	1	2.0
Depression	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Sleep disorder	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Stress	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Vascular disorders	3 (2.9)	3	5.7	2 (1.9)	2	3.9	5 (2.4)	5	4.8	1 (1.0)	1	2.0
Hypertension	1 (1.0)	1	1.9	2 (1.9)	2	3.9	3 (1.4)	3	2.9	0		
Arteriosclerosis	0			0			0			1 (1.0)	1	2.0
Orthostatic hypotension	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Peripheral arterial occlusive disease	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Reproductive system and breast disorders	2 (1.9)	2	3.8	2 (1.9)	3	5.9	4 (1.9)	5	4.8	0		
Priapism	0			1 (1.0)	2	3.9	1 (0.5)	2	1.9	0		
Benign prostatic hyperplasia	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Gynaecomastia	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Vulvovaginal inflammation	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Blood and lymphatic system disorders	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	3 (3.0)	3	6.0
Anaemia	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	2 (2.0)	2	4.0
Iron deficiency anaemia	0			0			0			1 (1.0)	1	2.0
Ear and labyrinth disorders	2 (1.9)	2	3.8	1 (1.0)	2	3.9	3 (1.4)	4	3.8	0		
Tinnitus	1 (1.0)	1	1.9	1 (1.0)	1	2.0	2 (1.0)	2	1.9	0		
Ear pain	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Sudden hearing loss	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Renal and urinary disorders	2 (1.9)	2	3.8	2 (1.9)	2	3.9	4 (1.9)	4	3.8	0		
Acute kidney injury	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Bladder pain	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Haematuria	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Renal failure	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Cardiac disorders	1 (1.0)	1	1.9	2 (1.9)	2	3.9	3 (1.4)	3	2.9	0		
Myocardial ischaemia	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Palpitations	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Ventricular extrasystoles	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0)	1	1.9	2 (1.9)	2	3.9	3 (1.4)	3	2.9	0		
Bladder transitional cell carcinoma	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Conjunctival neoplasm	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Skin papilloma	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Surgical and medical procedures	2 (1.9)	2	3.8	0			2 (1.0)	2	1.9	1 (1.0)	1	2.0
Cataract operation	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Endodontic procedure	0			0			0			1 (1.0)	1	2.0

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Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - 25 <= BMI at baseline < 30 kg/m^2 - trial 4131 - on -treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Haemorrhoid operation	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Endocrine disorders	0			1 (1.0)	2	3.9	1 (0.5)	2	1.9	0		
Goitre	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Thyroid cyst	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Hepatobiliary disorders	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	1 (1.0)	1	2.0
Hepatic steatosis	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	1 (1.0)	1	2.0

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MedDRA version 20.0.

2.7.4.7.3.2.7. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインの BMI（kg/m^2）が 30 以上の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N	(%)	E R	N	(%)	E R	N	(%)	E R	N	(%)	E R
Number of subjects	47			52			99			49		
Total exposure (yrs)	23.4			26.3			49.7			24.4		
Total events	36	(76.6)	104 444.2	39	(75.0)	125 475.2	75	(75.8)	229 460.6	40	(81.6)	112 459.6
Infections and infestations	24	(51.1)	39 166.6	26	(50.0)	57 216.7	50	(50.5)	96 193.1	27	(55.1)	47 192.9
Viral upper respiratory tract infection	10	(21.3)	13 55.5	15	(28.8)	23 87.4	25	(25.3)	36 72.4	13	(26.5)	21 86.2
Upper respiratory tract infection	5	(10.6)	7 29.9	4	(7.7)	5 19.0	9	(9.1)	12 24.1	8	(16.3)	9 36.9
Influenza	5	(10.6)	5 21.4	6	(11.5)	6 22.8	11	(11.1)	11 22.1	1	(2.0)	1 4.1
Gastroenteritis	2	(4.3)	3 12.8	3	(5.8)	4 15.2	5	(5.1)	7 14.1	1	(2.0)	3 12.3
Urinary tract infection	1	(2.1)	1 4.3	4	(7.7)	6 22.8	5	(5.1)	7 14.1	1	(2.0)	1 4.1
Sinusitis	1	(2.1)	1 4.3	3	(5.8)	3 11.4	4	(4.0)	4 8.0	3	(6.1)	3 12.3
Tonsillitis	1	(2.1)	3 12.8	1	(1.9)	1 3.8	2	(2.0)	4 8.0	0		
Bronchitis	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	2	(4.1)	2 8.2
Gastroenteritis viral	2	(4.3)	2 8.5	0			2	(2.0)	2 4.0	1	(2.0)	1 4.1
Acute sinusitis	1	(2.1)	1 4.3	1	(1.9)	1 3.8	2	(2.0)	2 4.0	0		
Onychomycosis	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	1	(2.0)	1 4.1
Rhinitis	0			0			0			2	(4.1)	2 8.2
Conjunctivitis	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	0		
Cystitis	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	0		
Herpes ophthalmic	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	0		
Infectious mononucleosis	0			0			0			1	(2.0)	1 4.1
Otitis media	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	0		
Otitis media acute	0			0			0			1	(2.0)	1 4.1
Pharyngitis	1	(2.1)	1 4.3	0			1	(1.0)	1 2.0	0		
Pharyngitis streptococcal	1	(2.1)	1 4.3	0			1	(1.0)	1 2.0	0		
Skin infection	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	0		
Urethritis	0			0			0			1	(2.0)	1 4.1

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - BMI at baseline >= 30 kg/m^2 - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Viral infection	0				1	(1.9)	1	3.8	1	(1.0)	1	2.0	0			
Viral rhinitis	1	(2.1)	1	4.3	0				1	(1.0)	1	2.0	0			
Investigations	7	(14.9)	10	42.7	16	(30.8)	18	68.4	23	(23.2)	28	56.3	8	(16.3)	12	49.2
Blood glucose decreased	6	(12.8)	9	38.4	15	(28.8)	17	64.6	21	(21.2)	26	52.3	6	(12.2)	6	24.6
Blood creatinine increased	0				0				0				1	(2.0)	1	4.1
Blood thyroid stimulating hormone	1	(2.1)	1	4.3	0				1	(1.0)	1	2.0	0			
Electrocardiogram change	0				0				0				1	(2.0)	1	4.1
Haematocrit decreased	0				0				0				1	(2.0)	1	4.1
Haemoglobin decreased	0				0				0				1	(2.0)	1	4.1
Heart rate increased	0				0				0				1	(2.0)	1	4.1
Hepatic enzyme increased	0				0				0				1	(2.0)	1	4.1
Weight increased	0				1	(1.9)	1	3.8	1	(1.0)	1	2.0	0			
Musculoskeletal and connective tissue disorders	11	(23.4)	16	68.3	7	(13.5)	8	30.4	18	(18.2)	24	48.3	5	(10.2)	5	20.5
Back pain	1	(2.1)	1	4.3	3	(5.8)	4	15.2	4	(4.0)	5	10.1	1	(2.0)	1	4.1
Pain in extremity	4	(8.5)	4	17.1	0				4	(4.0)	4	8.0	1	(2.0)	1	4.1
Muscle spasms	2	(4.3)	2	8.5	0				2	(2.0)	2	4.0	1	(2.0)	1	4.1
Myalgia	2	(4.3)	3	12.8	0				2	(2.0)	3	6.0	0			
Arthralgia	1	(2.1)	1	4.3	1	(1.9)	1	3.8	2	(2.0)	2	4.0	0			
Arthritis	1	(2.1)	1	4.3	0				1	(1.0)	1	2.0	0			
Intervertebral disc degeneration	0				0				0				1	(2.0)	1	4.1
Intervertebral disc disorder	0				1	(1.9)	1	3.8	1	(1.0)	1	2.0	0			
Joint effusion	1	(2.1)	1	4.3	0				1	(1.0)	1	2.0	0			
Joint swelling	0				1	(1.9)	1	3.8	1	(1.0)	1	2.0	0			
Neck pain	1	(2.1)	1	4.3	0				1	(1.0)	1	2.0	0			
Plantar fasciitis	0				1	(1.9)	1	3.8	1	(1.0)	1	2.0	0			
Rotator cuff syndrome	1	(2.1)	1	4.3	0				1	(1.0)	1	2.0	0			
Spinal osteoarthritis	1	(2.1)	1	4.3	0				1	(1.0)	1	2.0	0			

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - BMI at baseline >= 30 kg/m^2 - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Tenosynovitis	0				0				0				1	(2.0)	1	4.1
Injury, poisoning and procedural complications	5	(10.6)	5	21.4	8	(15.4)	9	34.2	13	(13.1)	14	28.2	5	(10.2)	5	20.5
Wrong drug administered	1	(2.1)	1	4.3	2	(3.8)	2	7.6	3	(3.0)	3	6.0	2	(4.1)	2	8.2
Fall	1	(2.1)	1	4.3	2	(3.8)	2	7.6	3	(3.0)	3	6.0	0			
Ligament sprain	1	(2.1)	1	4.3	2	(3.8)	2	7.6	3	(3.0)	3	6.0	0			
Contusion	0				1	(1.9)	1	3.8	1	(1.0)	1	2.0	1	(2.0)	1	4.1
Muscle strain	2	(4.3)	2	8.5	0				2	(2.0)	2	4.0	0			
Accidental underdose	0				1	(1.9)	1	3.8	1	(1.0)	1	2.0	0			
Eyelid injury	0				0				0				1	(2.0)	1	4.1
Foot fracture	0				0				0				1	(2.0)	1	4.1
Tendon rupture	0				1	(1.9)	1	3.8	1	(1.0)	1	2.0	0			
Metabolism and nutrition disorders	7	(14.9)	7	29.9	5	(9.6)	6	22.8	12	(12.1)	13	26.1	4	(8.2)	5	20.5
Hypoglycaemia	5	(10.6)	5	21.4	3	(5.8)	3	11.4	8	(8.1)	8	16.1	2	(4.1)	3	12.3
Hyperlipidaemia	1	(2.1)	1	4.3	1	(1.9)	1	3.8	2	(2.0)	2	4.0	1	(2.0)	1	4.1
Diabetic metabolic decompensation	0				0				0				1	(2.0)	1	4.1
Fluid retention	0				1	(1.9)	1	3.8	1	(1.0)	1	2.0	0			
Gout	1	(2.1)	1	4.3	0				1	(1.0)	1	2.0	0			
Vitamin D deficiency	0				1	(1.9)	1	3.8	1	(1.0)	1	2.0	0			
Nervous system disorders	6	(12.8)	6	25.6	2	(3.8)	2	7.6	8	(8.1)	8	16.1	3	(6.1)	10	41.0
Headache	0				1	(1.9)	1	3.8	1	(1.0)	1	2.0	1	(2.0)	8	32.8
Hypoglycaemic unconsciousness	2	(4.3)	2	8.5	0				2	(2.0)	2	4.0	0			
Carpal tunnel syndrome	1	(2.1)	1	4.3	0				1	(1.0)	1	2.0	0			
Hypoaesthesia	0				1	(1.9)	1	3.8	1	(1.0)	1	2.0	0			
Lethargy	1	(2.1)	1	4.3	0				1	(1.0)	1	2.0	0			
Paraesthesia	1	(2.1)	1	4.3	0				1	(1.0)	1	2.0	0			
Syncope	0				0				0				1	(2.0)	1	4.1

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - BMI at baseline >= 30 kg/m^2 - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Tension headache	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		
Tremor	0			0			0			1 (2.0)	1	4.1
Gastrointestinal disorders	3 (6.4)	3	12.8	5 (9.6)	7	26.6	8 (8.1)	10	20.1	7 (14.3)	7	28.7
Nausea	1 (2.1)	1	4.3	1 (1.9)	1	3.8	2 (2.0)	2	4.0	1 (2.0)	1	4.1
Toothache	0			2 (3.8)	2	7.6	2 (2.0)	2	4.0	1 (2.0)	1	4.1
Abdominal pain	0			0			0			2 (4.1)	2	8.2
Hiatus hernia	0			2 (3.8)	2	7.6	2 (2.0)	2	4.0	0		
Abdominal discomfort	0			0			0			1 (2.0)	1	4.1
Coeliac disease	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		
Colitis ulcerative	0			1 (1.9)	1	3.8	1 (1.0)	1	2.0	0		
Dental caries	0			1 (1.9)	1	3.8	1 (1.0)	1	2.0	0		
Diarrhoea	0			0			0			1 (2.0)	1	4.1
Gastrooesophageal reflux disease	0			0			0			1 (2.0)	1	4.1
Vomiting	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		
Eye disorders	4 (8.5)	4	17.1	4 (7.7)	5	19.0	8 (8.1)	9	18.1	4 (8.2)	4	16.4
Diabetic retinopathy	2 (4.3)	2	8.5	1 (1.9)	1	3.8	3 (3.0)	3	6.0	1 (2.0)	1	4.1
Retinopathy proliferative	0			1 (1.9)	1	3.8	1 (1.0)	1	2.0	1 (2.0)	1	4.1
Blepharochalasis	0			0			0			1 (2.0)	1	4.1
Chalazion	0			1 (1.9)	1	3.8	1 (1.0)	1	2.0	0		
Iritis	0			0			0			1 (2.0)	1	4.1
Normal tension glaucoma	0			1 (1.9)	1	3.8	1 (1.0)	1	2.0	0		
Retinal haemorrhage	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		
Retinopathy	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		
Vitreous haemorrhage	0			1 (1.9)	1	3.8	1 (1.0)	1	2.0	0		
Respiratory, thoracic and mediastinal disorders	4 (8.5)	4	17.1	2 (3.8)	2	7.6	6 (6.1)	6	12.1	5 (10.2)	6	24.6
Oropharyngeal pain	0			0			0			2 (4.1)	3	12.3

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - BMI at baseline >= 30 kg/m^2 - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Epistaxis	0			1 (1.9)	1	3.8	1 (1.0)	1	2.0	1 (2.0)	1	4.1
Rhinorrhoea	2 (4.3)	2	8.5	0			2 (2.0)	2	4.0	0		
Asthma	0			1 (1.9)	1	3.8	1 (1.0)	1	2.0	0		
Chronic obstructive pulmonary disease	0			0			0			1 (2.0)	1	4.1
Dyspnoea	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		
Sinus congestion	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		
Throat irritation	0			0			0			1 (2.0)	1	4.1
Skin and subcutaneous tissue disorders	2 (4.3)	3	12.8	4 (7.7)	4	15.2	6 (6.1)	7	14.1	5 (10.2)	5	20.5
Dermatitis	0			2 (3.8)	2	7.6	2 (2.0)	2	4.0	0		
Urticaria	0			1 (1.9)	1	3.8	1 (1.0)	1	2.0	1 (2.0)	1	4.1
Actinic keratosis	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		
Eczema asteatotic	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		
Nail pigmentation	0			0			0			1 (2.0)	1	4.1
Onychomadesis	0			0			0			1 (2.0)	1	4.1
Pruritus	0			1 (1.9)	1	3.8	1 (1.0)	1	2.0	0		
Rash	0			0			0			1 (2.0)	1	4.1
Rash pruritic	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		
Skin lesion	0			0			0			1 (2.0)	1	4.1
General disorders and administration site conditions	6 (12.8)	6	25.6	1 (1.9)	1	3.8	7 (7.1)	7	14.1	2 (4.1)	2	8.2
Oedema peripheral	0			1 (1.9)	1	3.8	1 (1.0)	1	2.0	1 (2.0)	1	4.1
Pyrexia	2 (4.3)	2	8.5	0			2 (2.0)	2	4.0	0		
Fatigue	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		
Inflammation	0			0			0			1 (2.0)	1	4.1
Influenza like illness	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		
Injection site haematoma	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		
Injection site pain	1 (2.1)	1	4.3	0			1 (1.0)	1	2.0	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - BMI at baseline >= 30 kg/m^2 - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N	(%)	E R	N	(%)	E R	N	(%)	E R	N	(%)	E R
Endocrine disorders	0			2	(3.8)	2 7.6	2	(2.0)	2 4.0	1	(2.0)	1 4.1
Goitre	0			0			0			1	(2.0)	1 4.1
Hyperadrenalism	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	0		
Hypothyroidism	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	0		
Renal and urinary disorders	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	1	(2.0)	2 8.2
Dysuria	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	0		
Haematuria	0			0			0			1	(2.0)	1 4.1
Microalbuminuria	0			0			0			1	(2.0)	1 4.1
Ear and labyrinth disorders	0			2	(3.8)	2 7.6	2	(2.0)	2 4.0	0		
Ear discomfort	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	0		
Ear pain	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	0		
Psychiatric disorders	1	(2.1)	1 4.3	1	(1.9)	1 3.8	2	(2.0)	2 4.0	0		
Depression	1	(2.1)	1 4.3	0			1	(1.0)	1 2.0	0		
Stress	0			1	(1.9)	1 3.8	1	(1.0)	1 2.0	0		
Vascular disorders	0			0			0			1	(2.0)	1 4.1
Hypertension	0			0			0			1	(2.0)	1 4.1

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.8. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインの HbA1c が 8%未満の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	265				280				545				276			
Total exposure (yrs)	132.7				139.7				272.4				137.1			
Total events	180	(67.9)	488	367.8	195	(69.6)	536	383.7	375	(68.8)	1024	376.0	200	(72.5)	515	375.7
Infections and infestations	105	(39.6)	176	132.6	105	(37.5)	188	134.6	210	(38.5)	364	133.6	118	(42.8)	194	141.5
Viral upper respiratory tract infection	56	(21.1)	79	59.5	62	(22.1)	88	63.0	118	(21.7)	167	61.3	69	(25.0)	101	73.7
Upper respiratory tract infection	22	(8.3)	29	21.9	21	(7.5)	29	20.8	43	(7.9)	58	21.3	17	(6.2)	20	14.6
Gastroenteritis	7	(2.6)	8	6.0	10	(3.6)	11	7.9	17	(3.1)	19	7.0	9	(3.3)	11	8.0
Influenza	11	(4.2)	11	8.3	10	(3.6)	10	7.2	21	(3.9)	21	7.7	9	(3.3)	9	6.6
Urinary tract infection	5	(1.9)	6	4.5	5	(1.8)	7	5.0	10	(1.8)	13	4.8	4	(1.4)	4	2.9
Sinusitis	4	(1.5)	4	3.0	5	(1.8)	5	3.6	9	(1.7)	9	3.3	3	(1.1)	3	2.2
Viral infection	3	(1.1)	5	3.8	3	(1.1)	4	2.9	6	(1.1)	9	3.3	3	(1.1)	3	2.2
Pharyngitis	2	(0.8)	2	1.5	1	(0.4)	1	0.7	3	(0.6)	3	1.1	2	(0.7)	5	3.6
Rhinitis	3	(1.1)	3	2.3	0				3	(0.6)	3	1.1	5	(1.8)	5	3.6
Bronchitis	0				4	(1.4)	4	2.9	4	(0.7)	4	1.5	3	(1.1)	3	2.2
Cystitis	1	(0.4)	2	1.5	2	(0.7)	2	1.4	3	(0.6)	4	1.5	2	(0.7)	2	1.5
Gastroenteritis viral	2	(0.8)	2	1.5	0				2	(0.4)	2	0.7	4	(1.4)	4	2.9
Otitis media	3	(1.1)	3	2.3	1	(0.4)	1	0.7	4	(0.7)	4	1.5	1	(0.4)	1	0.7
Acute sinusitis	1	(0.4)	1	0.8	2	(0.7)	2	1.4	3	(0.6)	3	1.1	0			
Cellulitis	2	(0.8)	2	1.5	1	(0.4)	1	0.7	3	(0.6)	3	1.1	0			
Ear infection	1	(0.4)	2	1.5	1	(0.4)	1	0.7	2	(0.4)	3	1.1	0			
Herpes zoster	2	(0.8)	2	1.5	1	(0.4)	1	0.7	3	(0.6)	3	1.1	0			
Otitis externa	2	(0.8)	2	1.5	1	(0.4)	1	0.7	3	(0.6)	3	1.1	0			
Tonsillitis	1	(0.4)	3	2.3	0				1	(0.2)	3	1.1	0			
Conjunctivitis	0				2	(0.7)	2	1.4	2	(0.4)	2	0.7	0			
Fungal infection	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	1	(0.4)	1	0.7
Onychomycosis	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	1	(0.4)	1	0.7

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Adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline < 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Periodontitis	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Respiratory tract infection	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	0		
Respiratory tract infection viral	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	0		
Skin infection	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Abscess limb	0			0			0			1 (0.4)	1	0.7
Adenoiditis	0			0			0			1 (0.4)	1	0.7
Angular cheilitis	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Candida infection	0			0			0			1 (0.4)	1	0.7
Cytomegalovirus infection	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Diverticulitis	0			0			0			1 (0.4)	1	0.7
Epstein-Barr virus infection	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Folliculitis	0			0			0			1 (0.4)	1	0.7
Fungal skin infection	0			0			0			1 (0.4)	1	0.7
Furuncle	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Gastrointestinal viral infection	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Gingivitis	0			0			0			1 (0.4)	1	0.7
Herpes ophthalmic	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Impetigo	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Infectious mononucleosis	0			0			0			1 (0.4)	1	0.7
Labyrinthitis	0			0			0			1 (0.4)	1	0.7
Laryngitis	0			0			0			1 (0.4)	1	0.7
Localised infection	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Lower respiratory tract infection bacterial	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Molluscum contagiosum	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Nasopharyngitis	0			0			0			1 (0.4)	1	0.7
Oral herpes	0			0			0			1 (0.4)	1	0.7
Oral infection	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Otitis media acute	0			0			0			1 (0.4)	1	0.7
Paronychia	0			0			0			1 (0.4)	1	0.7

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Adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline < 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Pharyngitis streptococcal	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Pilonidal cyst	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Pneumonia	0				0				0				1	(0.4)	1	0.7
Pulpitis dental	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Pyelonephritis chronic	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Spermatic cord funiculitis	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Subcutaneous abscess	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Syphilis	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Tooth abscess	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Urethritis	0				0				0				1	(0.4)	1	0.7
Varicella	0				0				0				1	(0.4)	1	0.7
Viral rhinitis	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Vulvovaginal candidiasis	0				0				0				1	(0.4)	1	0.7
Vulvovaginal mycotic infection	0				0				0				1	(0.4)	1	0.7
Investigations	48	(18.1)	68	51.2	65	(23.2)	83	59.4	113	(20.7)	151	55.4	60	(21.7)	75	54.7
Blood glucose decreased	41	(15.5)	60	45.2	60	(21.4)	73	52.3	101	(18.5)	133	48.8	56	(20.3)	67	48.9
Blood pressure increased	2	(0.8)	2	1.5	0				2	(0.4)	2	0.7	1	(0.4)	1	0.7
Hepatic enzyme increased	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	2	(0.7)	2	1.5
Blood creatinine increased	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	1	(0.4)	1	0.7
Urine albumin/creatinine ratio increased	1	(0.4)	1	0.8	1	(0.4)	1	0.7	2	(0.4)	2	0.7	0			
Weight increased	0				2	(0.7)	2	1.4	2	(0.4)	2	0.7	0			
Alanine aminotransferase increased	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Aspartate aminotransferase increased	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Blood 1,5-anhydroglucitol decreased	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Blood bilirubin increased	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Blood thyroid stimulating hormone	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Blood urine present	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Electrocardiogram change	0				0				0				1	(0.4)	1	0.7

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline < 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Haematocrit decreased	0			0			0			1 (0.4)	1	0.7
Haemoglobin decreased	0			0			0			1 (0.4)	1	0.7
Heart rate increased	0			0			0			1 (0.4)	1	0.7
Helicobacter test positive	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Lipids abnormal	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Protein urine present	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Transaminases increased	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Gastrointestinal disorders	25 (9.4)	40	30.1	26 (9.3)	38	27.2	51 (9.4)	78	28.6	33 (12.0)	41	29.9
Nausea	8 (3.0)	9	6.8	2 (0.7)	2	1.4	10 (1.8)	11	4.0	7 (2.5)	9	6.6
Diarrhoea	2 (0.8)	2	1.5	7 (2.5)	7	5.0	9 (1.7)	9	3.3	4 (1.4)	4	2.9
Gastritis	2 (0.8)	3	2.3	5 (1.8)	6	4.3	7 (1.3)	9	3.3	3 (1.1)	3	2.2
Vomiting	3 (1.1)	4	3.0	2 (0.7)	2	1.4	5 (0.9)	6	2.2	4 (1.4)	4	2.9
Toothache	2 (0.8)	2	1.5	3 (1.1)	3	2.1	5 (0.9)	5	1.8	2 (0.7)	2	1.5
Food poisoning	2 (0.8)	2	1.5	2 (0.7)	2	1.4	4 (0.7)	4	1.5	2 (0.7)	2	1.5
Gastrooesophageal reflux disease	3 (1.1)	3	2.3	0			3 (0.6)	3	1.1	3 (1.1)	3	2.2
Abdominal pain upper	1 (0.4)	1	0.8	3 (1.1)	3	2.1	4 (0.7)	4	1.5	1 (0.4)	1	0.7
Abdominal discomfort	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	2 (0.7)	2	1.5
Constipation	4 (1.5)	4	3.0	0			4 (0.7)	4	1.5	0		
Dental caries	1 (0.4)	1	0.8	2 (0.7)	2	1.4	3 (0.6)	3	1.1	1 (0.4)	1	0.7
Dyspepsia	1 (0.4)	1	0.8	2 (0.7)	2	1.4	3 (0.6)	3	1.1	1 (0.4)	1	0.7
Abdominal pain	0			0			0			3 (1.1)	3	2.2
Aphthous ulcer	0			1 (0.4)	2	1.4	1 (0.2)	2	0.7	1 (0.4)	1	0.7
Abdominal distension	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	0		
Enteritis	0			2 (0.7)	2	1.4	2 (0.4)	2	0.7	0		
Stomatitis	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Coeliac disease	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Enterocolitis	0			0			0			1 (0.4)	1	0.7
Gastric polyps	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Gastric ulcer	0			0			0			1 (0.4)	1	0.7

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Adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline < 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Gastritis erosive	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Gastrointestinal disorder	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Haemorrhoids	0			0			0			1 (0.4)	1	0.7
Hiatus hernia	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Hyperchlorhydria	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Periodontal disease	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Proctalgia	0			0			0			1 (0.4)	1	0.7
Retching	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Musculoskeletal and connective tissue disorders	21 (7.9)	28	21.1	23 (8.2)	25	17.9	44 (8.1)	53	19.5	27 (9.8)	35	25.5
Back pain	2 (0.8)	2	1.5	6 (2.1)	7	5.0	8 (1.5)	9	3.3	5 (1.8)	5	3.6
Pain in extremity	7 (2.6)	7	5.3	2 (0.7)	2	1.4	9 (1.7)	9	3.3	3 (1.1)	3	2.2
Arthralgia	2 (0.8)	2	1.5	4 (1.4)	4	2.9	6 (1.1)	6	2.2	2 (0.7)	2	1.5
Muscle spasms	2 (0.8)	2	1.5	1 (0.4)	1	0.7	3 (0.6)	3	1.1	4 (1.4)	4	2.9
Myalgia	3 (1.1)	4	3.0	0			3 (0.6)	4	1.5	2 (0.7)	3	2.2
Musculoskeletal pain	4 (1.5)	4	3.0	0			4 (0.7)	4	1.5	1 (0.4)	1	0.7
Trigger finger	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	2 (0.7)	3	2.2
Arthritis	2 (0.8)	2	1.5	0			2 (0.4)	2	0.7	1 (0.4)	1	0.7
Neck pain	1 (0.4)	1	0.8	2 (0.7)	2	1.4	3 (0.6)	3	1.1	0		
Intervertebral disc disorder	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Intervertebral disc protrusion	0			0			0			2 (0.7)	2	1.5
Musculoskeletal stiffness	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Periarthritis	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Arthropathy	0			0			0			1 (0.4)	1	0.7
Bursitis	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Collagen disorder	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Exostosis	0			0			0			1 (0.4)	1	0.7
Flank pain	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Intervertebral disc degeneration	0			0			0			1 (0.4)	1	0.7

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	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Joint swelling	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Muscular weakness	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Musculoskeletal chest pain	0			0			0			1 (0.4)	1	0.7
Myositis	0			0			0			1 (0.4)	1	0.7
Osteoarthritis	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Osteoporotic fracture	0			0			0			1 (0.4)	1	0.7
Plantar fasciitis	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Rheumatoid arthritis	0			0			0			1 (0.4)	1	0.7
Rotator cuff syndrome	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Spinal osteoarthritis	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Tenosynovitis	0			0			0			1 (0.4)	1	0.7
Nervous system disorders	19 (7.2)	23	17.3	21 (7.5)	31	22.2	40 (7.3)	54	19.8	14 (5.1)	25	18.2
Headache	4 (1.5)	6	4.5	10 (3.6)	17	12.2	14 (2.6)	23	8.4	4 (1.4)	14	10.2
Hypoglycaemic unconsciousness	2 (0.8)	2	1.5	3 (1.1)	3	2.1	5 (0.9)	5	1.8	2 (0.7)	2	1.5
Dizziness	1 (0.4)	1	0.8	3 (1.1)	3	2.1	4 (0.7)	4	1.5	2 (0.7)	2	1.5
Hypoaesthesia	0			2 (0.7)	2	1.4	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Hypoglycaemic seizure	2 (0.8)	2	1.5	1 (0.4)	1	0.7	3 (0.6)	3	1.1	0		
Paraesthesia	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Diabetic neuropathy	2 (0.8)	2	1.5	0			2 (0.4)	2	0.7	0		
Lethargy	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Migraine	2 (0.8)	2	1.5	0			2 (0.4)	2	0.7	0		
Presyncope	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Syncope	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Carotid arteriosclerosis	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Carpal tunnel syndrome	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Hypertonia	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Hypoglycaemic coma	0			0			0			1 (0.4)	1	0.7
Hyporeflexia	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Lumbar radiculopathy	0			0			0			1 (0.4)	1	0.7

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Memory impairment	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Polyneuropathy	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Post herpetic neuralgia	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Tension headache	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Injury, poisoning and procedural complications	26 (9.8)	32	24.1	19 (6.8)	21	15.0	45 (8.3)	53	19.5	22 (8.0)	25	18.2
Wrong drug administered	7 (2.6)	8	6.0	7 (2.5)	7	5.0	14 (2.6)	15	5.5	5 (1.8)	5	3.6
Ligament sprain	2 (0.8)	2	1.5	3 (1.1)	3	2.1	5 (0.9)	5	1.8	2 (0.7)	2	1.5
Contusion	1 (0.4)	1	0.8	3 (1.1)	3	2.1	4 (0.7)	4	1.5	1 (0.4)	1	0.7
Limb injury	3 (1.1)	3	2.3	0			3 (0.6)	3	1.1	1 (0.4)	1	0.7
Muscle strain	4 (1.5)	4	3.0	0			4 (0.7)	4	1.5	0		
Tooth fracture	3 (1.1)	3	2.3	0			3 (0.6)	3	1.1	1 (0.4)	1	0.7
Fall	2 (0.8)	2	1.5	1 (0.4)	1	0.7	3 (0.6)	3	1.1	0		
Skin abrasion	0			0			0			2 (0.7)	3	2.2
Foot fracture	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Laceration	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Radius fracture	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	0		
Thermal burn	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Accidental overdose	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Animal bite	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Buttock injury	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Extradural haematoma	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Eyelid injury	0			0			0			1 (0.4)	1	0.7
Facial bones fracture	0			0			0			1 (0.4)	1	0.7
Femoral neck fracture	0			0			0			1 (0.4)	1	0.7
Forearm fracture	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Hand fracture	0			0			0			1 (0.4)	1	0.7
Heat illness	0			0			0			1 (0.4)	1	0.7
Joint injury	0			0			0			1 (0.4)	1	0.7

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Ligament rupture	0			0			0			1 (0.4)	1	0.7
Post procedural discharge	0			0			0			1 (0.4)	1	0.7
Postoperative ileus	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Road traffic accident	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Skull fractured base	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Tendon rupture	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Traumatic fracture	0			0			0			1 (0.4)	1	0.7
Ulna fracture	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Wrist fracture	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
General disorders and administration site conditions	19 (7.2)	24	18.1	21 (7.5)	31	22.2	40 (7.3)	55	20.2	13 (4.7)	20	14.6
Pyrexia	5 (1.9)	5	3.8	6 (2.1)	6	4.3	11 (2.0)	11	4.0	2 (0.7)	2	1.5
Influenza like illness	4 (1.5)	6	4.5	3 (1.1)	3	2.1	7 (1.3)	9	3.3	2 (0.7)	3	2.2
Injection site haematoma	2 (0.8)	2	1.5	1 (0.4)	3	2.1	3 (0.6)	5	1.8	1 (0.4)	3	2.2
Oedema peripheral	1 (0.4)	1	0.8	2 (0.7)	2	1.4	3 (0.6)	3	1.1	2 (0.7)	2	1.5
Fatigue	1 (0.4)	1	0.8	2 (0.7)	3	2.1	3 (0.6)	4	1.5	0		
Injection site bruising	1 (0.4)	2	1.5	2 (0.7)	2	1.4	3 (0.6)	4	1.5	0		
Chest pain	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	2 (0.7)	2	1.5
Injection site pain	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Injection site reaction	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	2	1.5
Malaise	2 (0.8)	2	1.5	0			2 (0.4)	2	0.7	1 (0.4)	1	0.7
Asthenia	0			2 (0.7)	2	1.4	2 (0.4)	2	0.7	0		
Chest discomfort	0			0			0			2 (0.7)	2	1.5
Injection site hypertrophy	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	0		
Pain	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Peripheral swelling	0			2 (0.7)	2	1.4	2 (0.4)	2	0.7	0		
Drug therapeutic incompatibility	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Feeling abnormal	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
General symptom	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Injection site hypersensitivity	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Injection site induration	0			0			0			1 (0.4)	1	0.7
Injection site rash	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Oedema	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Metabolism and nutrition disorders	22 (8.3)	23	17.3	14 (5.0)	19	13.6	36 (6.6)	42	15.4	19 (6.9)	21	15.3
Hypoglycaemia	16 (6.0)	17	12.8	6 (2.1)	9	6.4	22 (4.0)	26	9.5	10 (3.6)	11	8.0
Hyperglycaemia	2 (0.8)	2	1.5	1 (0.4)	1	0.7	3 (0.6)	3	1.1	2 (0.7)	3	2.2
Hyperlipidaemia	1 (0.4)	1	0.8	2 (0.7)	2	1.4	3 (0.6)	3	1.1	2 (0.7)	2	1.5
Decreased appetite	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Diabetic metabolic decompensation	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Hypertriglyceridaemia	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Hypokalaemia	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Vitamin D deficiency	0			2 (0.7)	2	1.4	2 (0.4)	2	0.7	0		
Dehydration	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Fluid retention	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Gout	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Hypercholesterolaemia	0			0			0			1 (0.4)	1	0.7
Hypoglycaemia unawareness	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Eye disorders	10 (3.8)	10	7.5	20 (7.1)	26	18.6	30 (5.5)	36	13.2	18 (6.5)	20	14.6
Diabetic retinopathy	6 (2.3)	6	4.5	9 (3.2)	9	6.4	15 (2.8)	15	5.5	6 (2.2)	6	4.4
Retinal tear	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	2 (0.7)	2	1.5
Dry eye	0			2 (0.7)	2	1.4	2 (0.4)	2	0.7	0		
Macular oedema	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Retinopathy	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Retinopathy hypertensive	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Retinopathy proliferative	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Vitreous haemorrhage	0			2 (0.7)	2	1.4	2 (0.4)	2	0.7	0		
Astigmatism	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Blepharochalasis	0			0			0			1 (0.4)	1	0.7
Cataract	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Cataract nuclear	0			0			0			1 (0.4)	1	0.7
Conjunctival haemorrhage	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Conjunctivitis allergic	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Cystoid macular oedema	0			0			0			1 (0.4)	1	0.7
Eye disorder	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Eye inflammation	0			0			0			1 (0.4)	1	0.7
Eye pruritus	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Eye ulcer	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Eyelid oedema	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Iritis	0			0			0			1 (0.4)	1	0.7
Lacrimation increased	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Maculopathy	0			0			0			1 (0.4)	1	0.7
Myopia	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Normal tension glaucoma	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Ocular discomfort	0			0			0			1 (0.4)	1	0.7
Retinal ischaemia	0			0			0			1 (0.4)	1	0.7
Visual acuity reduced transiently	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Skin and subcutaneous tissue disorders	16 (6.0)	21	15.8	19 (6.8)	20	14.3	35 (6.4)	41	15.1	14 (5.1)	14	10.2
Dermatitis	1 (0.4)	3	2.3	4 (1.4)	4	2.9	5 (0.9)	7	2.6	0		
Urticaria	2 (0.8)	2	1.5	3 (1.1)	3	2.1	5 (0.9)	5	1.8	2 (0.7)	2	1.5
Lipohypertrophy	2 (0.8)	2	1.5	3 (1.1)	3	2.1	5 (0.9)	5	1.8	0		
Dry skin	0			2 (0.7)	2	1.4	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Eczema	2 (0.8)	2	1.5	0			2 (0.4)	2	0.7	1 (0.4)	1	0.7
Pruritus	0			2 (0.7)	2	1.4	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Dermatitis atopic	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Dermatitis contact	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Rash	0			0			0			2 (0.7)	2	1.5

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Skin ulcer	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Acne cystic	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Actinic keratosis	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Alopecia	0			0			0			1 (0.4)	1	0.7
Asteatosis	0			0			0			1 (0.4)	1	0.7
Blood blister	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Dermal cyst	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Eczema asteatotic	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Lipodystrophy acquired	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Miliaria	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Nail bed inflammation	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Onychomadesis	0			0			0			1 (0.4)	1	0.7
Papule	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Rash erythematous	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Rash papular	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Rash pruritic	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Skin exfoliation	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Skin fissures	0			0			0			1 (0.4)	1	0.7
Skin reaction	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Xeroderma	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Respiratory, thoracic and mediastinal disorders	13 (4.9)	14	10.6	18 (6.4)	21	15.0	31 (5.7)	35	12.8	16 (5.8)	17	12.4
Oropharyngeal pain	1 (0.4)	1	0.8	4 (1.4)	4	2.9	5 (0.9)	5	1.8	6 (2.2)	7	5.1
Cough	1 (0.4)	1	0.8	5 (1.8)	5	3.6	6 (1.1)	6	2.2	0		
Asthma	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	2 (0.7)	2	1.5
Rhinorrhoea	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	2 (0.7)	2	1.5
Sinus congestion	2 (0.8)	2	1.5	2 (0.7)	2	1.4	4 (0.7)	4	1.5	0		
Upper respiratory tract inflammation	0			2 (0.7)	3	2.1	2 (0.4)	3	1.1	1 (0.4)	1	0.7
Nasal congestion	2 (0.8)	2	1.5	1 (0.4)	1	0.7	3 (0.6)	3	1.1	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Respiratory disorder	2 (0.8)	2	1.5	1 (0.4)	1	0.7	3 (0.6)	3	1.1	0		
Rhinitis allergic	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Dyspnoea	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	0		
Chronic obstructive pulmonary disease	0			0			0			1 (0.4)	1	0.7
Epistaxis	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Paranasal sinus discomfort	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Pleurisy	0			0			0			1 (0.4)	1	0.7
Throat irritation	0			0			0			1 (0.4)	1	0.7
Tonsillar hypertrophy	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Upper respiratory tract congestion	0			0			0			1 (0.4)	1	0.7
Psychiatric disorders	5 (1.9)	6	4.5	7 (2.5)	8	5.7	12 (2.2)	14	5.1	0		
Depression	3 (1.1)	3	2.3	2 (0.7)	2	1.4	5 (0.9)	5	1.8	0		
Insomnia	2 (0.8)	2	1.5	1 (0.4)	1	0.7	3 (0.6)	3	1.1	0		
Anxiety	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	0		
Stress	0			2 (0.7)	2	1.4	2 (0.4)	2	0.7	0		
Affective disorder	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Sleep disorder	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Renal and urinary disorders	3 (1.1)	3	2.3	5 (1.8)	5	3.6	8 (1.5)	8	2.9	4 (1.4)	6	4.4
Haematuria	1 (0.4)	1	0.8	2 (0.7)	2	1.4	3 (0.6)	3	1.1	1 (0.4)	1	0.7
Microalbuminuria	0			0			0			3 (1.1)	4	2.9
Acute kidney injury	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Bladder pain	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Crystalluria	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Nephrolithiasis	0			0			0			1 (0.4)	1	0.7
Renal cyst	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Renal failure	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Blood and lymphatic system disorders	6 (2.3)	6	4.5	0			6 (1.1)	6	2.2	4 (1.4)	4	2.9

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline < 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Anaemia	3 (1.1)	3	2.3	0			3 (0.6)	3	1.1	4 (1.4)	4	2.9
Iron deficiency anaemia	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Leukopenia	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Lymphadenopathy	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Ear and labyrinth disorders	3 (1.1)	3	2.3	4 (1.4)	5	3.6	7 (1.3)	8	2.9	2 (0.7)	2	1.5
Ear discomfort	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	0		
Ear pain	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	0		
Tinnitus	1 (0.4)	1	0.8	1 (0.4)	1	0.7	2 (0.4)	2	0.7	0		
Vertigo	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Sudden hearing loss	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Tympanic membrane perforation	0			0			0			1 (0.4)	1	0.7
Vascular disorders	4 (1.5)	4	3.0	2 (0.7)	2	1.4	6 (1.1)	6	2.2	4 (1.4)	4	2.9
Hypertension	2 (0.8)	2	1.5	2 (0.7)	2	1.4	4 (0.7)	4	1.5	1 (0.4)	1	0.7
Hypotension	0			0			0			2 (0.7)	2	1.5
Arteriosclerosis	0			0			0			1 (0.4)	1	0.7
Peripheral arterial occlusive disease	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Thrombophlebitis superficial	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Immune system disorders	0			3 (1.1)	5	3.6	3 (0.6)	5	1.8	3 (1.1)	3	2.2
Hypersensitivity	0			1 (0.4)	3	2.1	1 (0.2)	3	1.1	1 (0.4)	1	0.7
Seasonal allergy	0			2 (0.7)	2	1.4	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Multiple allergies	0			0			0			1 (0.4)	1	0.7
Reproductive system and breast disorders	3 (1.1)	3	2.3	1 (0.4)	1	0.7	4 (0.7)	4	1.5	2 (0.7)	2	1.5
Benign prostatic hyperplasia	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Endometriosis	0			0			0			1 (0.4)	1	0.7
Genital haemorrhage	0			0			0			1 (0.4)	1	0.7
Gynaecomastia	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline < 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Testicular swelling	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Vulvovaginal inflammation	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Cardiac disorders	2 (0.8)	2	1.5	2 (0.7)	2	1.4	4 (0.7)	4	1.5	1 (0.4)	1	0.7
Palpitations	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Coronary artery disease	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Extrasystoles	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Sinus bradycardia	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Endocrine disorders	1 (0.4)	1	0.8	1 (0.4)	2	1.4	2 (0.4)	3	1.1	1 (0.4)	1	0.7
Goitre	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Hypothyroidism	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Thyroid cyst	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Hepatobiliary disorders	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	2 (0.7)	2	1.5
Hepatic steatosis	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Cholecystitis	0			0			0			1 (0.4)	1	0.7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	1	0.8	2 (0.7)	2	1.4	3 (0.6)	3	1.1	0		
Bladder transitional cell carcinoma	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Conjunctival neoplasm	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Skin papilloma	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Surgical and medical procedures	0			0			0			3 (1.1)	3	2.2
Endodontic procedure	0			0			0			1 (0.4)	1	0.7
Inguinal hernia repair	0			0			0			1 (0.4)	1	0.7
Tooth extraction	0			0			0			1 (0.4)	1	0.7

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MedDRA version 20.0.

2.7.4.7.3.2.9. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインの HbA1c が 8%以上の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	77			61			138			66		
Total exposure (yrs)	38.6			30.5			69.1			33.1		
Total events	60 (77.9)	161	417.3	42 (68.9)	120	393.1	102 (73.9)	281	406.6	48 (72.7)	112	338.4
Infections and infestations	41 (53.2)	57	147.7	25 (41.0)	36	117.9	66 (47.8)	93	134.6	31 (47.0)	50	151.1
Viral upper respiratory tract infection	17 (22.1)	22	57.0	8 (13.1)	12	39.3	25 (18.1)	34	49.2	11 (16.7)	17	51.4
Upper respiratory tract infection	8 (10.4)	9	23.3	5 (8.2)	5	16.4	13 (9.4)	14	20.3	10 (15.2)	14	42.3
Influenza	10 (13.0)	11	28.5	4 (6.6)	4	13.1	14 (10.1)	15	21.7	1 (1.5)	1	3.0
Urinary tract infection	1 (1.3)	1	2.6	2 (3.3)	2	6.6	3 (2.2)	3	4.3	3 (4.5)	3	9.1
Gastroenteritis	1 (1.3)	1	2.6	2 (3.3)	2	6.6	3 (2.2)	3	4.3	2 (3.0)	2	6.0
Gastroenteritis viral	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	3 (4.5)	3	9.1
Pharyngitis	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	3 (4.5)	3	9.1
Respiratory tract infection viral	1 (1.3)	2	5.2	1 (1.6)	1	3.3	2 (1.4)	3	4.3	0		
Sinusitis	1 (1.3)	2	5.2	0			1 (0.7)	2	2.9	1 (1.5)	1	3.0
Bronchitis	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	1 (1.5)	1	3.0
Tonsillitis	1 (1.3)	1	2.6	1 (1.6)	1	3.3	2 (1.4)	2	2.9	0		
Tooth abscess	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	1 (1.5)	1	3.0
Viral infection	1 (1.3)	1	2.6	1 (1.6)	1	3.3	2 (1.4)	2	2.9	0		
Cellulitis	0			0			0			1 (1.5)	1	3.0
Empyema	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Fungal infection	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Localised infection	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Lower respiratory tract infection	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Onychomycosis	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Otitis externa	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Periodontitis	0			0			0			1 (1.5)	1	3.0
Pneumonia	0			0			0			1 (1.5)	1	3.0

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Adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline >= 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Subcutaneous abscess	0				1	(1.6)	1	3.3	1	(0.7)	1	1.4	0			
Tinea cruris	0				0				0				1	(1.5)	1	3.0
Urinary tract infection fungal	1	(1.3)	1	2.6	0				1	(0.7)	1	1.4	0			
Varicella	1	(1.3)	1	2.6	0				1	(0.7)	1	1.4	0			
Vulvovaginal candidiasis	0				1	(1.6)	1	3.3	1	(0.7)	1	1.4	0			
Vulvovaginal mycotic infection	0				1	(1.6)	1	3.3	1	(0.7)	1	1.4	0			
Investigations	21	(27.3)	25	64.8	8	(13.1)	11	36.0	29	(21.0)	36	52.1	13	(19.7)	16	48.3
Blood glucose decreased	17	(22.1)	21	54.4	7	(11.5)	10	32.8	24	(17.4)	31	44.9	12	(18.2)	15	45.3
Blood creatinine increased	1	(1.3)	1	2.6	0				1	(0.7)	1	1.4	0			
Blood glucose fluctuation	0				0				0				1	(1.5)	1	3.0
Blood potassium increased	1	(1.3)	1	2.6	0				1	(0.7)	1	1.4	0			
Blood thyroid stimulating hormone increased	1	(1.3)	1	2.6	0				1	(0.7)	1	1.4	0			
Haemoglobin decreased	0				1	(1.6)	1	3.3	1	(0.7)	1	1.4	0			
Weight increased	1	(1.3)	1	2.6	0				1	(0.7)	1	1.4	0			
Gastrointestinal disorders	11	(14.3)	12	31.1	7	(11.5)	10	32.8	18	(13.0)	22	31.8	6	(9.1)	7	21.2
Nausea	4	(5.2)	5	13.0	1	(1.6)	1	3.3	5	(3.6)	6	8.7	2	(3.0)	3	9.1
Diarrhoea	1	(1.3)	1	2.6	2	(3.3)	2	6.6	3	(2.2)	3	4.3	1	(1.5)	1	3.0
Chronic gastritis	1	(1.3)	1	2.6	1	(1.6)	1	3.3	2	(1.4)	2	2.9	0			
Constipation	1	(1.3)	1	2.6	1	(1.6)	1	3.3	2	(1.4)	2	2.9	0			
Hiatus hernia	0				2	(3.3)	2	6.6	2	(1.4)	2	2.9	0			
Toothache	1	(1.3)	1	2.6	1	(1.6)	1	3.3	2	(1.4)	2	2.9	0			
Vomiting	1	(1.3)	1	2.6	1	(1.6)	1	3.3	2	(1.4)	2	2.9	0			
Abdominal pain	0				0				0				1	(1.5)	1	3.0
Apical granuloma	1	(1.3)	1	2.6	0				1	(0.7)	1	1.4	0			
Colitis ulcerative	0				1	(1.6)	1	3.3	1	(0.7)	1	1.4	0			
Gastritis	1	(1.3)	1	2.6	0				1	(0.7)	1	1.4	0			
Oral discomfort	0				0				0				1	(1.5)	1	3.0

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Adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline >= 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Periodontal disease	0			0			0			1 (1.5)	1	3.0
Injury, poisoning and procedural complications	8 (10.4)	8	20.7	6 (9.8)	11	36.0	14 (10.1)	19	27.5	6 (9.1)	6	18.1
Wrong drug administered	1 (1.3)	1	2.6	4 (6.6)	7	22.9	5 (3.6)	8	11.6	1 (1.5)	1	3.0
Fall	0			2 (3.3)	2	6.6	2 (1.4)	2	2.9	0		
Ligament sprain	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	1 (1.5)	1	3.0
Limb injury	2 (2.6)	2	5.2	0			2 (1.4)	2	2.9	0		
Accidental underdose	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Contusion	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Foot fracture	0			0			0			1 (1.5)	1	3.0
Foreign body in eye	0			0			0			1 (1.5)	1	3.0
Hand fracture	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Joint dislocation	0			0			0			1 (1.5)	1	3.0
Laceration	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Road traffic accident	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Tendon rupture	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Wound	0			0			0			1 (1.5)	1	3.0
Musculoskeletal and connective tissue disorders	10 (13.0)	10	25.9	8 (13.1)	10	32.8	18 (13.0)	20	28.9	3 (4.5)	4	12.1
Back pain	2 (2.6)	2	5.2	1 (1.6)	1	3.3	3 (2.2)	3	4.3	1 (1.5)	1	3.0
Pain in extremity	1 (1.3)	1	2.6	3 (4.9)	3	9.8	4 (2.9)	4	5.8	0		
Tenosynovitis	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	2 (3.0)	2	6.0
Myalgia	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	1 (1.5)	1	3.0
Plantar fasciitis	0			1 (1.6)	2	6.6	1 (0.7)	2	2.9	0		
Arthralgia	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Joint contracture	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Joint effusion	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Lumbar spinal stenosis	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline >= 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Muscle spasms	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Rheumatic disorder	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Rheumatoid arthritis	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Spinal pain	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Tendonitis	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Eye disorders	7 (9.1)	8	20.7	8 (13.1)	8	26.2	15 (10.9)	16	23.2	3 (4.5)	3	9.1
Diabetic retinopathy	1 (1.3)	1	2.6	3 (4.9)	3	9.8	4 (2.9)	4	5.8	1 (1.5)	1	3.0
Macular oedema	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	1 (1.5)	1	3.0
Retinal aneurysm	2 (2.6)	2	5.2	0			2 (1.4)	2	2.9	0		
Retinopathy	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	1 (1.5)	1	3.0
Chalazion	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Glaucoma	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Ocular hypertension	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Retinal exudates	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Retinal haemorrhage	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Retinopathy hypertensive	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Visual impairment	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Vitreous detachment	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
General disorders and administration site conditions	6 (7.8)	7	18.1	4 (6.6)	4	13.1	10 (7.2)	11	15.9	5 (7.6)	7	21.2
Influenza like illness	1 (1.3)	1	2.6	1 (1.6)	1	3.3	2 (1.4)	2	2.9	2 (3.0)	3	9.1
Pyrexia	3 (3.9)	3	7.8	1 (1.6)	1	3.3	4 (2.9)	4	5.8	0		
Injection site haematoma	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	1 (1.5)	1	3.0
Administration site induration	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Inflammation	0			0			0			1 (1.5)	1	3.0
Injection site haemorrhage	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Injection site hypertrophy	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Injection site pain	0			0			0			1 (1.5)	1	3.0

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline >= 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Injection site reaction	0			0			0			1 (1.5)	1	3.0
Injection site swelling	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Nervous system disorders	3 (3.9)	3	7.8	7 (11.5)	8	26.2	10 (7.2)	11	15.9	4 (6.1)	5	15.1
Dizziness	1 (1.3)	1	2.6	1 (1.6)	2	6.6	2 (1.4)	3	4.3	1 (1.5)	2	6.0
Headache	0			2 (3.3)	2	6.6	2 (1.4)	2	2.9	1 (1.5)	1	3.0
Cerebrovascular accident	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Diabetic neuropathy	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Migraine	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Neurodegenerative disorder	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Occipital neuralgia	0			0			0			1 (1.5)	1	3.0
Polyneuropathy	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Tension headache	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Tremor	0			0			0			1 (1.5)	1	3.0
Metabolism and nutrition disorders	7 (9.1)	7	18.1	2 (3.3)	3	9.8	9 (6.5)	10	14.5	2 (3.0)	2	6.0
Hypoglycaemia	5 (6.5)	5	13.0	0			5 (3.6)	5	7.2	2 (3.0)	2	6.0
Diabetic metabolic decompensation	1 (1.3)	1	2.6	1 (1.6)	1	3.3	2 (1.4)	2	2.9	0		
Dehydration	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Hypoglycaemia unawareness	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Vitamin D deficiency	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Respiratory, thoracic and mediastinal disorders	6 (7.8)	7	18.1	1 (1.6)	1	3.3	7 (5.1)	8	11.6	3 (4.5)	3	9.1
Epistaxis	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	1 (1.5)	1	3.0
Oropharyngeal pain	2 (2.6)	2	5.2	0			2 (1.4)	2	2.9	0		
Sinus congestion	2 (2.6)	2	5.2	0			2 (1.4)	2	2.9	0		
Cough	0			0			0			1 (1.5)	1	3.0
Nasal congestion	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Rhinitis allergic	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline >= 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Rhinorrhoea	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Throat irritation	0			0			0			1 (1.5)	1	3.0
Skin and subcutaneous tissue disorders	2 (2.6)	2	5.2	3 (4.9)	4	13.1	5 (3.6)	6	8.7	4 (6.1)	5	15.1
Ecchymosis	0			0			0			1 (1.5)	2	6.0
Blister	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Dermatitis contact	0			0			0			1 (1.5)	1	3.0
Hidradenitis	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Nail disorder	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Nail pigmentation	0			0			0			1 (1.5)	1	3.0
Parapsoriasis	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Skin lesion	0			0			0			1 (1.5)	1	3.0
Skin mass	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Skin ulcer	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Reproductive system and breast disorders	1 (1.3)	1	2.6	2 (3.3)	4	13.1	3 (2.2)	5	7.2	0		
Dysmenorrhoea	0			1 (1.6)	2	6.6	1 (0.7)	2	2.9	0		
Priapism	0			1 (1.6)	2	6.6	1 (0.7)	2	2.9	0		
Breast tenderness	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Vascular disorders	2 (2.6)	2	5.2	3 (4.9)	3	9.8	5 (3.6)	5	7.2	0		
Hypertension	1 (1.3)	1	2.6	2 (3.3)	2	6.6	3 (2.2)	3	4.3	0		
Orthostatic hypotension	1 (1.3)	1	2.6	1 (1.6)	1	3.3	2 (1.4)	2	2.9	0		
Psychiatric disorders	2 (2.6)	2	5.2	1 (1.6)	1	3.3	3 (2.2)	3	4.3	1 (1.5)	1	3.0
Depression	1 (1.3)	1	2.6	1 (1.6)	1	3.3	2 (1.4)	2	2.9	0		
Insomnia	0			0			0			1 (1.5)	1	3.0
Stress	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Endocrine disorders	0			2 (3.3)	2	6.6	2 (1.4)	2	2.9	1 (1.5)	1	3.0

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Adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline >= 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Goitre	0			0			0			1 (1.5)	1	3.0
Hyperadrenalism	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Hypothyroidism	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Renal and urinary disorders	1 (1.3)	1	2.6	2 (3.3)	2	6.6	3 (2.2)	3	4.3	0		
Dysuria	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Haematuria	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Microalbuminuria	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Blood and lymphatic system disorders	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	1 (1.5)	1	3.0
Iron deficiency anaemia	0			0			0			1 (1.5)	1	3.0
Lymphadenopathy	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Cardiac disorders	1 (1.3)	1	2.6	1 (1.6)	1	3.3	2 (1.4)	2	2.9	0		
Myocardial ischaemia	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Ventricular extrasystoles	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Immune system disorders	1 (1.3)	1	2.6	1 (1.6)	1	3.3	2 (1.4)	2	2.9	0		
Mycotic allergy	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Seasonal allergy	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	1 (1.5)	1	3.0
Haemangioma of liver	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	1 (1.5)	1	3.0
Surgical and medical procedures	2 (2.6)	2	5.2	0			2 (1.4)	2	2.9	0		
Cataract operation	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Haemorrhoid operation	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline >= 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Congenital, familial and genetic disorders	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Accessory spleen	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Hepatobiliary disorders	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Gallbladder polyp	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Pregnancy, puerperium and perinatal conditions	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Subchorionic haemorrhage	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		

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2.7.4.7.3.2.10. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインの糖尿病罹病期間が 15 年未満の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	177				190				367				175			
Total exposure (yrs)	88.6				93.9				182.5				86.8			
Total events	121	(68.4)	301	339.7	129	(67.9)	318	338.8	250	(68.1)	619	339.2	119	(68.0)	291	335.3
Infections and infestations	76	(42.9)	120	135.4	67	(35.3)	103	109.7	143	(39.0)	223	122.2	70	(40.0)	117	134.8
Viral upper respiratory tract infection	40	(22.6)	52	58.7	38	(20.0)	51	54.3	78	(21.3)	103	56.4	45	(25.7)	67	77.2
Upper respiratory tract infection	17	(9.6)	22	24.8	13	(6.8)	15	16.0	30	(8.2)	37	20.3	8	(4.6)	13	15.0
Influenza	13	(7.3)	13	14.7	7	(3.7)	7	7.5	20	(5.4)	20	11.0	7	(4.0)	7	8.1
Urinary tract infection	2	(1.1)	3	3.4	4	(2.1)	6	6.4	6	(1.6)	9	4.9	3	(1.7)	3	3.5
Gastroenteritis	1	(0.6)	1	1.1	6	(3.2)	6	6.4	7	(1.9)	7	3.8	2	(1.1)	2	2.3
Pharyngitis	1	(0.6)	1	1.1	1	(0.5)	1	1.1	2	(0.5)	2	1.1	4	(2.3)	7	8.1
Sinusitis	3	(1.7)	4	4.5	1	(0.5)	1	1.1	4	(1.1)	5	2.7	0			
Cystitis	1	(0.6)	2	2.3	2	(1.1)	2	2.1	3	(0.8)	4	2.2	0			
Gastroenteritis viral	1	(0.6)	1	1.1	0				1	(0.3)	1	0.5	3	(1.7)	3	3.5
Respiratory tract infection viral	2	(1.1)	3	3.4	1	(0.5)	1	1.1	3	(0.8)	4	2.2	0			
Tonsillitis	2	(1.1)	4	4.5	0				2	(0.5)	4	2.2	0			
Viral infection	0				3	(1.6)	3	3.2	3	(0.8)	3	1.6	1	(0.6)	1	1.2
Bronchitis	1	(0.6)	1	1.1	0				1	(0.3)	1	0.5	2	(1.1)	2	2.3
Otitis externa	1	(0.6)	1	1.1	2	(1.1)	2	2.1	3	(0.8)	3	1.6	0			
Rhinitis	1	(0.6)	1	1.1	0				1	(0.3)	1	0.5	2	(1.1)	2	2.3
Tooth abscess	1	(0.6)	1	1.1	1	(0.5)	1	1.1	2	(0.5)	2	1.1	1	(0.6)	1	1.2
Ear infection	1	(0.6)	2	2.3	0				1	(0.3)	2	1.1	0			
Periodontitis	1	(0.6)	1	1.1	0				1	(0.3)	1	0.5	1	(0.6)	1	1.2
Varicella	1	(0.6)	1	1.1	0				1	(0.3)	1	0.5	1	(0.6)	1	1.2
Acute sinusitis	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Cytomegalovirus infection	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Empyema	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			

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Adverse events by system organ class and preferred term - treatment emergent - summary - duration of diabetes at baseline < 15 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Epstein-Barr virus infection	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Fungal infection	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Furuncle	1	(0.6)	1	1.1	0				1	(0.3)	1	0.5	0			
Gingivitis	0				0				0				1	(0.6)	1	1.2
Herpes zoster	1	(0.6)	1	1.1	0				1	(0.3)	1	0.5	0			
Impetigo	1	(0.6)	1	1.1	0				1	(0.3)	1	0.5	0			
Labyrinthitis	0				0				0				1	(0.6)	1	1.2
Laryngitis	0				0				0				1	(0.6)	1	1.2
Lower respiratory tract infection bacterial	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Oral herpes	0				0				0				1	(0.6)	1	1.2
Oral infection	1	(0.6)	1	1.1	0				1	(0.3)	1	0.5	0			
Otitis media	1	(0.6)	1	1.1	0				1	(0.3)	1	0.5	0			
Paronychia	0				0				0				1	(0.6)	1	1.2
Pneumonia	0				0				0				1	(0.6)	1	1.2
Pyelonephritis chronic	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Syphilis	1	(0.6)	1	1.1	0				1	(0.3)	1	0.5	0			
Vulvovaginal mycotic infection	0				0				0				1	(0.6)	1	1.2
Investigations	35	(19.8)	46	51.9	46	(24.2)	60	63.9	81	(22.1)	106	58.1	40	(22.9)	47	54.2
Blood glucose decreased	30	(16.9)	41	46.3	42	(22.1)	51	54.3	72	(19.6)	92	50.4	39	(22.3)	46	53.0
Blood creatinine increased	1	(0.6)	1	1.1	1	(0.5)	1	1.1	2	(0.5)	2	1.1	0			
Urine albumin/creatinine ratio increased	1	(0.6)	1	1.1	1	(0.5)	1	1.1	2	(0.5)	2	1.1	0			
Alanine aminotransferase increased	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Aspartate aminotransferase increased	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Blood bilirubin increased	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Blood pressure increased	1	(0.6)	1	1.1	0				1	(0.3)	1	0.5	0			
Blood urine present	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Helicobacter test positive	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Hepatic enzyme increased	0			0			0			1 (0.6)	1	1.2
Lipids abnormal	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Protein urine present	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Transaminases increased	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Weight increased	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Gastrointestinal disorders	17 (9.6)	24	27.1	14 (7.4)	19	20.2	31 (8.4)	43	23.6	18 (10.3)	21	24.2
Nausea	4 (2.3)	5	5.6	1 (0.5)	1	1.1	5 (1.4)	6	3.3	2 (1.1)	3	3.5
Vomiting	2 (1.1)	3	3.4	3 (1.6)	3	3.2	5 (1.4)	6	3.3	3 (1.7)	3	3.5
Diarrhoea	1 (0.6)	1	1.1	4 (2.1)	4	4.3	5 (1.4)	5	2.7	2 (1.1)	2	2.3
Gastritis	2 (1.1)	2	2.3	2 (1.1)	3	3.2	4 (1.1)	5	2.7	1 (0.6)	1	1.2
Abdominal pain	0			0			0			4 (2.3)	4	4.6
Abdominal pain upper	1 (0.6)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	1 (0.6)	1	1.2
Aphthous ulcer	0			1 (0.5)	2	2.1	1 (0.3)	2	1.1	1 (0.6)	1	1.2
Constipation	2 (1.1)	2	2.3	1 (0.5)	1	1.1	3 (0.8)	3	1.6	0		
Gastrooesophageal reflux disease	3 (1.7)	3	3.4	0			3 (0.8)	3	1.6	0		
Toothache	2 (1.1)	2	2.3	1 (0.5)	1	1.1	3 (0.8)	3	1.6	0		
Abdominal discomfort	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.2
Abdominal distension	1 (0.6)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Apical granuloma	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Dyspepsia	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Enteritis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Enterocolitis	0			0			0			1 (0.6)	1	1.2
Food poisoning	0			0			0			1 (0.6)	1	1.2
Gastric polyps	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Gastritis erosive	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Haemorrhoids	0			0			0			1 (0.6)	1	1.2
Oral discomfort	0			0			0			1 (0.6)	1	1.2
Proctalgia	0			0			0			1 (0.6)	1	1.2

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Musculoskeletal and connective tissue disorders	13 (7.3)	17	19.2	16 (8.4)	17	18.1	29 (7.9)	34	18.6	15 (8.6)	21	24.2
Back pain	3 (1.7)	3	3.4	5 (2.6)	6	6.4	8 (2.2)	9	4.9	4 (2.3)	4	4.6
Pain in extremity	4 (2.3)	4	4.5	2 (1.1)	2	2.1	6 (1.6)	6	3.3	1 (0.6)	1	1.2
Arthralgia	2 (1.1)	2	2.3	2 (1.1)	2	2.1	4 (1.1)	4	2.2	2 (1.1)	2	2.3
Myalgia	1 (0.6)	2	2.3	0			1 (0.3)	2	1.1	2 (1.1)	3	3.5
Muscle spasms	2 (1.1)	2	2.3	1 (0.5)	1	1.1	3 (0.8)	3	1.6	1 (0.6)	1	1.2
Neck pain	1 (0.6)	1	1.1	2 (1.1)	2	2.1	3 (0.8)	3	1.6	0		
Musculoskeletal stiffness	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.2
Rheumatoid arthritis	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.2
Arthritis	0			0			0			1 (0.6)	1	1.2
Arthropathy	0			0			0			1 (0.6)	1	1.2
Exostosis	0			0			0			1 (0.6)	1	1.2
Flank pain	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Intervertebral disc disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Intervertebral disc protrusion	0			0			0			1 (0.6)	1	1.2
Lumbar spinal stenosis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Musculoskeletal chest pain	0			0			0			1 (0.6)	1	1.2
Osteoporotic fracture	0			0			0			1 (0.6)	1	1.2
Rotator cuff syndrome	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Spinal pain	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Tenosynovitis	0			0			0			1 (0.6)	1	1.2
Trigger finger	0			0			0			1 (0.6)	1	1.2
General disorders and administration site conditions	9 (5.1)	11	12.4	13 (6.8)	17	18.1	22 (6.0)	28	15.3	10 (5.7)	17	19.6
Injection site haematoma	1 (0.6)	1	1.1	2 (1.1)	4	4.3	3 (0.8)	5	2.7	2 (1.1)	4	4.6
Pyrexia	3 (1.7)	3	3.4	5 (2.6)	5	5.3	8 (2.2)	8	4.4	1 (0.6)	1	1.2
Influenza like illness	2 (1.1)	2	2.3	2 (1.1)	2	2.1	4 (1.1)	4	2.2	1 (0.6)	2	2.3
Injection site reaction	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	2 (1.1)	3	3.5

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Chest discomfort	0			0			0			2 (1.1)	2	2.3
Chest pain	0			0			0			2 (1.1)	2	2.3
Injection site bruising	1 (0.6)	2	2.3	0			1 (0.3)	2	1.1	0		
Injection site pain	0			0			0			2 (1.1)	2	2.3
Administration site induration	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Asthenia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Feeling abnormal	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
General symptom	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Injection site haemorrhage	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Injection site hypersensitivity	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Injection site induration	0			0			0			1 (0.6)	1	1.2
Injection site rash	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Injection site swelling	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Injury, poisoning and procedural complications	14 (7.9)	15	16.9	13 (6.8)	16	17.0	27 (7.4)	31	17.0	14 (8.0)	14	16.1
Wrong drug administered	1 (0.6)	1	1.1	5 (2.6)	6	6.4	6 (1.6)	7	3.8	3 (1.7)	3	3.5
Ligament sprain	2 (1.1)	2	2.3	3 (1.6)	3	3.2	5 (1.4)	5	2.7	2 (1.1)	2	2.3
Limb injury	4 (2.3)	4	4.5	0			4 (1.1)	4	2.2	0		
Tooth fracture	2 (1.1)	2	2.3	0			2 (0.5)	2	1.1	1 (0.6)	1	1.2
Contusion	1 (0.6)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Accidental overdose	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Buttock injury	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Extradural haematoma	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Eyelid injury	0			0			0			1 (0.6)	1	1.2
Femoral neck fracture	0			0			0			1 (0.6)	1	1.2
Foot fracture	0			0			0			1 (0.6)	1	1.2
Forearm fracture	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Foreign body in eye	0			0			0			1 (0.6)	1	1.2
Hand fracture	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Joint dislocation	0			0			0			1 (0.6)	1	1.2
Joint injury	0			0			0			1 (0.6)	1	1.2
Muscle strain	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Postoperative ileus	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Radius fracture	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Road traffic accident	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Skull fractured base	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Tendon rupture	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Thermal burn	0			0			0			1 (0.6)	1	1.2
Wound	0			0			0			1 (0.6)	1	1.2
Nervous system disorders	9 (5.1)	9	10.2	17 (8.9)	26	27.7	26 (7.1)	35	19.2	6 (3.4)	7	8.1
Headache	2 (1.1)	2	2.3	8 (4.2)	14	14.9	10 (2.7)	16	8.8	1 (0.6)	2	2.3
Dizziness	1 (0.6)	1	1.1	3 (1.6)	4	4.3	4 (1.1)	5	2.7	1 (0.6)	1	1.2
Hypoglycaemic unconsciousness	0			2 (1.1)	2	2.1	2 (0.5)	2	1.1	1 (0.6)	1	1.2
Migraine	3 (1.7)	3	3.4	0			3 (0.8)	3	1.6	0		
Hypoaesthesia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.2
Polyneuropathy	0			2 (1.1)	2	2.1	2 (0.5)	2	1.1	0		
Tension headache	1 (0.6)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Carotid arteriosclerosis	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Cerebrovascular accident	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Lumbar radiculopathy	0			0			0			1 (0.6)	1	1.2
Occipital neuralgia	0			0			0			1 (0.6)	1	1.2
Paraesthesia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Syncope	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Metabolism and nutrition disorders	12 (6.8)	13	14.7	7 (3.7)	9	9.6	19 (5.2)	22	12.1	8 (4.6)	9	10.4
Hypoglycaemia	7 (4.0)	8	9.0	1 (0.5)	1	1.1	8 (2.2)	9	4.9	3 (1.7)	3	3.5
Hyperglycaemia	1 (0.6)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	2 (1.1)	3	3.5
Diabetic metabolic decompensation	2 (1.1)	2	2.3	1 (0.5)	1	1.1	3 (0.8)	3	1.6	1 (0.6)	1	1.2

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Hyperlipidaemia	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.2
Hypoglycaemia unawareness	0			2 (1.1)	2	2.1	2 (0.5)	2	1.1	0		
Hypokalaemia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.2
Decreased appetite	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Gout	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Hypertriglyceridaemia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Vitamin D deficiency	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Eye disorders	9 (5.1)	10	11.3	9 (4.7)	12	12.8	18 (4.9)	22	12.1	6 (3.4)	6	6.9
Diabetic retinopathy	4 (2.3)	4	4.5	5 (2.6)	5	5.3	9 (2.5)	9	4.9	2 (1.1)	2	2.3
Macular oedema	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.2
Retinal tear	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.2
Retinopathy hypertensive	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.2
Astigmatism	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Conjunctival haemorrhage	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Dry eye	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Eyelid oedema	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Lacrimation increased	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Myopia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Ocular discomfort	0			0			0			1 (0.6)	1	1.2
Ocular hypertension	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Retinopathy	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Visual acuity reduced transiently	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Vitreous detachment	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Respiratory, thoracic and mediastinal disorders	7 (4.0)	7	7.9	9 (4.7)	10	10.7	16 (4.4)	17	9.3	8 (4.6)	8	9.2
Oropharyngeal pain	2 (1.1)	2	2.3	2 (1.1)	2	2.1	4 (1.1)	4	2.2	3 (1.7)	3	3.5
Sinus congestion	2 (1.1)	2	2.3	1 (0.5)	1	1.1	3 (0.8)	3	1.6	0		
Asthma	0			0			0			2 (1.1)	2	2.3

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Rhinitis allergic	1 (0.6)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Rhinorrhoea	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.2
Upper respiratory tract inflammation	0			1 (0.5)	2	2.1	1 (0.3)	2	1.1	0		
Cough	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Dyspnoea	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Epistaxis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Pleurisy	0			0			0			1 (0.6)	1	1.2
Respiratory disorder	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Throat irritation	0			0			0			1 (0.6)	1	1.2
Tonsillar hypertrophy	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Skin and subcutaneous tissue disorders	7 (4.0)	7	7.9	6 (3.2)	7	7.5	13 (3.5)	14	7.7	7 (4.0)	7	8.1
Urticaria	0			2 (1.1)	2	2.1	2 (0.5)	2	1.1	1 (0.6)	1	1.2
Dermatitis	0			2 (1.1)	2	2.1	2 (0.5)	2	1.1	0		
Dermatitis atopic	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.2
Dermatitis contact	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.2
Dry skin	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.2
Dermal cyst	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Lipodystrophy acquired	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Lipohypertrophy	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Nail disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Parapsoriasis	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Pruritus	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Rash	0			0			0			1 (0.6)	1	1.2
Skin exfoliation	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Skin fissures	0			0			0			1 (0.6)	1	1.2
Skin ulcer	0			0			0			1 (0.6)	1	1.2
Blood and lymphatic system disorders	6 (3.4)	6	6.8	0			6 (1.6)	6	3.3	5 (2.9)	5	5.8
Anaemia	3 (1.7)	3	3.4	0			3 (0.8)	3	1.6	4 (2.3)	4	4.6

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Iron deficiency anaemia	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.2
Leukopenia	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Lymphadenopathy	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Renal and urinary disorders	3 (1.7)	3	3.4	4 (2.1)	4	4.3	7 (1.9)	7	3.8	2 (1.1)	2	2.3
Haematuria	1 (0.6)	1	1.1	2 (1.1)	2	2.1	3 (0.8)	3	1.6	0		
Microalbuminuria	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.2
Acute kidney injury	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Dysuria	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Nephrolithiasis	0			0			0			1 (0.6)	1	1.2
Renal failure	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Immune system disorders	0			4 (2.1)	6	6.4	4 (1.1)	6	3.3	2 (1.1)	2	2.3
Hypersensitivity	0			1 (0.5)	3	3.2	1 (0.3)	3	1.6	1 (0.6)	1	1.2
Seasonal allergy	0			3 (1.6)	3	3.2	3 (0.8)	3	1.6	1 (0.6)	1	1.2
Psychiatric disorders	3 (1.7)	3	3.4	2 (1.1)	2	2.1	5 (1.4)	5	2.7	0		
Depression	3 (1.7)	3	3.4	0			3 (0.8)	3	1.6	0		
Affective disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Insomnia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Reproductive system and breast disorders	1 (0.6)	1	1.1	2 (1.1)	3	3.2	3 (0.8)	4	2.2	1 (0.6)	1	1.2
Dysmenorrhoea	0			1 (0.5)	2	2.1	1 (0.3)	2	1.1	0		
Breast tenderness	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Genital haemorrhage	0			0			0			1 (0.6)	1	1.2
Vulvovaginal inflammation	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Ear and labyrinth disorders	1 (0.6)	1	1.1	1 (0.5)	2	2.1	2 (0.5)	3	1.6	1 (0.6)	1	1.2
Tinnitus	1 (0.6)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Sudden hearing loss	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		

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Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - duration of diabetes at baseline < 15 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Tympanic membrane perforation	0			0			0			1 (0.6)	1	1.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.6)	1	1.1	2 (1.1)	2	2.1	3 (0.8)	3	1.6	1 (0.6)	1	1.2
Haemangioma of liver	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.2
Conjunctival neoplasm	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Skin papilloma	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Vascular disorders	2 (1.1)	2	2.3	1 (0.5)	1	1.1	3 (0.8)	3	1.6	1 (0.6)	1	1.2
Hypertension	1 (0.6)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Hypotension	0			0			0			1 (0.6)	1	1.2
Thrombophlebitis superficial	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Surgical and medical procedures	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	2 (1.1)	2	2.3
Haemorrhoid operation	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Inguinal hernia repair	0			0			0			1 (0.6)	1	1.2
Tooth extraction	0			0			0			1 (0.6)	1	1.2
Cardiac disorders	1 (0.6)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	0		
Extrasystoles	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Sinus bradycardia	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Endocrine disorders	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.6)	1	1.2
Goitre	0			0			0			1 (0.6)	1	1.2
Hypothyroidism	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Hepatobiliary disorders	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.2
Cholecystitis	0			0			0			1 (0.6)	1	1.2
Gallbladder polyp	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - duration of diabetes at baseline < 15 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Congenital, familial and genetic disorders	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Accessory spleen	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Pregnancy, puerperium and perinatal conditions	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Subchorionic haemorrhage	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		

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2.7.4.7.3.2.11. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインの糖尿病罹病期間が 15 年以上の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	165				151				316				167			
Total exposure (yrs)	82.7				76.3				159.0				83.4			
Total events	119	(72.1)	348	421.0	108	(71.5)	338	442.7	227	(71.8)	686	431.4	129	(77.2)	336	402.9
Infections and infestations	70	(42.4)	113	136.7	63	(41.7)	121	158.5	133	(42.1)	234	147.2	79	(47.3)	127	152.3
Viral upper respiratory tract infection	33	(20.0)	49	59.3	32	(21.2)	49	64.2	65	(20.6)	98	61.6	35	(21.0)	51	61.2
Upper respiratory tract infection	13	(7.9)	16	19.4	13	(8.6)	19	24.9	26	(8.2)	35	22.0	19	(11.4)	21	25.2
Gastroenteritis	7	(4.2)	8	9.7	6	(4.0)	7	9.2	13	(4.1)	15	9.4	9	(5.4)	11	13.2
Influenza	8	(4.8)	9	10.9	7	(4.6)	7	9.2	15	(4.7)	16	10.1	3	(1.8)	3	3.6
Urinary tract infection	4	(2.4)	4	4.8	3	(2.0)	3	3.9	7	(2.2)	7	4.4	4	(2.4)	4	4.8
Sinusitis	2	(1.2)	2	2.4	4	(2.6)	4	5.2	6	(1.9)	6	3.8	4	(2.4)	4	4.8
Viral infection	4	(2.4)	6	7.3	1	(0.7)	2	2.6	5	(1.6)	8	5.0	2	(1.2)	2	2.4
Bronchitis	0				4	(2.6)	4	5.2	4	(1.3)	4	2.5	2	(1.2)	2	2.4
Gastroenteritis viral	2	(1.2)	2	2.4	0				2	(0.6)	2	1.3	4	(2.4)	4	4.8
Rhinitis	2	(1.2)	2	2.4	0				2	(0.6)	2	1.3	3	(1.8)	3	3.6
Cellulitis	2	(1.2)	2	2.4	1	(0.7)	1	1.3	3	(0.9)	3	1.9	1	(0.6)	1	1.2
Otitis media	2	(1.2)	2	2.4	1	(0.7)	1	1.3	3	(0.9)	3	1.9	1	(0.6)	1	1.2
Onychomycosis	0				2	(1.3)	2	2.6	2	(0.6)	2	1.3	1	(0.6)	1	1.2
Pharyngitis	2	(1.2)	2	2.4	0				2	(0.6)	2	1.3	1	(0.6)	1	1.2
Acute sinusitis	1	(0.6)	1	1.2	1	(0.7)	1	1.3	2	(0.6)	2	1.3	0			
Conjunctivitis	0				2	(1.3)	2	2.6	2	(0.6)	2	1.3	0			
Cystitis	0				0				0				2	(1.2)	2	2.4
Fungal infection	0				1	(0.7)	1	1.3	1	(0.3)	1	0.6	1	(0.6)	1	1.2
Herpes zoster	1	(0.6)	1	1.2	1	(0.7)	1	1.3	2	(0.6)	2	1.3	0			
Localised infection	0				2	(1.3)	2	2.6	2	(0.6)	2	1.3	0			
Respiratory tract infection	1	(0.6)	1	1.2	1	(0.7)	1	1.3	2	(0.6)	2	1.3	0			
Skin infection	0				1	(0.7)	1	1.3	1	(0.3)	1	0.6	1	(0.6)	1	1.2

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Adverse events by system organ class and preferred term - treatment emergent - summary - duration of diabetes at baseline >= 15 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Subcutaneous abscess	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Vulvovaginal candidiasis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Abscess limb	0			0			0			1 (0.6)	1	1.2
Adenoiditis	0			0			0			1 (0.6)	1	1.2
Angular cheilitis	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Candida infection	0			0			0			1 (0.6)	1	1.2
Diverticulitis	0			0			0			1 (0.6)	1	1.2
Ear infection	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Folliculitis	0			0			0			1 (0.6)	1	1.2
Fungal skin infection	0			0			0			1 (0.6)	1	1.2
Gastrointestinal viral infection	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Herpes ophthalmic	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Infectious mononucleosis	0			0			0			1 (0.6)	1	1.2
Lower respiratory tract infection	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Molluscum contagiosum	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Nasopharyngitis	0			0			0			1 (0.6)	1	1.2
Otitis externa	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Otitis media acute	0			0			0			1 (0.6)	1	1.2
Periodontitis	0			0			0			1 (0.6)	1	1.2
Pharyngitis streptococcal	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Pilonidal cyst	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Pneumonia	0			0			0			1 (0.6)	1	1.2
Pulpitis dental	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Respiratory tract infection viral	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Spermatic cord funiculitis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Tinea cruris	0			0			0			1 (0.6)	1	1.2
Tonsillitis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Urethritis	0			0			0			1 (0.6)	1	1.2
Urinary tract infection fungal	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Viral rhinitis	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - duration of diabetes at baseline >= 15 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Vulvovaginal mycotic infection	0				1	(0.7)	1	1.3	1	(0.3)	1	0.6	0			
Investigations	34	(20.6)	47	56.9	27	(17.9)	34	44.5	61	(19.3)	81	50.9	33	(19.8)	44	52.8
Blood glucose decreased	28	(17.0)	40	48.4	25	(16.6)	32	41.9	53	(16.8)	72	45.3	29	(17.4)	36	43.2
Blood pressure increased	1	(0.6)	1	1.2	0				1	(0.3)	1	0.6	1	(0.6)	1	1.2
Haemoglobin decreased	0				1	(0.7)	1	1.3	1	(0.3)	1	0.6	1	(0.6)	1	1.2
Hepatic enzyme increased	1	(0.6)	1	1.2	0				1	(0.3)	1	0.6	1	(0.6)	1	1.2
Weight increased	1	(0.6)	1	1.2	1	(0.7)	1	1.3	2	(0.6)	2	1.3	0			
Blood 1,5-anhydroglucitol decreased	1	(0.6)	1	1.2	0				1	(0.3)	1	0.6	0			
Blood creatinine increased	0				0				0				1	(0.6)	1	1.2
Blood glucose fluctuation	0				0				0				1	(0.6)	1	1.2
Blood potassium increased	1	(0.6)	1	1.2	0				1	(0.3)	1	0.6	0			
Blood thyroid stimulating hormone	1	(0.6)	1	1.2	0				1	(0.3)	1	0.6	0			
Blood thyroid stimulating hormone increased	1	(0.6)	1	1.2	0				1	(0.3)	1	0.6	0			
Electrocardiogram change	0				0				0				1	(0.6)	1	1.2
Haematocrit decreased	0				0				0				1	(0.6)	1	1.2
Heart rate increased	0				0				0				1	(0.6)	1	1.2
Gastrointestinal disorders	19	(11.5)	28	33.9	19	(12.6)	29	38.0	38	(12.0)	57	35.8	21	(12.6)	27	32.4
Nausea	8	(4.8)	9	10.9	2	(1.3)	2	2.6	10	(3.2)	11	6.9	7	(4.2)	9	10.8
Diarrhoea	2	(1.2)	2	2.4	5	(3.3)	5	6.5	7	(2.2)	7	4.4	3	(1.8)	3	3.6
Gastritis	1	(0.6)	2	2.4	3	(2.0)	3	3.9	4	(1.3)	5	3.1	2	(1.2)	2	2.4
Toothache	1	(0.6)	1	1.2	3	(2.0)	3	3.9	4	(1.3)	4	2.5	2	(1.2)	2	2.4
Food poisoning	2	(1.2)	2	2.4	2	(1.3)	2	2.6	4	(1.3)	4	2.5	1	(0.6)	1	1.2
Dental caries	1	(0.6)	1	1.2	2	(1.3)	2	2.6	3	(0.9)	3	1.9	1	(0.6)	1	1.2
Constipation	3	(1.8)	3	3.6	0				3	(0.9)	3	1.9	0			
Dyspepsia	0				2	(1.3)	2	2.6	2	(0.6)	2	1.3	1	(0.6)	1	1.2
Gastrooesophageal reflux disease	0				0				0				3	(1.8)	3	3.6
Hiatus hernia	0				3	(2.0)	3	3.9	3	(0.9)	3	1.9	0			

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Adverse events by system organ class and preferred term - treatment emergent - summary - duration of diabetes at baseline >= 15 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Vomiting	2 (1.2)	2	2.4	0			2 (0.6)	2	1.3	1 (0.6)	1	1.2
Abdominal discomfort	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Abdominal pain upper	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Chronic gastritis	1 (0.6)	1	1.2	1 (0.7)	1	1.3	2 (0.6)	2	1.3	0		
Periodontal disease	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Stomatitis	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Coeliac disease	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Colitis ulcerative	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Enteritis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Gastric ulcer	0			0			0			1 (0.6)	1	1.2
Gastrointestinal disorder	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Hyperchlorhydria	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Retching	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Injury, poisoning and procedural complications	20 (12.1)	25	30.2	12 (7.9)	16	21.0	32 (10.1)	41	25.8	14 (8.4)	17	20.4
Wrong drug administered	7 (4.2)	8	9.7	6 (4.0)	8	10.5	13 (4.1)	16	10.1	3 (1.8)	3	3.6
Fall	2 (1.2)	2	2.4	3 (2.0)	3	3.9	5 (1.6)	5	3.1	0		
Contusion	1 (0.6)	1	1.2	2 (1.3)	2	2.6	3 (0.9)	3	1.9	1 (0.6)	1	1.2
Laceration	2 (1.2)	2	2.4	0			2 (0.6)	2	1.3	1 (0.6)	1	1.2
Muscle strain	3 (1.8)	3	3.6	0			3 (0.9)	3	1.9	0		
Skin abrasion	0			0			0			2 (1.2)	3	3.6
Foot fracture	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Ligament sprain	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Limb injury	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Accidental underdose	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Animal bite	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Facial bones fracture	0			0			0			1 (0.6)	1	1.2
Hand fracture	0			0			0			1 (0.6)	1	1.2
Heat illness	0			0			0			1 (0.6)	1	1.2

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Adverse events by system organ class and preferred term - treatment emergent - summary - duration of diabetes at baseline >= 15 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Ligament rupture	0			0			0			1 (0.6)	1	1.2
Post procedural discharge	0			0			0			1 (0.6)	1	1.2
Radius fracture	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Road traffic accident	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Tendon rupture	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Thermal burn	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Tooth fracture	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Traumatic fracture	0			0			0			1 (0.6)	1	1.2
Ulna fracture	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Wrist fracture	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Musculoskeletal and connective tissue disorders	18 (10.9)	21	25.4	15 (9.9)	18	23.6	33 (10.4)	39	24.5	15 (9.0)	18	21.6
Pain in extremity	4 (2.4)	4	4.8	3 (2.0)	3	3.9	7 (2.2)	7	4.4	2 (1.2)	2	2.4
Back pain	1 (0.6)	1	1.2	2 (1.3)	2	2.6	3 (0.9)	3	1.9	2 (1.2)	2	2.4
Musculoskeletal pain	4 (2.4)	4	4.8	0			4 (1.3)	4	2.5	1 (0.6)	1	1.2
Muscle spasms	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	3 (1.8)	3	3.6
Myalgia	2 (1.2)	2	2.4	1 (0.7)	1	1.3	3 (0.9)	3	1.9	1 (0.6)	1	1.2
Arthralgia	1 (0.6)	1	1.2	2 (1.3)	2	2.6	3 (0.9)	3	1.9	0		
Plantar fasciitis	0			2 (1.3)	3	3.9	2 (0.6)	3	1.9	0		
Tenosynovitis	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	2 (1.2)	2	2.4
Trigger finger	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	1 (0.6)	2	2.4
Arthritis	2 (1.2)	2	2.4	0			2 (0.6)	2	1.3	0		
Periarthritis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Bursitis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Collagen disorder	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Intervertebral disc degeneration	0			0			0			1 (0.6)	1	1.2
Intervertebral disc disorder	0			0			0			1 (0.6)	1	1.2
Intervertebral disc protrusion	0			0			0			1 (0.6)	1	1.2
Joint contracture	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Joint effusion	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Joint swelling	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Muscular weakness	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Myositis	0			0			0			1 (0.6)	1	1.2
Osteoarthritis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Rheumatic disorder	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Spinal osteoarthritis	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Tendonitis	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Nervous system disorders	13 (7.9)	17	20.6	11 (7.3)	13	17.0	24 (7.6)	30	18.9	12 (7.2)	23	27.6
Headache	2 (1.2)	4	4.8	4 (2.6)	5	6.5	6 (1.9)	9	5.7	4 (2.4)	13	15.6
Dizziness	1 (0.6)	1	1.2	1 (0.7)	1	1.3	2 (0.6)	2	1.3	2 (1.2)	3	3.6
Hypoglycaemic unconsciousness	2 (1.2)	2	2.4	1 (0.7)	1	1.3	3 (0.9)	3	1.9	1 (0.6)	1	1.2
Diabetic neuropathy	3 (1.8)	3	3.6	0			3 (0.9)	3	1.9	0		
Hypoglycaemic seizure	2 (1.2)	2	2.4	1 (0.7)	1	1.3	3 (0.9)	3	1.9	0		
Lethargy	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Paraesthesia	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Presyncope	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Carpal tunnel syndrome	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Hypertonia	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Hypoaesthesia	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Hypoglycaemic coma	0			0			0			1 (0.6)	1	1.2
Hyporeflexia	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Memory impairment	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Neurodegenerative disorder	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Post herpetic neuralgia	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Syncope	0			0			0			1 (0.6)	1	1.2
Tremor	0			0			0			1 (0.6)	1	1.2

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
General disorders and administration site conditions	16 (9.7)	20	24.2	12 (7.9)	18	23.6	28 (8.9)	38	23.9	8 (4.8)	10	12.0
Influenza like illness	3 (1.8)	5	6.0	2 (1.3)	2	2.6	5 (1.6)	7	4.4	3 (1.8)	4	4.8
Pyrexia	5 (3.0)	5	6.0	2 (1.3)	2	2.6	7 (2.2)	7	4.4	1 (0.6)	1	1.2
Oedema peripheral	1 (0.6)	1	1.2	2 (1.3)	2	2.6	3 (0.9)	3	1.9	2 (1.2)	2	2.4
Fatigue	1 (0.6)	1	1.2	2 (1.3)	3	3.9	3 (0.9)	4	2.5	0		
Injection site hypertrophy	2 (1.2)	2	2.4	1 (0.7)	1	1.3	3 (0.9)	3	1.9	0		
Malaise	2 (1.2)	2	2.4	0			2 (0.6)	2	1.3	1 (0.6)	1	1.2
Injection site bruising	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Injection site pain	1 (0.6)	1	1.2	1 (0.7)	1	1.3	2 (0.6)	2	1.3	0		
Pain	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Peripheral swelling	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Asthenia	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Chest pain	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Drug therapeutic incompatibility	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Inflammation	0			0			0			1 (0.6)	1	1.2
Injection site haematoma	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Oedema	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Eye disorders	8 (4.8)	8	9.7	19 (12.6)	22	28.8	27 (8.5)	30	18.9	15 (9.0)	17	20.4
Diabetic retinopathy	3 (1.8)	3	3.6	7 (4.6)	7	9.2	10 (3.2)	10	6.3	5 (3.0)	5	6.0
Retinopathy	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	2 (1.2)	2	2.4
Macular oedema	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Retinal aneurysm	2 (1.2)	2	2.4	0			2 (0.6)	2	1.3	0		
Retinopathy proliferative	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Vitreous haemorrhage	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Blepharochalasis	0			0			0			1 (0.6)	1	1.2
Cataract	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Cataract nuclear	0			0			0			1 (0.6)	1	1.2
Chalazion	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Conjunctivitis allergic	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Cystoid macular oedema	0			0			0			1 (0.6)	1	1.2
Dry eye	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Eye disorder	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Eye inflammation	0			0			0			1 (0.6)	1	1.2
Eye pruritus	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Eye ulcer	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Glaucoma	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Iritis	0			0			0			1 (0.6)	1	1.2
Maculopathy	0			0			0			1 (0.6)	1	1.2
Normal tension glaucoma	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Retinal exudates	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Retinal haemorrhage	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Retinal ischaemia	0			0			0			1 (0.6)	1	1.2
Retinal tear	0			0			0			1 (0.6)	1	1.2
Retinopathy hypertensive	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Visual impairment	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Skin and subcutaneous tissue disorders	11 (6.7)	16	19.4	16 (10.6)	17	22.3	27 (8.5)	33	20.8	11 (6.6)	12	14.4
Dermatitis	1 (0.6)	3	3.6	2 (1.3)	2	2.6	3 (0.9)	5	3.1	0		
Lipohypertrophy	1 (0.6)	1	1.2	3 (2.0)	3	3.9	4 (1.3)	4	2.5	0		
Urticaria	2 (1.2)	2	2.4	1 (0.7)	1	1.3	3 (0.9)	3	1.9	1 (0.6)	1	1.2
Eczema	2 (1.2)	2	2.4	0			2 (0.6)	2	1.3	1 (0.6)	1	1.2
Ecchymosis	0			0			0			1 (0.6)	2	2.4
Pruritus	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Skin ulcer	2 (1.2)	2	2.4	0			2 (0.6)	2	1.3	0		
Acne cystic	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Actinic keratosis	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Alopecia	0			0			0			1 (0.6)	1	1.2
Asteatosis	0			0			0			1 (0.6)	1	1.2

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Blister	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Blood blister	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Dermatitis contact	0			0			0			1 (0.6)	1	1.2
Dry skin	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Eczema asteatotic	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Hidradenitis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Miliaria	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Nail bed inflammation	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Nail pigmentation	0			0			0			1 (0.6)	1	1.2
Onychomadesis	0			0			0			1 (0.6)	1	1.2
Papule	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Rash	0			0			0			1 (0.6)	1	1.2
Rash erythematous	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Rash papular	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Rash pruritic	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Skin lesion	0			0			0			1 (0.6)	1	1.2
Skin mass	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Skin reaction	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Xeroderma	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Metabolism and nutrition disorders	17 (10.3)	17	20.6	9 (6.0)	13	17.0	26 (8.2)	30	18.9	13 (7.8)	14	16.8
Hypoglycaemia	14 (8.5)	14	16.9	5 (3.3)	8	10.5	19 (6.0)	22	13.8	9 (5.4)	10	12.0
Hyperlipidaemia	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	1 (0.6)	1	1.2
Dehydration	2 (1.2)	2	2.4	0			2 (0.6)	2	1.3	0		
Vitamin D deficiency	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	0		
Decreased appetite	0			0			0			1 (0.6)	1	1.2
Fluid retention	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Hypercholesterolaemia	0			0			0			1 (0.6)	1	1.2
Hyperglycaemia	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Hypertriglyceridaemia	0			0			0			1 (0.6)	1	1.2

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Respiratory, thoracic and mediastinal disorders	12 (7.3)	14	16.9	10 (6.6)	12	15.7	22 (7.0)	26	16.4	11 (6.6)	12	14.4
Oropharyngeal pain	1 (0.6)	1	1.2	2 (1.3)	2	2.6	3 (0.9)	3	1.9	3 (1.8)	4	4.8
Cough	1 (0.6)	1	1.2	4 (2.6)	4	5.2	5 (1.6)	5	3.1	1 (0.6)	1	1.2
Nasal congestion	3 (1.8)	3	3.6	1 (0.7)	1	1.3	4 (1.3)	4	2.5	0		
Rhinorrhoea	1 (0.6)	1	1.2	1 (0.7)	1	1.3	2 (0.6)	2	1.3	1 (0.6)	1	1.2
Sinus congestion	2 (1.2)	2	2.4	1 (0.7)	1	1.3	3 (0.9)	3	1.9	0		
Asthma	1 (0.6)	1	1.2	1 (0.7)	1	1.3	2 (0.6)	2	1.3	0		
Epistaxis	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Respiratory disorder	1 (0.6)	1	1.2	1 (0.7)	1	1.3	2 (0.6)	2	1.3	0		
Rhinitis allergic	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Upper respiratory tract inflammation	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Chronic obstructive pulmonary disease	0			0			0			1 (0.6)	1	1.2
Dyspnoea	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Paranasal sinus discomfort	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Throat irritation	0			0			0			1 (0.6)	1	1.2
Upper respiratory tract congestion	0			0			0			1 (0.6)	1	1.2
Psychiatric disorders	4 (2.4)	5	6.0	6 (4.0)	7	9.2	10 (3.2)	12	7.5	1 (0.6)	1	1.2
Depression	1 (0.6)	1	1.2	3 (2.0)	3	3.9	4 (1.3)	4	2.5	0		
Insomnia	2 (1.2)	2	2.4	0			2 (0.6)	2	1.3	1 (0.6)	1	1.2
Stress	1 (0.6)	1	1.2	2 (1.3)	2	2.6	3 (0.9)	3	1.9	0		
Anxiety	1 (0.6)	1	1.2	1 (0.7)	1	1.3	2 (0.6)	2	1.3	0		
Sleep disorder	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Vascular disorders	4 (2.4)	4	4.8	4 (2.6)	4	5.2	8 (2.5)	8	5.0	3 (1.8)	3	3.6
Hypertension	2 (1.2)	2	2.4	3 (2.0)	3	3.9	5 (1.6)	5	3.1	1 (0.6)	1	1.2
Orthostatic hypotension	1 (0.6)	1	1.2	1 (0.7)	1	1.3	2 (0.6)	2	1.3	0		
Arteriosclerosis	0			0			0			1 (0.6)	1	1.2

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Hypotension	0			0			0			1 (0.6)	1	1.2
Peripheral arterial occlusive disease	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Renal and urinary disorders	1 (0.6)	1	1.2	3 (2.0)	3	3.9	4 (1.3)	4	2.5	2 (1.2)	4	4.8
Microalbuminuria	0			0			0			2 (1.2)	3	3.6
Haematuria	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Bladder pain	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Crystalluria	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Renal cyst	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Ear and labyrinth disorders	2 (1.2)	2	2.4	3 (2.0)	3	3.9	5 (1.6)	5	3.1	1 (0.6)	1	1.2
Ear discomfort	1 (0.6)	1	1.2	1 (0.7)	1	1.3	2 (0.6)	2	1.3	0		
Ear pain	1 (0.6)	1	1.2	1 (0.7)	1	1.3	2 (0.6)	2	1.3	0		
Vertigo	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Reproductive system and breast disorders	3 (1.8)	3	3.6	1 (0.7)	2	2.6	4 (1.3)	5	3.1	1 (0.6)	1	1.2
Priapism	0			1 (0.7)	2	2.6	1 (0.3)	2	1.3	0		
Benign prostatic hyperplasia	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Endometriosis	0			0			0			1 (0.6)	1	1.2
Gynaecomastia	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Testicular swelling	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Cardiac disorders	2 (1.2)	2	2.4	2 (1.3)	2	2.6	4 (1.3)	4	2.5	1 (0.6)	1	1.2
Palpitations	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Coronary artery disease	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Myocardial ischaemia	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Ventricular extrasystoles	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Endocrine disorders	1 (0.6)	1	1.2	2 (1.3)	3	3.9	3 (0.9)	4	2.5	1 (0.6)	1	1.2
Goitre	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - duration of diabetes at baseline >= 15 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Hyperadrenalism	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Hypothyroidism	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Thyroid cyst	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Hepatobiliary disorders	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Hepatic steatosis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	1 (0.6)	1	1.2
Immune system disorders	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Multiple allergies	0			0			0			1 (0.6)	1	1.2
Mycotic allergy	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Surgical and medical procedures	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	1 (0.6)	1	1.2
Cataract operation	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Endodontic procedure	0			0			0			1 (0.6)	1	1.2
Blood and lymphatic system disorders	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Lymphadenopathy	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Bladder transitional cell carcinoma	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.12. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインで正常肝機能を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	318				320				638				318			
Total exposure (yrs)	159.0				159.6				318.6				158.1			
Total events	224	(70.4)	595	374.2	224	(70.0)	622	389.8	448	(70.2)	1217	382.0	230	(72.3)	562	355.5
Infections and infestations	136	(42.8)	218	137.1	125	(39.1)	215	134.7	261	(40.9)	433	135.9	136	(42.8)	221	139.8
Viral upper respiratory tract infection	69	(21.7)	96	60.4	67	(20.9)	96	60.2	136	(21.3)	192	60.3	73	(23.0)	108	68.3
Upper respiratory tract infection	28	(8.8)	36	22.6	25	(7.8)	33	20.7	53	(8.3)	69	21.7	25	(7.9)	31	19.6
Influenza	18	(5.7)	19	12.0	13	(4.1)	13	8.1	31	(4.9)	32	10.0	10	(3.1)	10	6.3
Gastroenteritis	7	(2.2)	7	4.4	10	(3.1)	11	6.9	17	(2.7)	18	5.7	10	(3.1)	10	6.3
Urinary tract infection	5	(1.6)	6	3.8	7	(2.2)	9	5.6	12	(1.9)	15	4.7	6	(1.9)	6	3.8
Sinusitis	4	(1.3)	5	3.1	4	(1.3)	4	2.5	8	(1.3)	9	2.8	4	(1.3)	4	2.5
Viral infection	3	(0.9)	5	3.1	4	(1.3)	5	3.1	7	(1.1)	10	3.1	3	(0.9)	3	1.9
Pharyngitis	3	(0.9)	3	1.9	1	(0.3)	1	0.6	4	(0.6)	4	1.3	5	(1.6)	8	5.1
Bronchitis	1	(0.3)	1	0.6	4	(1.3)	4	2.5	5	(0.8)	5	1.6	4	(1.3)	4	2.5
Gastroenteritis viral	3	(0.9)	3	1.9	0				3	(0.5)	3	0.9	6	(1.9)	6	3.8
Rhinitis	3	(0.9)	3	1.9	0				3	(0.5)	3	0.9	4	(1.3)	4	2.5
Cystitis	1	(0.3)	2	1.3	2	(0.6)	2	1.3	3	(0.5)	4	1.3	2	(0.6)	2	1.3
Otitis media	3	(0.9)	3	1.9	1	(0.3)	1	0.6	4	(0.6)	4	1.3	1	(0.3)	1	0.6
Respiratory tract infection viral	2	(0.6)	3	1.9	2	(0.6)	2	1.3	4	(0.6)	5	1.6	0			
Tonsillitis	2	(0.6)	4	2.5	1	(0.3)	1	0.6	3	(0.5)	5	1.6	0			
Cellulitis	2	(0.6)	2	1.3	1	(0.3)	1	0.6	3	(0.5)	3	0.9	1	(0.3)	1	0.6
Otitis externa	2	(0.6)	2	1.3	2	(0.6)	2	1.3	4	(0.6)	4	1.3	0			
Acute sinusitis	1	(0.3)	1	0.6	2	(0.6)	2	1.3	3	(0.5)	3	0.9	0			
Ear infection	1	(0.3)	2	1.3	1	(0.3)	1	0.6	2	(0.3)	3	0.9	0			
Fungal infection	0				2	(0.6)	2	1.3	2	(0.3)	2	0.6	1	(0.3)	1	0.6
Herpes zoster	2	(0.6)	2	1.3	1	(0.3)	1	0.6	3	(0.5)	3	0.9	0			
Onychomycosis	0				2	(0.6)	2	1.3	2	(0.3)	2	0.6	1	(0.3)	1	0.6

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - hepatic impairment at baseline: no - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Tooth abscess	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Conjunctivitis	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Localised infection	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Periodontitis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Pneumonia	0			0			0			2 (0.6)	2	1.3
Respiratory tract infection	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Skin infection	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Subcutaneous abscess	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Varicella	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Vulvovaginal candidiasis	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Vulvovaginal mycotic infection	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Abscess limb	0			0			0			1 (0.3)	1	0.6
Adenoiditis	0			0			0			1 (0.3)	1	0.6
Angular cheilitis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Candida infection	0			0			0			1 (0.3)	1	0.6
Cytomegalovirus infection	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Diverticulitis	0			0			0			1 (0.3)	1	0.6
Empyema	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Epstein-Barr virus infection	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Folliculitis	0			0			0			1 (0.3)	1	0.6
Fungal skin infection	0			0			0			1 (0.3)	1	0.6
Furuncle	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Gastrointestinal viral infection	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Gingivitis	0			0			0			1 (0.3)	1	0.6
Herpes ophthalmic	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Impetigo	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Infectious mononucleosis	0			0			0			1 (0.3)	1	0.6
Labyrinthitis	0			0			0			1 (0.3)	1	0.6
Lower respiratory tract infection	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - hepatic impairment at baseline: no - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Lower respiratory tract infection bacterial	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Molluscum contagiosum	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Oral herpes	0				0				0				1	(0.3)	1	0.6
Oral infection	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Paronychia	0				0				0				1	(0.3)	1	0.6
Pharyngitis streptococcal	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Pilonidal cyst	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Pulpitis dental	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Pyelonephritis chronic	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Spermatic cord funiculitis	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Syphilis	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Tinea cruris	0				0				0				1	(0.3)	1	0.6
Urethritis	0				0				0				1	(0.3)	1	0.6
Urinary tract infection fungal	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Viral rhinitis	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Investigations	61	(19.2)	81	50.9	66	(20.6)	83	52.0	127	(19.9)	164	51.5	65	(20.4)	78	49.3
Blood glucose decreased	54	(17.0)	74	46.5	62	(19.4)	78	48.9	116	(18.2)	152	47.7	62	(19.5)	75	47.4
Blood pressure increased	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	1	(0.3)	1	0.6
Weight increased	0				2	(0.6)	2	1.3	2	(0.3)	2	0.6	0			
Blood 1,5-anhydroglucitol decreased	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Blood bilirubin increased	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Blood creatinine increased	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Blood glucose fluctuation	0				0				0				1	(0.3)	1	0.6
Blood potassium increased	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Blood thyroid stimulating hormone	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Blood urine present	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Helicobacter test positive	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Hepatic enzyme increased	0				0				0				1	(0.3)	1	0.6

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - hepatic impairment at baseline: no - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Lipids abnormal	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Urine albumin/creatinine ratio increased	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Gastrointestinal disorders	33 (10.4)	47	29.6	33 (10.3)	48	30.1	66 (10.3)	95	29.8	35 (11.0)	44	27.8
Nausea	10 (3.1)	12	7.5	3 (0.9)	3	1.9	13 (2.0)	15	4.7	8 (2.5)	11	7.0
Diarrhoea	3 (0.9)	3	1.9	9 (2.8)	9	5.6	12 (1.9)	12	3.8	5 (1.6)	5	3.2
Gastritis	2 (0.6)	2	1.3	5 (1.6)	6	3.8	7 (1.1)	8	2.5	3 (0.9)	3	1.9
Vomiting	3 (0.9)	4	2.5	3 (0.9)	3	1.9	6 (0.9)	7	2.2	4 (1.3)	4	2.5
Toothache	3 (0.9)	3	1.9	4 (1.3)	4	2.5	7 (1.1)	7	2.2	2 (0.6)	2	1.3
Constipation	5 (1.6)	5	3.1	1 (0.3)	1	0.6	6 (0.9)	6	1.9	0		
Food poisoning	2 (0.6)	2	1.3	2 (0.6)	2	1.3	4 (0.6)	4	1.3	2 (0.6)	2	1.3
Gastrooesophageal reflux disease	3 (0.9)	3	1.9	0			3 (0.5)	3	0.9	3 (0.9)	3	1.9
Abdominal pain upper	1 (0.3)	1	0.6	3 (0.9)	3	1.9	4 (0.6)	4	1.3	1 (0.3)	1	0.6
Abdominal discomfort	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	2 (0.6)	2	1.3
Dental caries	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	1 (0.3)	1	0.6
Aphthous ulcer	0			1 (0.3)	2	1.3	1 (0.2)	2	0.6	1 (0.3)	1	0.6
Dyspepsia	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	0		
Hiatus hernia	0			3 (0.9)	3	1.9	3 (0.5)	3	0.9	0		
Abdominal distension	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Abdominal pain	0			0			0			2 (0.6)	2	1.3
Chronic gastritis	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Enteritis	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Periodontal disease	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Stomatitis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Apical granuloma	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Coeliac disease	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Colitis ulcerative	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Enterocolitis	0			0			0			1 (0.3)	1	0.6
Gastric polyps	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - hepatic impairment at baseline: no - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Gastric ulcer	0			0			0			1 (0.3)	1	0.6
Gastritis erosive	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Gastrointestinal disorder	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Haemorrhoids	0			0			0			1 (0.3)	1	0.6
Hyperchlorhydria	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Oral discomfort	0			0			0			1 (0.3)	1	0.6
Proctalgia	0			0			0			1 (0.3)	1	0.6
Retching	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Musculoskeletal and connective tissue disorders	27 (8.5)	33	20.8	30 (9.4)	34	21.3	57 (8.9)	67	21.0	27 (8.5)	36	22.8
Back pain	4 (1.3)	4	2.5	7 (2.2)	8	5.0	11 (1.7)	12	3.8	5 (1.6)	5	3.2
Pain in extremity	7 (2.2)	7	4.4	5 (1.6)	5	3.1	12 (1.9)	12	3.8	3 (0.9)	3	1.9
Arthralgia	3 (0.9)	3	1.9	4 (1.3)	4	2.5	7 (1.1)	7	2.2	2 (0.6)	2	1.3
Myalgia	3 (0.9)	4	2.5	1 (0.3)	1	0.6	4 (0.6)	5	1.6	2 (0.6)	3	1.9
Muscle spasms	2 (0.6)	2	1.3	1 (0.3)	1	0.6	3 (0.5)	3	0.9	4 (1.3)	4	2.5
Musculoskeletal pain	3 (0.9)	3	1.9	0			3 (0.5)	3	0.9	1 (0.3)	1	0.6
Tenosynovitis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	3 (0.9)	3	1.9
Arthritis	2 (0.6)	2	1.3	0			2 (0.3)	2	0.6	1 (0.3)	1	0.6
Neck pain	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	0		
Plantar fasciitis	0			2 (0.6)	3	1.9	2 (0.3)	3	0.9	0		
Trigger finger	0			0			0			2 (0.6)	3	1.9
Intervertebral disc protrusion	0			0			0			2 (0.6)	2	1.3
Musculoskeletal stiffness	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Periarthritis	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Rheumatoid arthritis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Arthropathy	0			0			0			1 (0.3)	1	0.6
Bursitis	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Exostosis	0			0			0			1 (0.3)	1	0.6
Flank pain	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		

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	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Intervertebral disc degeneration	0				0				0				1	(0.3)	1	0.6
Intervertebral disc disorder	0				0				0				1	(0.3)	1	0.6
Joint contracture	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Joint effusion	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Joint swelling	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Lumbar spinal stenosis	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Muscular weakness	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Myositis	0				0				0				1	(0.3)	1	0.6
Osteoarthritis	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Osteoporotic fracture	0				0				0				1	(0.3)	1	0.6
Rheumatic disorder	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Rotator cuff syndrome	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Spinal osteoarthritis	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Spinal pain	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Tendonitis	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Injury, poisoning and procedural complications	32	(10.1)	38	23.9	24	(7.5)	31	19.4	56	(8.8)	69	21.7	27	(8.5)	30	19.0
Wrong drug administered	7	(2.2)	8	5.0	10	(3.1)	13	8.1	17	(2.7)	21	6.6	6	(1.9)	6	3.8
Ligament sprain	3	(0.9)	3	1.9	3	(0.9)	3	1.9	6	(0.9)	6	1.9	3	(0.9)	3	1.9
Contusion	2	(0.6)	2	1.3	3	(0.9)	3	1.9	5	(0.8)	5	1.6	1	(0.3)	1	0.6
Limb injury	5	(1.6)	5	3.1	0				5	(0.8)	5	1.6	1	(0.3)	1	0.6
Fall	2	(0.6)	2	1.3	3	(0.9)	3	1.9	5	(0.8)	5	1.6	0			
Tooth fracture	3	(0.9)	3	1.9	0				3	(0.5)	3	0.9	1	(0.3)	1	0.6
Foot fracture	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	2	(0.6)	2	1.3
Laceration	2	(0.6)	2	1.3	0				2	(0.3)	2	0.6	1	(0.3)	1	0.6
Muscle strain	3	(0.9)	3	1.9	0				3	(0.5)	3	0.9	0			
Skin abrasion	0				0				0				2	(0.6)	3	1.9
Hand fracture	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	1	(0.3)	1	0.6
Radius fracture	1	(0.3)	1	0.6	1	(0.3)	1	0.6	2	(0.3)	2	0.6	0			

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	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Road traffic accident	0				2	(0.6)	2	1.3	2	(0.3)	2	0.6	0			
Tendon rupture	1	(0.3)	1	0.6	1	(0.3)	1	0.6	2	(0.3)	2	0.6	0			
Thermal burn	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	1	(0.3)	1	0.6
Accidental overdose	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Accidental underdose	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Animal bite	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Buttock injury	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Extradural haematoma	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Eyelid injury	0				0				0				1	(0.3)	1	0.6
Facial bones fracture	0				0				0				1	(0.3)	1	0.6
Femoral neck fracture	0				0				0				1	(0.3)	1	0.6
Forearm fracture	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Foreign body in eye	0				0				0				1	(0.3)	1	0.6
Heat illness	0				0				0				1	(0.3)	1	0.6
Joint dislocation	0				0				0				1	(0.3)	1	0.6
Joint injury	0				0				0				1	(0.3)	1	0.6
Post procedural discharge	0				0				0				1	(0.3)	1	0.6
Postoperative ileus	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Skull fractured base	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Traumatic fracture	0				0				0				1	(0.3)	1	0.6
Ulna fracture	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Wound	0				0				0				1	(0.3)	1	0.6
Wrist fracture	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Nervous system disorders	21	(6.6)	25	15.7	27	(8.4)	38	23.8	48	(7.5)	63	19.8	17	(5.3)	28	17.7
Headache	4	(1.3)	6	3.8	11	(3.4)	18	11.3	15	(2.4)	24	7.5	4	(1.3)	13	8.2
Dizziness	2	(0.6)	2	1.3	4	(1.3)	5	3.1	6	(0.9)	7	2.2	3	(0.9)	4	2.5
Hypoglycaemic unconsciousness	1	(0.3)	1	0.6	3	(0.9)	3	1.9	4	(0.6)	4	1.3	2	(0.6)	2	1.3
Diabetic neuropathy	3	(0.9)	3	1.9	0				3	(0.5)	3	0.9	0			
Hypoaesthesia	0				2	(0.6)	2	1.3	2	(0.3)	2	0.6	1	(0.3)	1	0.6

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Hypoglycaemic seizure	2 (0.6)	2	1.3	1 (0.3)	1	0.6	3 (0.5)	3	0.9	0		
Migraine	3 (0.9)	3	1.9	0			3 (0.5)	3	0.9	0		
Paraesthesia	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Lethargy	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Polyneuropathy	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Presyncope	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Syncope	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Tension headache	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Carotid arteriosclerosis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Carpal tunnel syndrome	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Cerebrovascular accident	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Hypertonia	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Hypoglycaemic coma	0			0			0			1 (0.3)	1	0.6
Hyporeflexia	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Lumbar radiculopathy	0			0			0			1 (0.3)	1	0.6
Memory impairment	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Neurodegenerative disorder	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Occipital neuralgia	0			0			0			1 (0.3)	1	0.6
Post herpetic neuralgia	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Tremor	0			0			0			1 (0.3)	1	0.6
General disorders and administration site conditions	23 (7.2)	29	18.2	24 (7.5)	34	21.3	47 (7.4)	63	19.8	15 (4.7)	19	12.0
Influenza like illness	5 (1.6)	7	4.4	3 (0.9)	3	1.9	8 (1.3)	10	3.1	4 (1.3)	6	3.8
Pyrexia	8 (2.5)	8	5.0	7 (2.2)	7	4.4	15 (2.4)	15	4.7	1 (0.3)	1	0.6
Injection site haematoma	2 (0.6)	2	1.3	2 (0.6)	4	2.5	4 (0.6)	6	1.9	1 (0.3)	1	0.6
Injection site bruising	1 (0.3)	2	1.3	2 (0.6)	2	1.3	3 (0.5)	4	1.3	0		
Injection site pain	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	2 (0.6)	2	1.3
Oedema peripheral	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	1 (0.3)	1	0.6
Chest pain	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	2 (0.6)	2	1.3

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	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Fatigue	0				2	(0.6)	3	1.9	2	(0.3)	3	0.9	0			
Injection site hypertrophy	2	(0.6)	2	1.3	1	(0.3)	1	0.6	3	(0.5)	3	0.9	0			
Malaise	2	(0.6)	2	1.3	0				2	(0.3)	2	0.6	1	(0.3)	1	0.6
Asthenia	0				2	(0.6)	2	1.3	2	(0.3)	2	0.6	0			
Injection site reaction	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	1	(0.3)	1	0.6
Pain	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	1	(0.3)	1	0.6
Peripheral swelling	0				2	(0.6)	2	1.3	2	(0.3)	2	0.6	0			
Administration site induration	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Chest discomfort	0				0				0				1	(0.3)	1	0.6
Feeling abnormal	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
General symptom	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Inflammation	0				0				0				1	(0.3)	1	0.6
Injection site haemorrhage	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Injection site hypersensitivity	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Injection site induration	0				0				0				1	(0.3)	1	0.6
Injection site rash	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Injection site swelling	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Oedema	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Eye disorders	17	(5.3)	18	11.3	25	(7.8)	29	18.2	42	(6.6)	47	14.8	19	(6.0)	20	12.7
Diabetic retinopathy	7	(2.2)	7	4.4	11	(3.4)	11	6.9	18	(2.8)	18	5.7	7	(2.2)	7	4.4
Macular oedema	0				2	(0.6)	2	1.3	2	(0.3)	2	0.6	2	(0.6)	2	1.3
Retinal tear	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	2	(0.6)	2	1.3
Retinopathy	2	(0.6)	2	1.3	0				2	(0.3)	2	0.6	1	(0.3)	1	0.6
Retinal aneurysm	2	(0.6)	2	1.3	0				2	(0.3)	2	0.6	0			
Retinopathy hypertensive	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	1	(0.3)	1	0.6
Retinopathy proliferative	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	1	(0.3)	1	0.6
Vitreous haemorrhage	0				2	(0.6)	2	1.3	2	(0.3)	2	0.6	0			
Blepharochalasis	0				0				0				1	(0.3)	1	0.6
Cataract	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			

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	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Cataract nuclear	0				0				0				1	(0.3)	1	0.6
Chalazion	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Conjunctival haemorrhage	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Conjunctivitis allergic	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Cystoid macular oedema	0				0				0				1	(0.3)	1	0.6
Dry eye	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Eye disorder	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Eye inflammation	0				0				0				1	(0.3)	1	0.6
Eye pruritus	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Eye ulcer	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Eyelid oedema	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Glaucoma	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Iritis	0				0				0				1	(0.3)	1	0.6
Lacrimation increased	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Normal tension glaucoma	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Ocular discomfort	0				0				0				1	(0.3)	1	0.6
Ocular hypertension	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Retinal exudates	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Retinal haemorrhage	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Visual acuity reduced transiently	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Visual impairment	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Vitreous detachment	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Metabolism and nutrition disorders	24	(7.5)	25	15.7	16	(5.0)	22	13.8	40	(6.3)	47	14.8	18	(5.7)	20	12.7
Hypoglycaemia	17	(5.3)	18	11.3	6	(1.9)	9	5.6	23	(3.6)	27	8.5	11	(3.5)	12	7.6
Hyperglycaemia	2	(0.6)	2	1.3	1	(0.3)	1	0.6	3	(0.5)	3	0.9	2	(0.6)	3	1.9
Hyperlipidaemia	0				2	(0.6)	2	1.3	2	(0.3)	2	0.6	2	(0.6)	2	1.3
Diabetic metabolic decompensation	2	(0.6)	2	1.3	1	(0.3)	1	0.6	3	(0.5)	3	0.9	0			
Vitamin D deficiency	0				3	(0.9)	3	1.9	3	(0.5)	3	0.9	0			
Decreased appetite	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	1	(0.3)	1	0.6

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - hepatic impairment at baseline: no - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Dehydration	2	(0.6)	2	1.3	0				2	(0.3)	2	0.6	0			
Hypertriglyceridaemia	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	1	(0.3)	1	0.6
Hypoglycaemia unawareness	0				2	(0.6)	2	1.3	2	(0.3)	2	0.6	0			
Hypokalaemia	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	1	(0.3)	1	0.6
Fluid retention	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Gout	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Skin and subcutaneous tissue disorders	14	(4.4)	18	11.3	22	(6.9)	24	15.0	36	(5.6)	42	13.2	17	(5.3)	18	11.4
Dermatitis	1	(0.3)	3	1.9	4	(1.3)	4	2.5	5	(0.8)	7	2.2	0			
Urticaria	2	(0.6)	2	1.3	3	(0.9)	3	1.9	5	(0.8)	5	1.6	2	(0.6)	2	1.3
Lipohypertrophy	1	(0.3)	1	0.6	3	(0.9)	3	1.9	4	(0.6)	4	1.3	0			
Dry skin	0				2	(0.6)	2	1.3	2	(0.3)	2	0.6	1	(0.3)	1	0.6
Eczema	2	(0.6)	2	1.3	0				2	(0.3)	2	0.6	1	(0.3)	1	0.6
Pruritus	0				2	(0.6)	2	1.3	2	(0.3)	2	0.6	1	(0.3)	1	0.6
Skin ulcer	2	(0.6)	2	1.3	0				2	(0.3)	2	0.6	1	(0.3)	1	0.6
Dermatitis atopic	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	1	(0.3)	1	0.6
Ecchymosis	0				0				0				1	(0.3)	2	1.3
Rash	0				0				0				2	(0.6)	2	1.3
Acne cystic	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Alopecia	0				0				0				1	(0.3)	1	0.6
Asteatosis	0				0				0				1	(0.3)	1	0.6
Blister	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Blood blister	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Dermal cyst	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Dermatitis contact	0				0				0				1	(0.3)	1	0.6
Hidradenitis	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Lipodystrophy acquired	1	(0.3)	1	0.6	0				1	(0.2)	1	0.3	0			
Miliaria	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Nail bed inflammation	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			
Nail disorder	0				1	(0.3)	1	0.6	1	(0.2)	1	0.3	0			

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Nail pigmentation	0			0			0			1 (0.3)	1	0.6
Onychomadesis	0			0			0			1 (0.3)	1	0.6
Papule	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Parapsoriasis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Rash erythematous	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Rash pruritic	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Skin exfoliation	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Skin fissures	0			0			0			1 (0.3)	1	0.6
Skin lesion	0			0			0			1 (0.3)	1	0.6
Skin mass	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Skin reaction	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Xeroderma	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Respiratory, thoracic and mediastinal disorders	19 (6.0)	21	13.2	18 (5.6)	21	13.2	37 (5.8)	42	13.2	16 (5.0)	17	10.8
Oropharyngeal pain	3 (0.9)	3	1.9	4 (1.3)	4	2.5	7 (1.1)	7	2.2	5 (1.6)	6	3.8
Cough	1 (0.3)	1	0.6	5 (1.6)	5	3.1	6 (0.9)	6	1.9	1 (0.3)	1	0.6
Sinus congestion	4 (1.3)	4	2.5	2 (0.6)	2	1.3	6 (0.9)	6	1.9	0		
Rhinorrhoea	2 (0.6)	2	1.3	1 (0.3)	1	0.6	3 (0.5)	3	0.9	2 (0.6)	2	1.3
Asthma	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	2 (0.6)	2	1.3
Nasal congestion	3 (0.9)	3	1.9	1 (0.3)	1	0.6	4 (0.6)	4	1.3	0		
Upper respiratory tract inflammation	0			2 (0.6)	3	1.9	2 (0.3)	3	0.9	1 (0.3)	1	0.6
Epistaxis	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Respiratory disorder	2 (0.6)	2	1.3	1 (0.3)	1	0.6	3 (0.5)	3	0.9	0		
Rhinitis allergic	2 (0.6)	2	1.3	0			2 (0.3)	2	0.6	1 (0.3)	1	0.6
Dyspnoea	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Paranasal sinus discomfort	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Pleurisy	0			0			0			1 (0.3)	1	0.6
Throat irritation	0			0			0			1 (0.3)	1	0.6
Tonsillar hypertrophy	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Upper respiratory tract congestion	0			0			0			1 (0.3)	1	0.6
Psychiatric disorders	6 (1.9)	7	4.4	8 (2.5)	9	5.6	14 (2.2)	16	5.0	1 (0.3)	1	0.6
Depression	3 (0.9)	3	1.9	3 (0.9)	3	1.9	6 (0.9)	6	1.9	0		
Insomnia	2 (0.6)	2	1.3	1 (0.3)	1	0.6	3 (0.5)	3	0.9	1 (0.3)	1	0.6
Stress	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	0		
Anxiety	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Affective disorder	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Sleep disorder	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Renal and urinary disorders	4 (1.3)	4	2.5	6 (1.9)	6	3.8	10 (1.6)	10	3.1	4 (1.3)	6	3.8
Microalbuminuria	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	3 (0.9)	4	2.5
Haematuria	1 (0.3)	1	0.6	2 (0.6)	2	1.3	3 (0.5)	3	0.9	1 (0.3)	1	0.6
Acute kidney injury	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Bladder pain	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Crystalluria	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Dysuria	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Nephrolithiasis	0			0			0			1 (0.3)	1	0.6
Renal cyst	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Renal failure	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Vascular disorders	6 (1.9)	6	3.8	5 (1.6)	5	3.1	11 (1.7)	11	3.5	3 (0.9)	3	1.9
Hypertension	3 (0.9)	3	1.9	4 (1.3)	4	2.5	7 (1.1)	7	2.2	0		
Hypotension	0			0			0			2 (0.6)	2	1.3
Orthostatic hypotension	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Arteriosclerosis	0			0			0			1 (0.3)	1	0.6
Peripheral arterial occlusive disease	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Thrombophlebitis superficial	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Blood and lymphatic system disorders	6 (1.9)	6	3.8	0			6 (0.9)	6	1.9	5 (1.6)	5	3.2

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Adverse events by system organ class and preferred term - treatment emergent - summary - hepatic impairment at baseline: no - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Anaemia	3 (0.9)	3	1.9	0			3 (0.5)	3	0.9	4 (1.3)	4	2.5
Iron deficiency anaemia	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Leukopenia	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Lymphadenopathy	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Ear and labyrinth disorders	3 (0.9)	3	1.9	4 (1.3)	5	3.1	7 (1.1)	8	2.5	2 (0.6)	2	1.3
Ear discomfort	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Ear pain	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Tinnitus	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Vertigo	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Sudden hearing loss	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Tympanic membrane perforation	0			0			0			1 (0.3)	1	0.6
Immune system disorders	1 (0.3)	1	0.6	4 (1.3)	6	3.8	5 (0.8)	7	2.2	3 (0.9)	3	1.9
Hypersensitivity	0			1 (0.3)	3	1.9	1 (0.2)	3	0.9	1 (0.3)	1	0.6
Seasonal allergy	0			3 (0.9)	3	1.9	3 (0.5)	3	0.9	1 (0.3)	1	0.6
Multiple allergies	0			0			0			1 (0.3)	1	0.6
Mycotic allergy	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Reproductive system and breast disorders	4 (1.3)	4	2.5	2 (0.6)	3	1.9	6 (0.9)	7	2.2	2 (0.6)	2	1.3
Dysmenorrhoea	0			1 (0.3)	2	1.3	1 (0.2)	2	0.6	0		
Benign prostatic hyperplasia	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Breast tenderness	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Endometriosis	0			0			0			1 (0.3)	1	0.6
Genital haemorrhage	0			0			0			1 (0.3)	1	0.6
Gynaecomastia	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Testicular swelling	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Vulvovaginal inflammation	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Endocrine disorders	1 (0.3)	1	0.6	3 (0.9)	4	2.5	4 (0.6)	5	1.6	2 (0.6)	2	1.3

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Goitre	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	2 (0.6)	2	1.3
Hypothyroidism	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Hyperadrenalism	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Thyroid cyst	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Cardiac disorders	3 (0.9)	3	1.9	2 (0.6)	2	1.3	5 (0.8)	5	1.6	1 (0.3)	1	0.6
Coronary artery disease	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Extrasystoles	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Myocardial ischaemia	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Palpitations	0			0			0			1 (0.3)	1	0.6
Sinus bradycardia	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Ventricular extrasystoles	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.6)	2	1.3	2 (0.6)	2	1.3	4 (0.6)	4	1.3	1 (0.3)	1	0.6
Haemangioma of liver	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Bladder transitional cell carcinoma	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Conjunctival neoplasm	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Skin papilloma	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Surgical and medical procedures	2 (0.6)	2	1.3	0			2 (0.3)	2	0.6	3 (0.9)	3	1.9
Cataract operation	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Endodontic procedure	0			0			0			1 (0.3)	1	0.6
Haemorrhoid operation	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Inguinal hernia repair	0			0			0			1 (0.3)	1	0.6
Tooth extraction	0			0			0			1 (0.3)	1	0.6
Hepatobiliary disorders	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	2 (0.6)	2	1.3
Hepatic steatosis	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Cholecystitis	0			0			0			1 (0.3)	1	0.6

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Gallbladder polyp	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Congenital, familial and genetic disorders	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Accessory spleen	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Pregnancy, puerperium and perinatal conditions	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Subchorionic haemorrhage	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		

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2.7.4.7.3.2.13. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインで肝機能障害を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	24			21			45			24		
Total exposure (yrs)	12.3			10.6			22.9			12.1		
Total events	16 (66.7)	54	439.7	13 (61.9)	34	319.7	29 (64.4)	88	384.0	18 (75.0)	65	538.0
Infections and infestations	10 (41.7)	15	122.1	5 (23.8)	9	84.6	15 (33.3)	24	104.7	13 (54.2)	23	190.4
Viral upper respiratory tract infection	4 (16.7)	5	40.7	3 (14.3)	4	37.6	7 (15.6)	9	39.3	7 (29.2)	10	82.8
Gastroenteritis	1 (4.2)	2	16.3	2 (9.5)	2	18.8	3 (6.7)	4	17.5	1 (4.2)	3	24.8
Upper respiratory tract infection	2 (8.3)	2	16.3	1 (4.8)	1	9.4	3 (6.7)	3	13.1	2 (8.3)	3	24.8
Influenza	3 (12.5)	3	24.4	1 (4.8)	1	9.4	4 (8.9)	4	17.5	0		
Sinusitis	1 (4.2)	1	8.1	1 (4.8)	1	9.4	2 (4.4)	2	8.7	0		
Urinary tract infection	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	1 (4.2)	1	8.3
Gastroenteritis viral	0			0			0			1 (4.2)	1	8.3
Laryngitis	0			0			0			1 (4.2)	1	8.3
Nasopharyngitis	0			0			0			1 (4.2)	1	8.3
Otitis media acute	0			0			0			1 (4.2)	1	8.3
Periodontitis	0			0			0			1 (4.2)	1	8.3
Rhinitis	0			0			0			1 (4.2)	1	8.3
Viral infection	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Investigations	8 (33.3)	12	97.7	7 (33.3)	11	103.4	15 (33.3)	23	100.4	8 (33.3)	13	107.6
Blood glucose decreased	4 (16.7)	7	57.0	5 (23.8)	5	47.0	9 (20.0)	12	52.4	6 (25.0)	7	57.9
Blood creatinine increased	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	1 (4.2)	1	8.3
Haemoglobin decreased	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	1 (4.2)	1	8.3
Hepatic enzyme increased	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	1 (4.2)	1	8.3
Alanine aminotransferase increased	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Aspartate aminotransferase increased	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Blood pressure increased	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - hepatic impairment at baseline: yes - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Blood thyroid stimulating hormone increased	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Electrocardiogram change	0			0			0			1 (4.2)	1	8.3
Haematocrit decreased	0			0			0			1 (4.2)	1	8.3
Heart rate increased	0			0			0			1 (4.2)	1	8.3
Protein urine present	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Transaminases increased	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Urine albumin/creatinine ratio increased	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Weight increased	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
General disorders and administration site conditions	2 (8.3)	2	16.3	1 (4.8)	1	9.4	3 (6.7)	3	13.1	3 (12.5)	8	66.2
Injection site haematoma	0			0			0			1 (4.2)	3	24.8
Injection site reaction	0			0			0			1 (4.2)	2	16.6
Chest discomfort	0			0			0			1 (4.2)	1	8.3
Drug therapeutic incompatibility	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Fatigue	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Influenza like illness	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Oedema peripheral	0			0			0			1 (4.2)	1	8.3
Pyrexia	0			0			0			1 (4.2)	1	8.3
Gastrointestinal disorders	3 (12.5)	5	40.7	0			3 (6.7)	5	21.8	4 (16.7)	4	33.1
Nausea	2 (8.3)	2	16.3	0			2 (4.4)	2	8.7	1 (4.2)	1	8.3
Abdominal pain	0			0			0			2 (8.3)	2	16.6
Gastritis	1 (4.2)	2	16.3	0			1 (2.2)	2	8.7	0		
Dyspepsia	0			0			0			1 (4.2)	1	8.3
Vomiting	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - hepatic impairment at baseline: yes - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Musculoskeletal and connective tissue disorders	4 (16.7)	5	40.7	1 (4.8)	1	9.4	5 (11.1)	6	26.2	3 (12.5)	3	24.8
Back pain	0			0			0			1 (4.2)	1	8.3
Collagen disorder	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Intervertebral disc disorder	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Muscle spasms	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Musculoskeletal chest pain	0			0			0			1 (4.2)	1	8.3
Musculoskeletal pain	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Myalgia	0			0			0			1 (4.2)	1	8.3
Pain in extremity	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Trigger finger	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Eye disorders	0			3 (14.3)	5	47.0	3 (6.7)	5	21.8	2 (8.3)	3	24.8
Astigmatism	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Diabetic retinopathy	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Dry eye	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Maculopathy	0			0			0			1 (4.2)	1	8.3
Myopia	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Retinal ischaemia	0			0			0			1 (4.2)	1	8.3
Retinopathy	0			0			0			1 (4.2)	1	8.3
Retinopathy hypertensive	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Metabolism and nutrition disorders	5 (20.8)	5	40.7	0			5 (11.1)	5	21.8	3 (12.5)	3	24.8
Hypoglycaemia	4 (16.7)	4	32.6	0			4 (8.9)	4	17.5	1 (4.2)	1	8.3
Diabetic metabolic decompensation	0			0			0			1 (4.2)	1	8.3
Hypercholesterolaemia	0			0			0			1 (4.2)	1	8.3
Hyperlipidaemia	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Skin and subcutaneous tissue disorders	4 (16.7)	5	40.7	0			4 (8.9)	5	21.8	1 (4.2)	1	8.3
Dermatitis contact	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	1 (4.2)	1	8.3

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Adverse events by system organ class and preferred term - treatment emergent - summary - hepatic impairment at baseline: yes - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Actinic keratosis	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Eczema asteatotic	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Lipohypertrophy	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Rash papular	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Injury, poisoning and procedural complications	2 (8.3)	2	16.3	1 (4.8)	1	9.4	3 (6.7)	3	13.1	1 (4.2)	1	8.3
Wrong drug administered	1 (4.2)	1	8.1	1 (4.8)	1	9.4	2 (4.4)	2	8.7	0		
Ligament rupture	0			0			0			1 (4.2)	1	8.3
Muscle strain	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Nervous system disorders	1 (4.2)	1	8.1	1 (4.8)	1	9.4	2 (4.4)	2	8.7	1 (4.2)	2	16.6
Headache	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	1 (4.2)	2	16.6
Hypoglycaemic unconsciousness	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Respiratory, thoracic and mediastinal disorders	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	3 (12.5)	3	24.8
Chronic obstructive pulmonary disease	0			0			0			1 (4.2)	1	8.3
Oropharyngeal pain	0			0			0			1 (4.2)	1	8.3
Rhinitis allergic	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Throat irritation	0			0			0			1 (4.2)	1	8.3
Reproductive system and breast disorders	0			1 (4.8)	2	18.8	1 (2.2)	2	8.7	0		
Priapism	0			1 (4.8)	2	18.8	1 (2.2)	2	8.7	0		
Blood and lymphatic system disorders	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Lymphadenopathy	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Cardiac disorders	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Palpitations	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - hepatic impairment at baseline: yes - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Psychiatric disorders	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Depression	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Renal and urinary disorders	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Haematuria	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Vascular disorders	0			0			0			1 (4.2)	1	8.3
Hypertension	0			0			0			1 (4.2)	1	8.3

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2.7.4.7.3.2.14. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインで正常腎機能を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	272			263			535			277		
Total exposure (yrs)	136.2			131.5			267.7			138.1		
Total events	184 (67.6)	474	348.0	182 (69.2)	519	394.7	366 (68.4)	993	370.9	199 (71.8)	495	358.3
Infections and infestations	107 (39.3)	175	128.5	105 (39.9)	188	143.0	212 (39.6)	363	135.6	118 (42.6)	197	142.6
Viral upper respiratory tract infection	51 (18.8)	72	52.9	55 (20.9)	80	60.8	106 (19.8)	152	56.8	60 (21.7)	91	65.9
Upper respiratory tract infection	26 (9.6)	34	25.0	22 (8.4)	30	22.8	48 (9.0)	64	23.9	21 (7.6)	28	20.3
Influenza	18 (6.6)	18	13.2	12 (4.6)	12	9.1	30 (5.6)	30	11.2	8 (2.9)	8	5.8
Gastroenteritis	4 (1.5)	5	3.7	11 (4.2)	12	9.1	15 (2.8)	17	6.4	11 (4.0)	13	9.4
Urinary tract infection	3 (1.1)	4	2.9	6 (2.3)	8	6.1	9 (1.7)	12	4.5	6 (2.2)	6	4.3
Sinusitis	3 (1.1)	4	2.9	5 (1.9)	5	3.8	8 (1.5)	9	3.4	4 (1.4)	4	2.9
Pharyngitis	3 (1.1)	3	2.2	1 (0.4)	1	0.8	4 (0.7)	4	1.5	4 (1.4)	7	5.1
Gastroenteritis viral	3 (1.1)	3	2.2	0			3 (0.6)	3	1.1	6 (2.2)	6	4.3
Viral infection	2 (0.7)	2	1.5	3 (1.1)	3	2.3	5 (0.9)	5	1.9	3 (1.1)	3	2.2
Bronchitis	1 (0.4)	1	0.7	4 (1.5)	4	3.0	5 (0.9)	5	1.9	2 (0.7)	2	1.4
Rhinitis	2 (0.7)	2	1.5	0			2 (0.4)	2	0.7	5 (1.8)	5	3.6
Respiratory tract infection viral	2 (0.7)	3	2.2	2 (0.8)	2	1.5	4 (0.7)	5	1.9	0		
Tonsillitis	2 (0.7)	4	2.9	1 (0.4)	1	0.8	3 (0.6)	5	1.9	0		
Otitis media	2 (0.7)	2	1.5	1 (0.4)	1	0.8	3 (0.6)	3	1.1	1 (0.4)	1	0.7
Acute sinusitis	1 (0.4)	1	0.7	2 (0.8)	2	1.5	3 (0.6)	3	1.1	0		
Cellulitis	2 (0.7)	2	1.5	0			2 (0.4)	2	0.7	1 (0.4)	1	0.7
Cystitis	1 (0.4)	2	1.5	1 (0.4)	1	0.8	2 (0.4)	3	1.1	0		
Fungal infection	0			2 (0.8)	2	1.5	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Herpes zoster	2 (0.7)	2	1.5	1 (0.4)	1	0.8	3 (0.6)	3	1.1	0		
Onychomycosis	0			2 (0.8)	2	1.5	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Tooth abscess	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Conjunctivitis	0			2 (0.8)	2	1.5	2 (0.4)	2	0.7	0		

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Adverse events by system organ class and preferred term - treatment emergent - summary - renal impairment at baseline: normal - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Localised infection	0			2 (0.8)	2	1.5	2 (0.4)	2	0.7	0		
Otitis externa	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	0		
Periodontitis	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Skin infection	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Subcutaneous abscess	0			2 (0.8)	2	1.5	2 (0.4)	2	0.7	0		
Varicella	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Vulvovaginal candidiasis	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Vulvovaginal mycotic infection	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Abscess limb	0			0			0			1 (0.4)	1	0.7
Adenoiditis	0			0			0			1 (0.4)	1	0.7
Cytomegalovirus infection	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Diverticulitis	0			0			0			1 (0.4)	1	0.7
Ear infection	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Epstein-Barr virus infection	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Folliculitis	0			0			0			1 (0.4)	1	0.7
Fungal skin infection	0			0			0			1 (0.4)	1	0.7
Furuncle	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Gingivitis	0			0			0			1 (0.4)	1	0.7
Herpes ophthalmic	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Impetigo	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Infectious mononucleosis	0			0			0			1 (0.4)	1	0.7
Laryngitis	0			0			0			1 (0.4)	1	0.7
Lower respiratory tract infection bacterial	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Molluscum contagiosum	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Oral herpes	0			0			0			1 (0.4)	1	0.7
Oral infection	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Otitis media acute	0			0			0			1 (0.4)	1	0.7
Paronychia	0			0			0			1 (0.4)	1	0.7
Pharyngitis streptococcal	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		

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	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Pilonidal cyst	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Pneumonia	0				0				0				1	(0.4)	1	0.7
Pulpitis dental	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Pyelonephritis chronic	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Spermatic cord funiculitis	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Syphilis	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Tinea cruris	0				0				0				1	(0.4)	1	0.7
Urethritis	0				0				0				1	(0.4)	1	0.7
Urinary tract infection fungal	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Viral rhinitis	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Investigations	49	(18.0)	61	44.8	59	(22.4)	73	55.5	108	(20.2)	134	50.1	58	(20.9)	67	48.5
Blood glucose decreased	41	(15.1)	53	38.9	54	(20.5)	64	48.7	95	(17.8)	117	43.7	54	(19.5)	59	42.7
Blood creatinine increased	1	(0.4)	1	0.7	1	(0.4)	1	0.8	2	(0.4)	2	0.7	1	(0.4)	1	0.7
Haemoglobin decreased	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	1	(0.4)	1	0.7
Hepatic enzyme increased	0				0				0				2	(0.7)	2	1.4
Urine albumin/creatinine ratio increased	1	(0.4)	1	0.7	1	(0.4)	1	0.8	2	(0.4)	2	0.7	0			
Weight increased	0				2	(0.8)	2	1.5	2	(0.4)	2	0.7	0			
Alanine aminotransferase increased	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Aspartate aminotransferase increased	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Blood bilirubin increased	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Blood glucose fluctuation	0				0				0				1	(0.4)	1	0.7
Blood potassium increased	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Blood pressure increased	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Blood thyroid stimulating hormone	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Blood thyroid stimulating hormone increased	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Electrocardiogram change	0				0				0				1	(0.4)	1	0.7
Haematocrit decreased	0				0				0				1	(0.4)	1	0.7

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Adverse events by system organ class and preferred term - treatment emergent - summary - renal impairment at baseline: normal - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Heart rate increased	0				0				0				1	(0.4)	1	0.7
Lipids abnormal	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Protein urine present	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Transaminases increased	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Gastrointestinal disorders	25	(9.2)	37	27.2	23	(8.7)	37	28.1	48	(9.0)	74	27.6	31	(11.2)	39	28.2
Nausea	8	(2.9)	8	5.9	2	(0.8)	2	1.5	10	(1.9)	10	3.7	8	(2.9)	11	8.0
Diarrhoea	2	(0.7)	2	1.5	6	(2.3)	6	4.6	8	(1.5)	8	3.0	3	(1.1)	3	2.2
Gastritis	2	(0.7)	2	1.5	4	(1.5)	5	3.8	6	(1.1)	7	2.6	2	(0.7)	2	1.4
Vomiting	3	(1.1)	4	2.9	1	(0.4)	1	0.8	4	(0.7)	5	1.9	4	(1.4)	4	2.9
Gastrooesophageal reflux disease	3	(1.1)	3	2.2	0				3	(0.6)	3	1.1	3	(1.1)	3	2.2
Toothache	1	(0.4)	1	0.7	4	(1.5)	4	3.0	5	(0.9)	5	1.9	1	(0.4)	1	0.7
Abdominal pain upper	1	(0.4)	1	0.7	3	(1.1)	3	2.3	4	(0.7)	4	1.5	1	(0.4)	1	0.7
Constipation	4	(1.5)	4	2.9	1	(0.4)	1	0.8	5	(0.9)	5	1.9	0			
Food poisoning	2	(0.7)	2	1.5	2	(0.8)	2	1.5	4	(0.7)	4	1.5	1	(0.4)	1	0.7
Abdominal pain	0				0				0				4	(1.4)	4	2.9
Dental caries	1	(0.4)	1	0.7	2	(0.8)	2	1.5	3	(0.6)	3	1.1	1	(0.4)	1	0.7
Abdominal discomfort	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	2	(0.7)	2	1.4
Dyspepsia	1	(0.4)	1	0.7	2	(0.8)	2	1.5	3	(0.6)	3	1.1	0			
Aphthous ulcer	0				1	(0.4)	2	1.5	1	(0.2)	2	0.7	0			
Hiatus hernia	0				2	(0.8)	2	1.5	2	(0.4)	2	0.7	0			
Periodontal disease	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	1	(0.4)	1	0.7
Stomatitis	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	1	(0.4)	1	0.7
Abdominal distension	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Apical granuloma	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Chronic gastritis	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Coeliac disease	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Colitis ulcerative	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Enteritis	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Enterocolitis	0				0				0				1	(0.4)	1	0.7

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Gastric polyps	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Gastric ulcer	0			0			0			1 (0.4)	1	0.7
Gastrointestinal disorder	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Haemorrhoids	0			0			0			1 (0.4)	1	0.7
Hyperchlorhydria	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Proctalgia	0			0			0			1 (0.4)	1	0.7
Retching	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Musculoskeletal and connective tissue disorders	22 (8.1)	27	19.8	24 (9.1)	28	21.3	46 (8.6)	55	20.5	21 (7.6)	26	18.8
Pain in extremity	6 (2.2)	6	4.4	5 (1.9)	5	3.8	11 (2.1)	11	4.1	3 (1.1)	3	2.2
Back pain	3 (1.1)	3	2.2	4 (1.5)	5	3.8	7 (1.3)	8	3.0	5 (1.8)	5	3.6
Arthralgia	2 (0.7)	2	1.5	4 (1.5)	4	3.0	6 (1.1)	6	2.2	0		
Muscle spasms	3 (1.1)	3	2.2	0			3 (0.6)	3	1.1	3 (1.1)	3	2.2
Myalgia	2 (0.7)	3	2.2	1 (0.4)	1	0.8	3 (0.6)	4	1.5	2 (0.7)	2	1.4
Neck pain	1 (0.4)	1	0.7	2 (0.8)	2	1.5	3 (0.6)	3	1.1	0		
Plantar fasciitis	0			2 (0.8)	3	2.3	2 (0.4)	3	1.1	0		
Tenosynovitis	0			0			0			3 (1.1)	3	2.2
Trigger finger	0			0			0			2 (0.7)	3	2.2
Musculoskeletal pain	2 (0.7)	2	1.5	0			2 (0.4)	2	0.7	0		
Musculoskeletal stiffness	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Rheumatoid arthritis	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Arthritis	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Arthropathy	0			0			0			1 (0.4)	1	0.7
Intervertebral disc degeneration	0			0			0			1 (0.4)	1	0.7
Intervertebral disc disorder	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Intervertebral disc protrusion	0			0			0			1 (0.4)	1	0.7
Joint contracture	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Joint effusion	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Joint swelling	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Muscular weakness	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Musculoskeletal chest pain	0			0			0			1 (0.4)	1	0.7
Osteoarthritis	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Osteoporotic fracture	0			0			0			1 (0.4)	1	0.7
Periarthritis	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Rheumatic disorder	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Rotator cuff syndrome	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Spinal osteoarthritis	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Spinal pain	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Tendonitis	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
General disorders and administration site conditions	22 (8.1)	28	20.6	19 (7.2)	26	19.8	41 (7.7)	54	20.2	17 (6.1)	26	18.8
Influenza like illness	5 (1.8)	7	5.1	4 (1.5)	4	3.0	9 (1.7)	11	4.1	4 (1.4)	6	4.3
Pyrexia	8 (2.9)	8	5.9	5 (1.9)	5	3.8	13 (2.4)	13	4.9	2 (0.7)	2	1.4
Injection site haematoma	2 (0.7)	2	1.5	2 (0.8)	4	3.0	4 (0.7)	6	2.2	2 (0.7)	4	2.9
Fatigue	1 (0.4)	1	0.7	2 (0.8)	3	2.3	3 (0.6)	4	1.5	0		
Injection site bruising	1 (0.4)	2	1.5	2 (0.8)	2	1.5	3 (0.6)	4	1.5	0		
Injection site pain	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	2 (0.7)	2	1.4
Injection site reaction	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	2 (0.7)	3	2.2
Oedema peripheral	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Chest discomfort	0			0			0			2 (0.7)	2	1.4
Chest pain	0			0			0			2 (0.7)	2	1.4
Injection site hypertrophy	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	0		
Malaise	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Asthenia	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Drug therapeutic incompatibility	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
General symptom	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Inflammation	0			0			0			1 (0.4)	1	0.7
Injection site haemorrhage	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		

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	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Injection site hypersensitivity	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Injection site induration	0				0				0				1	(0.4)	1	0.7
Injection site rash	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Injection site swelling	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Pain	0				0				0				1	(0.4)	1	0.7
Peripheral swelling	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Nervous system disorders	18	(6.6)	18	13.2	21	(8.0)	31	23.6	39	(7.3)	49	18.3	15	(5.4)	27	19.5
Headache	3	(1.1)	3	2.2	10	(3.8)	17	12.9	13	(2.4)	20	7.5	5	(1.8)	15	10.9
Dizziness	2	(0.7)	2	1.5	2	(0.8)	3	2.3	4	(0.7)	5	1.9	2	(0.7)	3	2.2
Hypoglycaemic unconsciousness	2	(0.7)	2	1.5	2	(0.8)	2	1.5	4	(0.7)	4	1.5	2	(0.7)	2	1.4
Paraesthesia	1	(0.4)	1	0.7	1	(0.4)	1	0.8	2	(0.4)	2	0.7	1	(0.4)	1	0.7
Diabetic neuropathy	2	(0.7)	2	1.5	0				2	(0.4)	2	0.7	0			
Hypoglycaemic seizure	1	(0.4)	1	0.7	1	(0.4)	1	0.8	2	(0.4)	2	0.7	0			
Lethargy	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	1	(0.4)	1	0.7
Migraine	2	(0.7)	2	1.5	0				2	(0.4)	2	0.7	0			
Presyncope	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	1	(0.4)	1	0.7
Syncope	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	1	(0.4)	1	0.7
Tension headache	1	(0.4)	1	0.7	1	(0.4)	1	0.8	2	(0.4)	2	0.7	0			
Carpal tunnel syndrome	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Cerebrovascular accident	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Hypertonia	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Hypoaesthesia	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Hypoglycaemic coma	0				0				0				1	(0.4)	1	0.7
Hyporeflexia	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Occipital neuralgia	0				0				0				1	(0.4)	1	0.7
Polyneuropathy	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	0			
Post herpetic neuralgia	1	(0.4)	1	0.7	0				1	(0.2)	1	0.4	0			
Tremor	0				0				0				1	(0.4)	1	0.7

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Injury, poisoning and procedural complications	23 (8.5)	26	19.1	18 (6.8)	23	17.5	41 (7.7)	49	18.3	23 (8.3)	25	18.1
Wrong drug administered	3 (1.1)	4	2.9	8 (3.0)	10	7.6	11 (2.1)	14	5.2	5 (1.8)	5	3.6
Ligament sprain	3 (1.1)	3	2.2	3 (1.1)	3	2.3	6 (1.1)	6	2.2	2 (0.7)	2	1.4
Contusion	2 (0.7)	2	1.5	3 (1.1)	3	2.3	5 (0.9)	5	1.9	1 (0.4)	1	0.7
Limb injury	5 (1.8)	5	3.7	0			5 (0.9)	5	1.9	1 (0.4)	1	0.7
Fall	1 (0.4)	1	0.7	3 (1.1)	3	2.3	4 (0.7)	4	1.5	0		
Foot fracture	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	2 (0.7)	2	1.4
Muscle strain	3 (1.1)	3	2.2	0			3 (0.6)	3	1.1	0		
Tooth fracture	2 (0.7)	2	1.5	0			2 (0.4)	2	0.7	1 (0.4)	1	0.7
Skin abrasion	0			0			0			1 (0.4)	2	1.4
Thermal burn	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Accidental underdose	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Animal bite	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Extradural haematoma	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Eyelid injury	0			0			0			1 (0.4)	1	0.7
Facial bones fracture	0			0			0			1 (0.4)	1	0.7
Femoral neck fracture	0			0			0			1 (0.4)	1	0.7
Foreign body in eye	0			0			0			1 (0.4)	1	0.7
Hand fracture	0			0			0			1 (0.4)	1	0.7
Heat illness	0			0			0			1 (0.4)	1	0.7
Joint dislocation	0			0			0			1 (0.4)	1	0.7
Joint injury	0			0			0			1 (0.4)	1	0.7
Laceration	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Ligament rupture	0			0			0			1 (0.4)	1	0.7
Radius fracture	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Road traffic accident	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Skull fractured base	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Tendon rupture	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Wound	0			0			0			1 (0.4)	1	0.7

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Metabolism and nutrition disorders	24 (8.8)	25	18.4	14 (5.3)	20	15.2	38 (7.1)	45	16.8	15 (5.4)	16	11.6
Hypoglycaemia	19 (7.0)	20	14.7	6 (2.3)	9	6.8	25 (4.7)	29	10.8	9 (3.2)	10	7.2
Hyperlipidaemia	1 (0.4)	1	0.7	2 (0.8)	2	1.5	3 (0.6)	3	1.1	1 (0.4)	1	0.7
Diabetic metabolic decompensation	2 (0.7)	2	1.5	0			2 (0.4)	2	0.7	1 (0.4)	1	0.7
Hyperglycaemia	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Vitamin D deficiency	0			3 (1.1)	3	2.3	3 (0.6)	3	1.1	0		
Hypertriglyceridaemia	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Hypoglycaemia unawareness	0			2 (0.8)	2	1.5	2 (0.4)	2	0.7	0		
Hypokalaemia	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Decreased appetite	0			0			0			1 (0.4)	1	0.7
Fluid retention	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Gout	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Skin and subcutaneous tissue disorders	14 (5.1)	19	13.9	18 (6.8)	20	15.2	32 (6.0)	39	14.6	14 (5.1)	15	10.9
Dermatitis	1 (0.4)	3	2.2	4 (1.5)	4	3.0	5 (0.9)	7	2.6	0		
Urticaria	1 (0.4)	1	0.7	3 (1.1)	3	2.3	4 (0.7)	4	1.5	1 (0.4)	1	0.7
Lipohypertrophy	2 (0.7)	2	1.5	2 (0.8)	2	1.5	4 (0.7)	4	1.5	0		
Dermatitis contact	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	2 (0.7)	2	1.4
Eczema	2 (0.7)	2	1.5	0			2 (0.4)	2	0.7	1 (0.4)	1	0.7
Pruritus	0			2 (0.8)	2	1.5	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Ecchymosis	0			0			0			1 (0.4)	2	1.4
Rash	0			0			0			2 (0.7)	2	1.4
Skin ulcer	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Acne cystic	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Actinic keratosis	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Blister	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Blood blister	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Dermal cyst	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Dermatitis atopic	0			0			0			1 (0.4)	1	0.7

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Adverse events by system organ class and preferred term - treatment emergent - summary - renal impairment at baseline: normal - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Dry skin	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Eczema asteatotic	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Hidradenitis	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Lipodystrophy acquired	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Nail disorder	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Nail pigmentation	0			0			0			1 (0.4)	1	0.7
Onychomadesis	0			0			0			1 (0.4)	1	0.7
Papule	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Parapsoriasis	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Rash erythematous	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Rash pruritic	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Skin exfoliation	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Skin fissures	0			0			0			1 (0.4)	1	0.7
Skin lesion	0			0			0			1 (0.4)	1	0.7
Skin mass	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Skin reaction	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Xeroderma	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Eye disorders	9 (3.3)	10	7.3	20 (7.6)	26	19.8	29 (5.4)	36	13.4	14 (5.1)	14	10.1
Diabetic retinopathy	2 (0.7)	2	1.5	7 (2.7)	7	5.3	9 (1.7)	9	3.4	6 (2.2)	6	4.3
Retinopathy	2 (0.7)	2	1.5	0			2 (0.4)	2	0.7	1 (0.4)	1	0.7
Dry eye	0			2 (0.8)	2	1.5	2 (0.4)	2	0.7	0		
Macular oedema	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Retinal aneurysm	2 (0.7)	2	1.5	0			2 (0.4)	2	0.7	0		
Retinopathy hypertensive	0			2 (0.8)	2	1.5	2 (0.4)	2	0.7	0		
Retinopathy proliferative	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Vitreous haemorrhage	0			2 (0.8)	2	1.5	2 (0.4)	2	0.7	0		
Astigmatism	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Blepharochalasis	0			0			0			1 (0.4)	1	0.7
Cataract	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Chalazion	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Conjunctivitis allergic	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Eye disorder	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Eye inflammation	0			0			0			1 (0.4)	1	0.7
Eye pruritus	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Eye ulcer	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Iritis	0			0			0			1 (0.4)	1	0.7
Myopia	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Normal tension glaucoma	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Ocular hypertension	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Retinal exudates	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Retinal haemorrhage	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Retinal ischaemia	0			0			0			1 (0.4)	1	0.7
Retinal tear	0			0			0			1 (0.4)	1	0.7
Visual acuity reduced transiently	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Visual impairment	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Vitreous detachment	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Respiratory, thoracic and mediastinal disorders	15 (5.5)	16	11.7	13 (4.9)	13	9.9	28 (5.2)	29	10.8	16 (5.8)	17	12.3
Oropharyngeal pain	2 (0.7)	2	1.5	2 (0.8)	2	1.5	4 (0.7)	4	1.5	5 (1.8)	6	4.3
Cough	1 (0.4)	1	0.7	3 (1.1)	3	2.3	4 (0.7)	4	1.5	1 (0.4)	1	0.7
Rhinorrhoea	2 (0.7)	2	1.5	1 (0.4)	1	0.8	3 (0.6)	3	1.1	2 (0.7)	2	1.4
Sinus congestion	2 (0.7)	2	1.5	2 (0.8)	2	1.5	4 (0.7)	4	1.5	0		
Asthma	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	2 (0.7)	2	1.4
Epistaxis	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Dyspnoea	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	0		
Nasal congestion	2 (0.7)	2	1.5	0			2 (0.4)	2	0.7	0		
Respiratory disorder	2 (0.7)	2	1.5	0			2 (0.4)	2	0.7	0		
Rhinitis allergic	2 (0.7)	2	1.5	0			2 (0.4)	2	0.7	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Throat irritation	0			0			0			2 (0.7)	2	1.4
Upper respiratory tract inflammation	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Chronic obstructive pulmonary disease	0			0			0			1 (0.4)	1	0.7
Paranasal sinus discomfort	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Tonsillar hypertrophy	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Upper respiratory tract congestion	0			0			0			1 (0.4)	1	0.7
Psychiatric disorders	6 (2.2)	7	5.1	4 (1.5)	5	3.8	10 (1.9)	12	4.5	1 (0.4)	1	0.7
Depression	4 (1.5)	4	2.9	2 (0.8)	2	1.5	6 (1.1)	6	2.2	0		
Anxiety	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	0		
Insomnia	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Stress	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	0		
Sleep disorder	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Renal and urinary disorders	4 (1.5)	4	2.9	6 (2.3)	6	4.6	10 (1.9)	10	3.7	2 (0.7)	3	2.2
Haematuria	1 (0.4)	1	0.7	2 (0.8)	2	1.5	3 (0.6)	3	1.1	1 (0.4)	1	0.7
Microalbuminuria	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	2 (0.7)	2	1.4
Acute kidney injury	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Bladder pain	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Crystalluria	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Dysuria	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Renal cyst	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Renal failure	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Blood and lymphatic system disorders	6 (2.2)	6	4.4	0			6 (1.1)	6	2.2	5 (1.8)	5	3.6
Anaemia	3 (1.1)	3	2.2	0			3 (0.6)	3	1.1	4 (1.4)	4	2.9
Iron deficiency anaemia	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Leukopenia	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Lymphadenopathy	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Vascular disorders	4 (1.5)	4	2.9	3 (1.1)	3	2.3	7 (1.3)	7	2.6	4 (1.4)	4	2.9
Hypertension	2 (0.7)	2	1.5	2 (0.8)	2	1.5	4 (0.7)	4	1.5	1 (0.4)	1	0.7
Hypotension	0			0			0			2 (0.7)	2	1.4
Orthostatic hypotension	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	0		
Arteriosclerosis	0			0			0			1 (0.4)	1	0.7
Thrombophlebitis superficial	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Reproductive system and breast disorders	2 (0.7)	2	1.5	3 (1.1)	5	3.8	5 (0.9)	7	2.6	2 (0.7)	2	1.4
Dysmenorrhoea	0			1 (0.4)	2	1.5	1 (0.2)	2	0.7	0		
Priapism	0			1 (0.4)	2	1.5	1 (0.2)	2	0.7	0		
Breast tenderness	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Endometriosis	0			0			0			1 (0.4)	1	0.7
Genital haemorrhage	0			0			0			1 (0.4)	1	0.7
Gynaecomastia	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Vulvovaginal inflammation	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Immune system disorders	0			3 (1.1)	5	3.8	3 (0.6)	5	1.9	3 (1.1)	3	2.2
Hypersensitivity	0			1 (0.4)	3	2.3	1 (0.2)	3	1.1	1 (0.4)	1	0.7
Seasonal allergy	0			2 (0.8)	2	1.5	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Multiple allergies	0			0			0			1 (0.4)	1	0.7
Endocrine disorders	0			3 (1.1)	4	3.0	3 (0.6)	4	1.5	2 (0.7)	2	1.4
Goitre	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	2 (0.7)	2	1.4
Hyperadrenalism	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Hypothyroidism	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Thyroid cyst	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Ear and labyrinth disorders	2 (0.7)	2	1.5	2 (0.8)	2	1.5	4 (0.7)	4	1.5	1 (0.4)	1	0.7
Ear discomfort	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	0		
Ear pain	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Tinnitus	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Vertigo	0			0			0			1 (0.4)	1	0.7
Hepatobiliary disorders	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	2 (0.7)	2	1.4
Hepatic steatosis	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	1 (0.4)	1	0.7
Cholecystitis	0			0			0			1 (0.4)	1	0.7
Gallbladder polyp	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Surgical and medical procedures	2 (0.7)	2	1.5	0			2 (0.4)	2	0.7	2 (0.7)	2	1.4
Cataract operation	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Endodontic procedure	0			0			0			1 (0.4)	1	0.7
Haemorrhoid operation	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Tooth extraction	0			0			0			1 (0.4)	1	0.7
Cardiac disorders	1 (0.4)	1	0.7	2 (0.8)	2	1.5	3 (0.6)	3	1.1	0		
Extrasystoles	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Myocardial ischaemia	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Palpitations	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Haemangioma of liver	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Skin papilloma	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Congenital, familial and genetic disorders	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Accessory spleen	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Pregnancy, puerperium and perinatal conditions	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Subchorionic haemorrhage	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		

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2.7.4.7.3.2.15. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインで軽度腎機能障害を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	69				68				137				58			
Total exposure (yrs)	34.6				34.1				68.7				28.5			
Total events	55	(79.7)	173	500.6	49	(72.1)	119	348.6	104	(75.9)	292	425.0	44	(75.9)	117	410.5
Infections and infestations	38	(55.1)	57	164.9	23	(33.8)	34	99.6	61	(44.5)	91	132.5	27	(46.6)	40	140.3
Viral upper respiratory tract infection	21	(30.4)	28	81.0	13	(19.1)	18	52.7	34	(24.8)	46	67.0	17	(29.3)	23	80.7
Upper respiratory tract infection	4	(5.8)	4	11.6	4	(5.9)	4	11.7	8	(5.8)	8	11.6	6	(10.3)	6	21.0
Influenza	3	(4.3)	4	11.6	2	(2.9)	2	5.9	5	(3.6)	6	8.7	2	(3.4)	2	7.0
Viral infection	2	(2.9)	4	11.6	1	(1.5)	2	5.9	3	(2.2)	6	8.7	0			
Gastroenteritis	4	(5.8)	4	11.6	1	(1.5)	1	2.9	5	(3.6)	5	7.3	0			
Urinary tract infection	3	(4.3)	3	8.7	1	(1.5)	1	2.9	4	(2.9)	4	5.8	0			
Cystitis	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	2	(3.4)	2	7.0
Bronchitis	0				0				0				2	(3.4)	2	7.0
Ear infection	1	(1.4)	2	5.8	0				1	(0.7)	2	2.9	0			
Otitis externa	1	(1.4)	1	2.9	1	(1.5)	1	2.9	2	(1.5)	2	2.9	0			
Respiratory tract infection	1	(1.4)	1	2.9	1	(1.5)	1	2.9	2	(1.5)	2	2.9	0			
Sinusitis	2	(2.9)	2	5.8	0				2	(1.5)	2	2.9	0			
Angular cheilitis	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Candida infection	0				0				0				1	(1.7)	1	3.5
Cellulitis	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Empyema	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Gastrointestinal viral infection	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Labyrinthitis	0				0				0				1	(1.7)	1	3.5
Lower respiratory tract infection	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Nasopharyngitis	0				0				0				1	(1.7)	1	3.5
Otitis media	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Periodontitis	0				0				0				1	(1.7)	1	3.5

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	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Pharyngitis	0				0				0				1	(1.7)	1	3.5
Rhinitis	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Investigations	20	(29.0)	32	92.6	11	(16.2)	18	52.7	31	(22.6)	50	72.8	12	(20.7)	18	63.1
Blood glucose decreased	17	(24.6)	28	81.0	10	(14.7)	16	46.9	27	(19.7)	44	64.0	11	(19.0)	17	59.6
Blood pressure increased	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	1	(1.7)	1	3.5
Blood 1,5-anhydroglucitol decreased	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Blood urine present	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Helicobacter test positive	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Hepatic enzyme increased	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Weight increased	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Gastrointestinal disorders	11	(15.9)	15	43.4	8	(11.8)	9	26.4	19	(13.9)	24	34.9	8	(13.8)	9	31.6
Nausea	4	(5.8)	6	17.4	1	(1.5)	1	2.9	5	(3.6)	7	10.2	1	(1.7)	1	3.5
Diarrhoea	1	(1.4)	1	2.9	3	(4.4)	3	8.8	4	(2.9)	4	5.8	2	(3.4)	2	7.0
Gastritis	1	(1.4)	2	5.8	0				1	(0.7)	2	2.9	1	(1.7)	1	3.5
Toothache	2	(2.9)	2	5.8	0				2	(1.5)	2	2.9	1	(1.7)	1	3.5
Vomiting	1	(1.4)	1	2.9	2	(2.9)	2	5.9	3	(2.2)	3	4.4	0			
Abdominal distension	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Aphthous ulcer	0				0				0				1	(1.7)	1	3.5
Chronic gastritis	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Constipation	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Dyspepsia	0				0				0				1	(1.7)	1	3.5
Enteritis	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Food poisoning	0				0				0				1	(1.7)	1	3.5
Gastritis erosive	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Hiatus hernia	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Oral discomfort	0				0				0				1	(1.7)	1	3.5

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Musculoskeletal and connective tissue disorders	9 (13.0)	11	31.8	4 (5.9)	4	11.7	13 (9.5)	15	21.8	9 (15.5)	13	45.6
Back pain	1 (1.4)	1	2.9	2 (2.9)	2	5.9	3 (2.2)	3	4.4	1 (1.7)	1	3.5
Arthralgia	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	2 (3.4)	2	7.0
Musculoskeletal pain	2 (2.9)	2	5.8	0			2 (1.5)	2	2.9	1 (1.7)	1	3.5
Myalgia	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	1 (1.7)	2	7.0
Arthritis	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	1 (1.7)	1	3.5
Pain in extremity	2 (2.9)	2	5.8	0			2 (1.5)	2	2.9	0		
Bursitis	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Collagen disorder	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Exostosis	0			0			0			1 (1.7)	1	3.5
Flank pain	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Intervertebral disc disorder	0			0			0			1 (1.7)	1	3.5
Intervertebral disc protrusion	0			0			0			1 (1.7)	1	3.5
Muscle spasms	0			0			0			1 (1.7)	1	3.5
Myositis	0			0			0			1 (1.7)	1	3.5
Periarthritis	0			0			0			1 (1.7)	1	3.5
Tenosynovitis	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Trigger finger	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Injury, poisoning and procedural complications	10 (14.5)	13	37.6	6 (8.8)	8	23.4	16 (11.7)	21	30.6	5 (8.6)	6	21.0
Wrong drug administered	5 (7.2)	5	14.5	3 (4.4)	4	11.7	8 (5.8)	9	13.1	1 (1.7)	1	3.5
Laceration	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	1 (1.7)	1	3.5
Accidental overdose	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Fall	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Forearm fracture	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Hand fracture	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Ligament sprain	0			0			0			1 (1.7)	1	3.5
Muscle strain	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Post procedural discharge	0			0			0			1 (1.7)	1	3.5
Postoperative ileus	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Radius fracture	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Road traffic accident	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Skin abrasion	0			0			0			1 (1.7)	1	3.5
Tendon rupture	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Tooth fracture	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Traumatic fracture	0			0			0			1 (1.7)	1	3.5
Ulna fracture	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Eye disorders	8 (11.6)	8	23.1	7 (10.3)	7	20.5	15 (10.9)	15	21.8	7 (12.1)	9	31.6
Diabetic retinopathy	5 (7.2)	5	14.5	5 (7.4)	5	14.6	10 (7.3)	10	14.6	1 (1.7)	1	3.5
Macular oedema	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	1 (1.7)	1	3.5
Retinal tear	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	1 (1.7)	1	3.5
Cataract nuclear	0			0			0			1 (1.7)	1	3.5
Conjunctival haemorrhage	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Cystoid macular oedema	0			0			0			1 (1.7)	1	3.5
Glaucoma	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Lacrimation increased	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Maculopathy	0			0			0			1 (1.7)	1	3.5
Ocular discomfort	0			0			0			1 (1.7)	1	3.5
Retinopathy	0			0			0			1 (1.7)	1	3.5
Retinopathy hypertensive	0			0			0			1 (1.7)	1	3.5
Nervous system disorders	4 (5.8)	8	23.1	5 (7.4)	5	14.6	9 (6.6)	13	18.9	2 (3.4)	2	7.0
Headache	1 (1.4)	3	8.7	1 (1.5)	1	2.9	2 (1.5)	4	5.8	0		
Dizziness	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	1 (1.7)	1	3.5
Carotid arteriosclerosis	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Diabetic neuropathy	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Hypoglycaemic seizure	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Hypoglycaemic unconsciousness	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Lumbar radiculopathy	0			0			0			1 (1.7)	1	3.5
Memory impairment	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Migraine	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Neurodegenerative disorder	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Polyneuropathy	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Respiratory, thoracic and mediastinal disorders	4 (5.8)	5	14.5	5 (7.4)	8	23.4	9 (6.6)	13	18.9	2 (3.4)	2	7.0
Oropharyngeal pain	1 (1.4)	1	2.9	1 (1.5)	1	2.9	2 (1.5)	2	2.9	1 (1.7)	1	3.5
Cough	0			2 (2.9)	2	5.9	2 (1.5)	2	2.9	0		
Nasal congestion	1 (1.4)	1	2.9	1 (1.5)	1	2.9	2 (1.5)	2	2.9	0		
Sinus congestion	2 (2.9)	2	5.8	0			2 (1.5)	2	2.9	0		
Upper respiratory tract inflammation	0			1 (1.5)	2	5.9	1 (0.7)	2	2.9	0		
Asthma	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Pleurisy	0			0			0			1 (1.7)	1	3.5
Respiratory disorder	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Rhinitis allergic	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Metabolism and nutrition disorders	5 (7.2)	5	14.5	2 (2.9)	2	5.9	7 (5.1)	7	10.2	6 (10.3)	7	24.6
Hypoglycaemia	2 (2.9)	2	5.8	0			2 (1.5)	2	2.9	3 (5.2)	3	10.5
Hyperglycaemia	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	1 (1.7)	2	7.0
Dehydration	2 (2.9)	2	5.8	0			2 (1.5)	2	2.9	0		
Decreased appetite	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Diabetic metabolic decompensation	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Hypercholesterolaemia	0			0			0			1 (1.7)	1	3.5
Hyperlipidaemia	0			0			0			1 (1.7)	1	3.5
General disorders and administration site conditions	3 (4.3)	3	8.7	5 (7.4)	8	23.4	8 (5.8)	11	16.0	1 (1.7)	1	3.5

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	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Oedema peripheral	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	1	(1.7)	1	3.5
Pyrexia	0				2	(2.9)	2	5.9	2	(1.5)	2	2.9	0			
Administration site induration	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Asthenia	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Chest pain	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Injection site hypertrophy	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Malaise	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Oedema	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Pain	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Peripheral swelling	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Skin and subcutaneous tissue disorders	4	(5.8)	4	11.6	4	(5.9)	4	11.7	8	(5.8)	8	11.6	4	(6.9)	4	14.0
Dry skin	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	1	(1.7)	1	3.5
Urticaria	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	1	(1.7)	1	3.5
Alopecia	0				0				0				1	(1.7)	1	3.5
Asteatosis	0				0				0				1	(1.7)	1	3.5
Dermatitis atopic	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Lipohypertrophy	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Miliaria	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Nail bed inflammation	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Rash papular	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Skin ulcer	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Psychiatric disorders	1	(1.4)	1	2.9	4	(5.9)	4	11.7	5	(3.6)	5	7.3	0			
Insomnia	1	(1.4)	1	2.9	1	(1.5)	1	2.9	2	(1.5)	2	2.9	0			
Affective disorder	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Depression	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Stress	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Cardiac disorders	2	(2.9)	2	5.8	1	(1.5)	1	2.9	3	(2.2)	3	4.4	1	(1.7)	1	3.5

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Coronary artery disease	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Palpitations	0			0			0			1 (1.7)	1	3.5
Sinus bradycardia	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Ventricular extrasystoles	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Ear and labyrinth disorders	1 (1.4)	1	2.9	1 (1.5)	2	5.9	2 (1.5)	3	4.4	1 (1.7)	1	3.5
Ear pain	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Sudden hearing loss	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Tinnitus	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Tympanic membrane perforation	0			0			0			1 (1.7)	1	3.5
Renal and urinary disorders	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	2 (3.4)	3	10.5
Microalbuminuria	0			0			0			1 (1.7)	2	7.0
Haematuria	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Nephrolithiasis	0			0			0			1 (1.7)	1	3.5
Vascular disorders	2 (2.9)	2	5.8	2 (2.9)	2	5.9	4 (2.9)	4	5.8	0		
Hypertension	1 (1.4)	1	2.9	2 (2.9)	2	5.9	3 (2.2)	3	4.4	0		
Peripheral arterial occlusive disease	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Immune system disorders	1 (1.4)	1	2.9	1 (1.5)	1	2.9	2 (1.5)	2	2.9	0		
Mycotic allergy	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Seasonal allergy	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.4)	1	2.9	1 (1.5)	1	2.9	2 (1.5)	2	2.9	0		
Bladder transitional cell carcinoma	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Conjunctival neoplasm	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Reproductive system and breast disorders	2 (2.9)	2	5.8	0			2 (1.5)	2	2.9	0		

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Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - renal impairment at baseline: mild - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Benign prostatic hyperplasia	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Testicular swelling	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Blood and lymphatic system disorders	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Lymphadenopathy	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Endocrine disorders	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Hypothyroidism	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Surgical and medical procedures	0			0			0			1 (1.7)	1	3.5
Inguinal hernia repair	0			0			0			1 (1.7)	1	3.5

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.16. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインで中等度腎機能障害を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	1				10				11				7			
Total exposure (yrs)	0.5				4.6				5.1				3.5			
Total events	1	(100)	2	397.0	6	(60.0)	18	392.7	7	(63.6)	20	393.2	5	(71.4)	15	425.7
Infections and infestations	1	(100)	1	198.5	2	(20.0)	2	43.6	3	(27.3)	3	59.0	4	(57.1)	7	198.7
Viral upper respiratory tract infection	1	(100)	1	198.5	2	(20.0)	2	43.6	3	(27.3)	3	59.0	3	(42.9)	4	113.5
Gastroenteritis viral	0				0				0				1	(14.3)	1	28.4
Pneumonia	0				0				0				1	(14.3)	1	28.4
Urinary tract infection	0				0				0				1	(14.3)	1	28.4
Investigations	0				3	(30.0)	3	65.5	3	(27.3)	3	59.0	3	(42.9)	6	170.3
Blood glucose decreased	0				3	(30.0)	3	65.5	3	(27.3)	3	59.0	3	(42.9)	6	170.3
Nervous system disorders	0				2	(20.0)	3	65.5	2	(18.2)	3	59.0	1	(14.3)	1	28.4
Hypoaesthesia	0				1	(10.0)	1	21.8	1	(9.1)	1	19.7	1	(14.3)	1	28.4
Dizziness	0				1	(10.0)	1	21.8	1	(9.1)	1	19.7	0			
Headache	0				1	(10.0)	1	21.8	1	(9.1)	1	19.7	0			
Musculoskeletal and connective tissue disorders	0				3	(30.0)	3	65.5	3	(27.3)	3	59.0	0			
Back pain	0				1	(10.0)	1	21.8	1	(9.1)	1	19.7	0			
Lumbar spinal stenosis	0				1	(10.0)	1	21.8	1	(9.1)	1	19.7	0			
Muscle spasms	0				1	(10.0)	1	21.8	1	(9.1)	1	19.7	0			
Gastrointestinal disorders	0				2	(20.0)	2	43.6	2	(18.2)	2	39.3	0			
Abdominal discomfort	0				1	(10.0)	1	21.8	1	(9.1)	1	19.7	0			
Gastritis	0				1	(10.0)	1	21.8	1	(9.1)	1	19.7	0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - renal impairment at baseline: moderate - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Injury, poisoning and procedural complications	1 (100)	1	198.5	1 (10.0)	1	21.8	2 (18.2)	2	39.3	0		
Buttock injury	0			1 (10.0)	1	21.8	1 (9.1)	1	19.7	0		
Wrist fracture	1 (100)	1	198.5	0			1 (9.1)	1	19.7	0		
Respiratory, thoracic and mediastinal disorders	0			1 (10.0)	1	21.8	1 (9.1)	1	19.7	1 (14.3)	1	28.4
Oropharyngeal pain	0			1 (10.0)	1	21.8	1 (9.1)	1	19.7	0		
Rhinitis allergic	0			0			0			1 (14.3)	1	28.4
Ear and labyrinth disorders	0			1 (10.0)	1	21.8	1 (9.1)	1	19.7	0		
Vertigo	0			1 (10.0)	1	21.8	1 (9.1)	1	19.7	0		
Eye disorders	0			1 (10.0)	1	21.8	1 (9.1)	1	19.7	0		
Eyelid oedema	0			1 (10.0)	1	21.8	1 (9.1)	1	19.7	0		
General disorders and administration site conditions	0			1 (10.0)	1	21.8	1 (9.1)	1	19.7	0		
Feeling abnormal	0			1 (10.0)	1	21.8	1 (9.1)	1	19.7	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:06:11 - t_ae_on.sas/t_ae_sum_ren_mod_on_sas.txt

2.7.4.7.3.2.17. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- ベースラインで重度腎機能障害を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:06:12 - t_ae_on.sas/t_ae_sum_ren_sev_on_sas.txt

2.7.4.7.3.2.18. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- Bolus インスリン投与量調節アルゴリズムを用いた被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	200			191			391			206		
Total exposure (yrs)	100.7			95.0			195.7			102.4		
Total events	126 (63.0)	311	308.8	127 (66.5)	310	326.3	253 (64.7)	621	317.3	142 (68.9)	329	321.4
Infections and infestations	64 (32.0)	96	95.3	60 (31.4)	88	92.6	124 (31.7)	184	94.0	72 (35.0)	110	107.5
Viral upper respiratory tract infection	25 (12.5)	31	30.8	36 (18.8)	46	48.4	61 (15.6)	77	39.3	35 (17.0)	51	49.8
Upper respiratory tract infection	16 (8.0)	21	20.9	8 (4.2)	9	9.5	24 (6.1)	30	15.3	9 (4.4)	12	11.7
Influenza	9 (4.5)	10	9.9	5 (2.6)	5	5.3	14 (3.6)	15	7.7	5 (2.4)	5	4.9
Gastroenteritis	4 (2.0)	5	5.0	2 (1.0)	2	2.1	6 (1.5)	7	3.6	9 (4.4)	11	10.7
Urinary tract infection	3 (1.5)	4	4.0	4 (2.1)	6	6.3	7 (1.8)	10	5.1	2 (1.0)	2	2.0
Viral infection	2 (1.0)	3	3.0	2 (1.0)	2	2.1	4 (1.0)	5	2.6	1 (0.5)	1	1.0
Pharyngitis	2 (1.0)	2	2.0	0			2 (0.5)	2	1.0	3 (1.5)	3	2.9
Sinusitis	3 (1.5)	4	4.0	1 (0.5)	1	1.1	4 (1.0)	5	2.6	0		
Bronchitis	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	2 (1.0)	2	2.0
Cystitis	1 (0.5)	2	2.0	1 (0.5)	1	1.1	2 (0.5)	3	1.5	1 (0.5)	1	1.0
Respiratory tract infection viral	2 (1.0)	3	3.0	1 (0.5)	1	1.1	3 (0.8)	4	2.0	0		
Rhinitis	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	3 (1.5)	3	2.9
Gastroenteritis viral	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	2 (1.0)	2	2.0
Cellulitis	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Herpes zoster	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	0		
Onychomycosis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Pneumonia	0			0			0			2 (1.0)	2	2.0
Tooth abscess	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	0		
Varicella	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Abscess limb	0			0			0			1 (0.5)	1	1.0
Acute sinusitis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Adenoiditis	0			0			0			1 (0.5)	1	1.0

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Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - bolus dosing algorithm - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Angular cheilitis	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Conjunctivitis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Cytomegalovirus infection	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Diverticulitis	0			0			0			1 (0.5)	1	1.0
Empyema	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Epstein-Barr virus infection	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Folliculitis	0			0			0			1 (0.5)	1	1.0
Fungal infection	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Fungal skin infection	0			0			0			1 (0.5)	1	1.0
Furuncle	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Labyrinthitis	0			0			0			1 (0.5)	1	1.0
Laryngitis	0			0			0			1 (0.5)	1	1.0
Localised infection	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Molluscum contagiosum	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Nasopharyngitis	0			0			0			1 (0.5)	1	1.0
Otitis externa	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Otitis media acute	0			0			0			1 (0.5)	1	1.0
Periodontitis	0			0			0			1 (0.5)	1	1.0
Skin infection	0			0			0			1 (0.5)	1	1.0
Subcutaneous abscess	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Syphilis	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Tonsillitis	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Urethritis	0			0			0			1 (0.5)	1	1.0
Vulvovaginal candidiasis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Investigations	44 (22.0)	59	58.6	47 (24.6)	57	60.0	91 (23.3)	116	59.3	52 (25.2)	65	63.5
Blood glucose decreased	39 (19.5)	54	53.6	43 (22.5)	52	54.7	82 (21.0)	106	54.2	49 (23.8)	58	56.7
Blood creatinine increased	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Haemoglobin decreased	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Weight increased	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	0		

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Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - bolus dosing algorithm - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Blood bilirubin increased	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Blood glucose fluctuation	0			0			0			1 (0.5)	1	1.0
Blood pressure increased	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Blood urine present	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Electrocardiogram change	0			0			0			1 (0.5)	1	1.0
Haematocrit decreased	0			0			0			1 (0.5)	1	1.0
Heart rate increased	0			0			0			1 (0.5)	1	1.0
Helicobacter test positive	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Hepatic enzyme increased	0			0			0			1 (0.5)	1	1.0
Transaminases increased	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Urine albumin/creatinine ratio increased	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Gastrointestinal disorders	13 (6.5)	21	20.9	15 (7.9)	23	24.2	28 (7.2)	44	22.5	21 (10.2)	27	26.4
Nausea	3 (1.5)	4	4.0	1 (0.5)	1	1.1	4 (1.0)	5	2.6	5 (2.4)	8	7.8
Diarrhoea	2 (1.0)	2	2.0	5 (2.6)	5	5.3	7 (1.8)	7	3.6	2 (1.0)	2	2.0
Gastritis	1 (0.5)	1	1.0	5 (2.6)	6	6.3	6 (1.5)	7	3.6	1 (0.5)	1	1.0
Vomiting	2 (1.0)	3	3.0	1 (0.5)	1	1.1	3 (0.8)	4	2.0	3 (1.5)	3	2.9
Gastrooesophageal reflux disease	3 (1.5)	3	3.0	0			3 (0.8)	3	1.5	2 (1.0)	2	2.0
Constipation	4 (2.0)	4	4.0	0			4 (1.0)	4	2.0	0		
Abdominal pain	0			0			0			3 (1.5)	3	2.9
Abdominal discomfort	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	0		
Abdominal pain upper	0			2 (1.0)	2	2.1	2 (0.5)	2	1.0	0		
Enteritis	0			2 (1.0)	2	2.1	2 (0.5)	2	1.0	0		
Stomatitis	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Toothache	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Chronic gastritis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Dyspepsia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Enterocolitis	0			0			0			1 (0.5)	1	1.0
Gastric polyps	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		

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Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - bolus dosing algorithm - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Gastric ulcer	0			0			0			1 (0.5)	1	1.0
Gastrointestinal disorder	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Haemorrhoids	0			0			0			1 (0.5)	1	1.0
Hiatus hernia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Hyperchlorhydria	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Oral discomfort	0			0			0			1 (0.5)	1	1.0
Periodontal disease	0			0			0			1 (0.5)	1	1.0
Proctalgia	0			0			0			1 (0.5)	1	1.0
General disorders and administration site conditions	15 (7.5)	15	14.9	16 (8.4)	16	16.8	31 (7.9)	31	15.8	13 (6.3)	21	20.5
Pyrexia	7 (3.5)	7	7.0	6 (3.1)	6	6.3	13 (3.3)	13	6.6	2 (1.0)	2	2.0
Influenza like illness	0			2 (1.0)	2	2.1	2 (0.5)	2	1.0	3 (1.5)	5	4.9
Injection site haematoma	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	2 (1.0)	4	3.9
Oedema peripheral	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	2 (1.0)	2	2.0
Injection site hypertrophy	2 (1.0)	2	2.0	1 (0.5)	1	1.1	3 (0.8)	3	1.5	0		
Injection site reaction	0			0			0			2 (1.0)	3	2.9
Administration site induration	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Asthenia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Chest discomfort	0			0			0			1 (0.5)	1	1.0
Chest pain	0			0			0			1 (0.5)	1	1.0
Fatigue	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Feeling abnormal	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
General symptom	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Injection site haemorrhage	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Injection site hypersensitivity	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Injection site induration	0			0			0			1 (0.5)	1	1.0
Injection site pain	0			0			0			1 (0.5)	1	1.0
Injection site rash	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Malaise	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
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Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - bolus dosing algorithm - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Pain	0			0			0			1 (0.5)	1	1.0
Peripheral swelling	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Musculoskeletal and connective tissue disorders	10 (5.0)	12	11.9	18 (9.4)	22	23.2	28 (7.2)	34	17.4	13 (6.3)	15	14.7
Back pain	1 (0.5)	1	1.0	4 (2.1)	5	5.3	5 (1.3)	6	3.1	3 (1.5)	3	2.9
Pain in extremity	2 (1.0)	2	2.0	4 (2.1)	4	4.2	6 (1.5)	6	3.1	1 (0.5)	1	1.0
Arthralgia	2 (1.0)	2	2.0	2 (1.0)	2	2.1	4 (1.0)	4	2.0	1 (0.5)	1	1.0
Myalgia	1 (0.5)	2	2.0	1 (0.5)	1	1.1	2 (0.5)	3	1.5	2 (1.0)	2	2.0
Muscle spasms	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	1 (0.5)	1	1.0
Plantar fasciitis	0			1 (0.5)	2	2.1	1 (0.3)	2	1.0	0		
Tenosynovitis	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Trigger finger	0			0			0			1 (0.5)	2	2.0
Arthritis	0			0			0			1 (0.5)	1	1.0
Flank pain	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Intervertebral disc disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Intervertebral disc protrusion	0			0			0			1 (0.5)	1	1.0
Joint contracture	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Lumbar spinal stenosis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Musculoskeletal pain	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Musculoskeletal stiffness	0			0			0			1 (0.5)	1	1.0
Osteoarthritis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Osteoporotic fracture	0			0			0			1 (0.5)	1	1.0
Periarthritis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Rheumatic disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Rheumatoid arthritis	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Rotator cuff syndrome	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Injury, poisoning and procedural complications	18 (9.0)	22	21.8	7 (3.7)	12	12.6	25 (6.4)	34	17.4	13 (6.3)	13	12.7

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Wrong drug administered	5 (2.5)	5	5.0	3 (1.6)	6	6.3	8 (2.0)	11	5.6	2 (1.0)	2	2.0
Limb injury	4 (2.0)	4	4.0	0			4 (1.0)	4	2.0	1 (0.5)	1	1.0
Ligament sprain	2 (1.0)	2	2.0	1 (0.5)	1	1.1	3 (0.8)	3	1.5	1 (0.5)	1	1.0
Fall	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	0		
Foot fracture	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Laceration	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Road traffic accident	0			2 (1.0)	2	2.1	2 (0.5)	2	1.0	0		
Thermal burn	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Contusion	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Extradural haematoma	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Femoral neck fracture	0			0			0			1 (0.5)	1	1.0
Forearm fracture	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Foreign body in eye	0			0			0			1 (0.5)	1	1.0
Heat illness	0			0			0			1 (0.5)	1	1.0
Joint dislocation	0			0			0			1 (0.5)	1	1.0
Muscle strain	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Post procedural discharge	0			0			0			1 (0.5)	1	1.0
Postoperative ileus	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Radius fracture	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Skull fractured base	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Ulna fracture	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Wound	0			0			0			1 (0.5)	1	1.0
Wrist fracture	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Nervous system disorders	11 (5.5)	15	14.9	16 (8.4)	17	17.9	27 (6.9)	32	16.4	10 (4.9)	14	13.7
Headache	3 (1.5)	5	5.0	5 (2.6)	5	5.3	8 (2.0)	10	5.1	3 (1.5)	6	5.9
Dizziness	2 (1.0)	2	2.0	3 (1.6)	3	3.2	5 (1.3)	5	2.6	1 (0.5)	2	2.0
Hypoglycaemic unconsciousness	1 (0.5)	1	1.0	3 (1.6)	3	3.2	4 (1.0)	4	2.0	2 (1.0)	2	2.0
Diabetic neuropathy	3 (1.5)	3	3.0	0			3 (0.8)	3	1.5	0		
Hypoglycaemic seizure	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Polyneuropathy	0			2 (1.0)	2	2.1	2 (0.5)	2	1.0	0		
Carotid arteriosclerosis	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Cerebrovascular accident	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Hypertonia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Hypoaesthesia	0			0			0			1 (0.5)	1	1.0
Hypoglycaemic coma	0			0			0			1 (0.5)	1	1.0
Memory impairment	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Neurodegenerative disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Post herpetic neuralgia	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Presyncope	0			0			0			1 (0.5)	1	1.0
Tremor	0			0			0			1 (0.5)	1	1.0
Metabolism and nutrition disorders	19 (9.5)	20	19.9	8 (4.2)	11	11.6	27 (6.9)	31	15.8	11 (5.3)	12	11.7
Hypoglycaemia	16 (8.0)	17	16.9	4 (2.1)	7	7.4	20 (5.1)	24	12.3	7 (3.4)	8	7.8
Diabetic metabolic decompensation	2 (1.0)	2	2.0	1 (0.5)	1	1.1	3 (0.8)	3	1.5	1 (0.5)	1	1.0
Hypertriglyceridaemia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Decreased appetite	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Hypercholesterolaemia	0			0			0			1 (0.5)	1	1.0
Hyperglycaemia	0			0			0			1 (0.5)	1	1.0
Hyperlipidaemia	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Hypokalaemia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Eye disorders	9 (4.5)	9	8.9	17 (8.9)	20	21.1	26 (6.6)	29	14.8	13 (6.3)	13	12.7
Diabetic retinopathy	5 (2.5)	5	5.0	8 (4.2)	8	8.4	13 (3.3)	13	6.6	5 (2.4)	5	4.9
Macular oedema	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Retinal aneurysm	2 (1.0)	2	2.0	0			2 (0.5)	2	1.0	0		
Vitreous haemorrhage	0			2 (1.0)	2	2.1	2 (0.5)	2	1.0	0		
Blepharochalasis	0			0			0			1 (0.5)	1	1.0
Cataract	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Conjunctival haemorrhage	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Conjunctivitis allergic	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Dry eye	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Eye disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Eye inflammation	0			0			0			1 (0.5)	1	1.0
Eye pruritus	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Iritis	0			0			0			1 (0.5)	1	1.0
Lacrimation increased	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Ocular discomfort	0			0			0			1 (0.5)	1	1.0
Retinal exudates	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Retinal ischaemia	0			0			0			1 (0.5)	1	1.0
Retinal tear	0			0			0			1 (0.5)	1	1.0
Retinopathy hypertensive	0			0			0			1 (0.5)	1	1.0
Retinopathy proliferative	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Visual acuity reduced transiently	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Visual impairment	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Skin and subcutaneous tissue disorders	9 (4.5)	14	13.9	13 (6.8)	14	14.7	22 (5.6)	28	14.3	10 (4.9)	11	10.7
Dermatitis	1 (0.5)	3	3.0	3 (1.6)	3	3.2	4 (1.0)	6	3.1	0		
Urticaria	2 (1.0)	2	2.0	1 (0.5)	1	1.1	3 (0.8)	3	1.5	1 (0.5)	1	1.0
Eczema	2 (1.0)	2	2.0	0			2 (0.5)	2	1.0	1 (0.5)	1	1.0
Dermatitis contact	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Ecchymosis	0			0			0			1 (0.5)	2	2.0
Lipohypertrophy	0			2 (1.0)	2	2.1	2 (0.5)	2	1.0	0		
Acne cystic	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Actinic keratosis	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Asteatosis	0			0			0			1 (0.5)	1	1.0
Blister	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Dermal cyst	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Dermatitis atopic	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Dry skin	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Eczema asteatotic	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Hidradenitis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Lipodystrophy acquired	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Miliaria	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Nail disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Nail pigmentation	0			0			0			1 (0.5)	1	1.0
Onychomadesis	0			0			0			1 (0.5)	1	1.0
Pruritus	0			0			0			1 (0.5)	1	1.0
Rash	0			0			0			1 (0.5)	1	1.0
Skin lesion	0			0			0			1 (0.5)	1	1.0
Skin mass	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Skin reaction	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Xeroderma	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Respiratory, thoracic and mediastinal disorders	8 (4.0)	9	8.9	9 (4.7)	11	11.6	17 (4.3)	20	10.2	9 (4.4)	9	8.8
Cough	1 (0.5)	1	1.0	4 (2.1)	4	4.2	5 (1.3)	5	2.6	1 (0.5)	1	1.0
Oropharyngeal pain	0			3 (1.6)	3	3.2	3 (0.8)	3	1.5	2 (1.0)	2	2.0
Rhinitis allergic	2 (1.0)	2	2.0	1 (0.5)	1	1.1	3 (0.8)	3	1.5	1 (0.5)	1	1.0
Epistaxis	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Nasal congestion	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	0		
Respiratory disorder	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	0		
Rhinorrhoea	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Upper respiratory tract inflammation	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Asthma	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Chronic obstructive pulmonary disease	0			0			0			1 (0.5)	1	1.0
Sinus congestion	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Throat irritation	0			0			0			1 (0.5)	1	1.0
Renal and urinary disorders	3 (1.5)	3	3.0	2 (1.0)	2	2.1	5 (1.3)	5	2.6	3 (1.5)	5	4.9

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Microalbuminuria	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	2 (1.0)	3	2.9
Haematuria	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Acute kidney injury	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Crystalluria	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Nephrolithiasis	0			0			0			1 (0.5)	1	1.0
Renal cyst	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Vascular disorders	4 (2.0)	4	4.0	3 (1.6)	3	3.2	7 (1.8)	7	3.6	3 (1.5)	3	2.9
Hypertension	3 (1.5)	3	3.0	2 (1.0)	2	2.1	5 (1.3)	5	2.6	1 (0.5)	1	1.0
Orthostatic hypotension	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	0		
Arteriosclerosis	0			0			0			1 (0.5)	1	1.0
Hypotension	0			0			0			1 (0.5)	1	1.0
Blood and lymphatic system disorders	3 (1.5)	3	3.0	0			3 (0.8)	3	1.5	3 (1.5)	3	2.9
Anaemia	3 (1.5)	3	3.0	0			3 (0.8)	3	1.5	3 (1.5)	3	2.9
Ear and labyrinth disorders	1 (0.5)	1	1.0	2 (1.0)	3	3.2	3 (0.8)	4	2.0	1 (0.5)	1	1.0
Tinnitus	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	0		
Sudden hearing loss	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Tympanic membrane perforation	0			0			0			1 (0.5)	1	1.0
Vertigo	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Psychiatric disorders	3 (1.5)	3	3.0	1 (0.5)	1	1.1	4 (1.0)	4	2.0	1 (0.5)	1	1.0
Depression	2 (1.0)	2	2.0	0			2 (0.5)	2	1.0	0		
Insomnia	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Stress	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Cardiac disorders	1 (0.5)	1	1.0	3 (1.6)	3	3.2	4 (1.0)	4	2.0	0		
Extrasystoles	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Myocardial ischaemia	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Palpitations	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Ventricular extrasystoles	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Reproductive system and breast disorders	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	2 (1.0)	2	2.0
Benign prostatic hyperplasia	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Endometriosis	0			0			0			1 (0.5)	1	1.0
Genital haemorrhage	0			0			0			1 (0.5)	1	1.0
Vulvovaginal inflammation	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Endocrine disorders	0			1 (0.5)	2	2.1	1 (0.3)	2	1.0	1 (0.5)	1	1.0
Goitre	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Thyroid cyst	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Immune system disorders	0			2 (1.0)	2	2.1	2 (0.5)	2	1.0	1 (0.5)	1	1.0
Seasonal allergy	0			2 (1.0)	2	2.1	2 (0.5)	2	1.0	1 (0.5)	1	1.0
Hepatobiliary disorders	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Hepatic steatosis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	0		
Bladder transitional cell carcinoma	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Conjunctival neoplasm	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Surgical and medical procedures	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	1 (0.5)	1	1.0
Endodontic procedure	0			0			0			1 (0.5)	1	1.0
Haemorrhoid operation	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Congenital, familial and genetic disorders	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		

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Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - bolus dosing algorithm - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Accessory spleen	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
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Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.19. 治験薬投与下で発現した有害事象の要約（器官別大分類別及び基本語別）- カーボカウントを用いた被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	142			150			292			136		
Total exposure (yrs)	70.6			75.2			145.8			67.8		
Total events	114 (80.3)	338	479.0	110 (73.3)	346	460.1	224 (76.7)	684	469.2	106 (77.9)	298	439.5
Infections and infestations	82 (57.7)	137	194.1	70 (46.7)	136	180.8	152 (52.1)	273	187.3	77 (56.6)	134	197.6
Viral upper respiratory tract infection	48 (33.8)	70	99.2	34 (22.7)	54	71.8	82 (28.1)	124	85.1	45 (33.1)	67	98.8
Upper respiratory tract infection	14 (9.9)	17	24.1	18 (12.0)	25	33.2	32 (11.0)	42	28.8	18 (13.2)	22	32.4
Influenza	12 (8.5)	12	17.0	9 (6.0)	9	12.0	21 (7.2)	21	14.4	5 (3.7)	5	7.4
Gastroenteritis	4 (2.8)	4	5.7	10 (6.7)	11	14.6	14 (4.8)	15	10.3	2 (1.5)	2	2.9
Urinary tract infection	3 (2.1)	3	4.3	3 (2.0)	3	4.0	6 (2.1)	6	4.1	5 (3.7)	5	7.4
Sinusitis	2 (1.4)	2	2.8	4 (2.7)	4	5.3	6 (2.1)	6	4.1	4 (2.9)	4	5.9
Viral infection	2 (1.4)	3	4.3	2 (1.3)	3	4.0	4 (1.4)	6	4.1	2 (1.5)	2	2.9
Gastroenteritis viral	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	5 (3.7)	5	7.4
Pharyngitis	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	2 (1.5)	5	7.4
Bronchitis	0			3 (2.0)	3	4.0	3 (1.0)	3	2.1	2 (1.5)	2	2.9
Otitis media	3 (2.1)	3	4.3	1 (0.7)	1	1.3	4 (1.4)	4	2.7	1 (0.7)	1	1.5
Rhinitis	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	2 (1.5)	2	2.9
Tonsillitis	1 (0.7)	3	4.3	1 (0.7)	1	1.3	2 (0.7)	4	2.7	0		
Ear infection	1 (0.7)	2	2.8	1 (0.7)	1	1.3	2 (0.7)	3	2.1	0		
Otitis externa	2 (1.4)	2	2.8	1 (0.7)	1	1.3	3 (1.0)	3	2.1	0		
Acute sinusitis	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	0		
Cellulitis	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	0		
Cystitis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	1 (0.7)	1	1.5
Fungal infection	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	1 (0.7)	1	1.5
Periodontitis	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	1 (0.7)	1	1.5
Respiratory tract infection	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	0		
Vulvovaginal mycotic infection	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	1 (0.7)	1	1.5

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - carbohydrate counting - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Candida infection	0			0			0			1 (0.7)	1	1.5
Conjunctivitis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Gastrointestinal viral infection	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Gingivitis	0			0			0			1 (0.7)	1	1.5
Herpes ophthalmic	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Herpes zoster	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Impetigo	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Infectious mononucleosis	0			0			0			1 (0.7)	1	1.5
Localised infection	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Lower respiratory tract infection	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Lower respiratory tract infection bacterial	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Onychomycosis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Oral herpes	0			0			0			1 (0.7)	1	1.5
Oral infection	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Paronychia	0			0			0			1 (0.7)	1	1.5
Pharyngitis streptococcal	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Pilonidal cyst	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Pulpitis dental	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Pyelonephritis chronic	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Respiratory tract infection viral	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Skin infection	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Spermatic cord funiculitis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Subcutaneous abscess	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Tinea cruris	0			0			0			1 (0.7)	1	1.5
Tooth abscess	0			0			0			1 (0.7)	1	1.5
Urinary tract infection fungal	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Viral rhinitis	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Vulvovaginal candidiasis	0			0			0			1 (0.7)	1	1.5

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - carbohydrate counting - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Investigations	25 (17.6)	34	48.2	26 (17.3)	37	49.2	51 (17.5)	71	48.7	21 (15.4)	26	38.3
Blood glucose decreased	19 (13.4)	27	38.3	24 (16.0)	31	41.2	43 (14.7)	58	39.8	19 (14.0)	24	35.4
Blood pressure increased	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	1 (0.7)	1	1.5
Hepatic enzyme increased	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	1 (0.7)	1	1.5
Alanine aminotransferase increased	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Aspartate aminotransferase increased	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Blood 1,5-anhydroglucitol decreased	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Blood creatinine increased	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Blood potassium increased	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Blood thyroid stimulating hormone	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Blood thyroid stimulating hormone increased	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Lipids abnormal	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Protein urine present	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Urine albumin/creatinine ratio increased	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Weight increased	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Gastrointestinal disorders	23 (16.2)	31	43.9	18 (12.0)	25	33.2	41 (14.0)	56	38.4	18 (13.2)	21	31.0
Nausea	9 (6.3)	10	14.2	2 (1.3)	2	2.7	11 (3.8)	12	8.2	4 (2.9)	4	5.9
Diarrhoea	1 (0.7)	1	1.4	4 (2.7)	4	5.3	5 (1.7)	5	3.4	3 (2.2)	3	4.4
Toothache	3 (2.1)	3	4.3	3 (2.0)	3	4.0	6 (2.1)	6	4.1	1 (0.7)	1	1.5
Food poisoning	2 (1.4)	2	2.8	2 (1.3)	2	2.7	4 (1.4)	4	2.7	2 (1.5)	2	2.9
Gastritis	2 (1.4)	3	4.3	0			2 (0.7)	3	2.1	2 (1.5)	2	2.9
Vomiting	2 (1.4)	2	2.8	2 (1.3)	2	2.7	4 (1.4)	4	2.7	1 (0.7)	1	1.5
Dental caries	1 (0.7)	1	1.4	2 (1.3)	2	2.7	3 (1.0)	3	2.1	1 (0.7)	1	1.5
Abdominal pain upper	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	1 (0.7)	1	1.5
Aphthous ulcer	0			1 (0.7)	2	2.7	1 (0.3)	2	1.4	1 (0.7)	1	1.5
Dyspepsia	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	1 (0.7)	1	1.5
Abdominal discomfort	0			0			0			2 (1.5)	2	2.9

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MedDRA version 20.0.

Adverse events by system organ class and preferred term - treatment emergent - summary - carbohydrate counting - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Abdominal distension	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	0		
Constipation	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	0		
Hiatus hernia	0			2 (1.3)	2	2.7	2 (0.7)	2	1.4	0		
Abdominal pain	0			0			0			1 (0.7)	1	1.5
Apical granuloma	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Chronic gastritis	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Coeliac disease	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Colitis ulcerative	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Gastritis erosive	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Gastrooesophageal reflux disease	0			0			0			1 (0.7)	1	1.5
Periodontal disease	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Retching	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Musculoskeletal and connective tissue disorders	21 (14.8)	26	36.8	13 (8.7)	13	17.3	34 (11.6)	39	26.8	17 (12.5)	24	35.4
Back pain	3 (2.1)	3	4.3	3 (2.0)	3	4.0	6 (2.1)	6	4.1	3 (2.2)	3	4.4
Pain in extremity	6 (4.2)	6	8.5	1 (0.7)	1	1.3	7 (2.4)	7	4.8	2 (1.5)	2	2.9
Muscle spasms	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	3 (2.2)	3	4.4
Arthralgia	1 (0.7)	1	1.4	2 (1.3)	2	2.7	3 (1.0)	3	2.1	1 (0.7)	1	1.5
Musculoskeletal pain	3 (2.1)	3	4.3	0			3 (1.0)	3	2.1	1 (0.7)	1	1.5
Myalgia	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	1 (0.7)	2	2.9
Neck pain	1 (0.7)	1	1.4	2 (1.3)	2	2.7	3 (1.0)	3	2.1	0		
Arthritis	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	0		
Tenosynovitis	0			0			0			2 (1.5)	2	2.9
Trigger finger	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	1 (0.7)	1	1.5
Arthropathy	0			0			0			1 (0.7)	1	1.5
Bursitis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Collagen disorder	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Exostosis	0			0			0			1 (0.7)	1	1.5
Intervertebral disc degeneration	0			0			0			1 (0.7)	1	1.5

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Adverse events by system organ class and preferred term - treatment emergent - summary - carbohydrate counting - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Intervertebral disc disorder	0				0				0				1	(0.7)	1	1.5
Intervertebral disc protrusion	0				0				0				1	(0.7)	1	1.5
Joint effusion	1	(0.7)	1	1.4	0				1	(0.3)	1	0.7	0			
Joint swelling	0				1	(0.7)	1	1.3	1	(0.3)	1	0.7	0			
Muscular weakness	0				1	(0.7)	1	1.3	1	(0.3)	1	0.7	0			
Musculoskeletal chest pain	0				0				0				1	(0.7)	1	1.5
Musculoskeletal stiffness	0				1	(0.7)	1	1.3	1	(0.3)	1	0.7	0			
Myositis	0				0				0				1	(0.7)	1	1.5
Periarthritis	0				0				0				1	(0.7)	1	1.5
Plantar fasciitis	0				1	(0.7)	1	1.3	1	(0.3)	1	0.7	0			
Rheumatoid arthritis	0				0				0				1	(0.7)	1	1.5
Spinal osteoarthritis	1	(0.7)	1	1.4	0				1	(0.3)	1	0.7	0			
Spinal pain	1	(0.7)	1	1.4	0				1	(0.3)	1	0.7	0			
Tendonitis	1	(0.7)	1	1.4	0				1	(0.3)	1	0.7	0			
Injury, poisoning and procedural complications	16	(11.3)	18	25.5	18	(12.0)	20	26.6	34	(11.6)	38	26.1	15	(11.0)	18	26.5
Wrong drug administered	3	(2.1)	4	5.7	8	(5.3)	8	10.6	11	(3.8)	12	8.2	4	(2.9)	4	5.9
Contusion	1	(0.7)	1	1.4	3	(2.0)	3	4.0	4	(1.4)	4	2.7	1	(0.7)	1	1.5
Ligament sprain	1	(0.7)	1	1.4	2	(1.3)	2	2.7	3	(1.0)	3	2.1	2	(1.5)	2	2.9
Tooth fracture	3	(2.1)	3	4.3	0				3	(1.0)	3	2.1	1	(0.7)	1	1.5
Fall	1	(0.7)	1	1.4	2	(1.3)	2	2.7	3	(1.0)	3	2.1	0			
Muscle strain	3	(2.1)	3	4.3	0				3	(1.0)	3	2.1	0			
Skin abrasion	0				0				0				2	(1.5)	3	4.4
Hand fracture	1	(0.7)	1	1.4	0				1	(0.3)	1	0.7	1	(0.7)	1	1.5
Tendon rupture	1	(0.7)	1	1.4	1	(0.7)	1	1.3	2	(0.7)	2	1.4	0			
Accidental overdose	0				1	(0.7)	1	1.3	1	(0.3)	1	0.7	0			
Accidental underdose	0				1	(0.7)	1	1.3	1	(0.3)	1	0.7	0			
Animal bite	1	(0.7)	1	1.4	0				1	(0.3)	1	0.7	0			
Buttock injury	0				1	(0.7)	1	1.3	1	(0.3)	1	0.7	0			

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Adverse events by system organ class and preferred term - treatment emergent - summary - carbohydrate counting - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Eyelid injury	0			0			0			1 (0.7)	1	1.5
Facial bones fracture	0			0			0			1 (0.7)	1	1.5
Foot fracture	0			0			0			1 (0.7)	1	1.5
Joint injury	0			0			0			1 (0.7)	1	1.5
Laceration	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Ligament rupture	0			0			0			1 (0.7)	1	1.5
Limb injury	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Radius fracture	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Traumatic fracture	0			0			0			1 (0.7)	1	1.5
Nervous system disorders	11 (7.7)	11	15.6	12 (8.0)	22	29.3	23 (7.9)	33	22.6	8 (5.9)	16	23.6
Headache	1 (0.7)	1	1.4	7 (4.7)	14	18.6	8 (2.7)	15	10.3	2 (1.5)	9	13.3
Dizziness	0			1 (0.7)	2	2.7	1 (0.3)	2	1.4	2 (1.5)	2	2.9
Migraine	3 (2.1)	3	4.3	0			3 (1.0)	3	2.1	0		
Paraesthesia	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	1 (0.7)	1	1.5
Hypoaesthesia	0			2 (1.3)	2	2.7	2 (0.7)	2	1.4	0		
Lethargy	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	1 (0.7)	1	1.5
Syncope	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	1 (0.7)	1	1.5
Tension headache	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	0		
Carpal tunnel syndrome	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Hypoglycaemic seizure	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Hypoglycaemic unconsciousness	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Hyporeflexia	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Lumbar radiculopathy	0			0			0			1 (0.7)	1	1.5
Occipital neuralgia	0			0			0			1 (0.7)	1	1.5
Presyncope	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
General disorders and administration site conditions	10 (7.0)	16	22.7	9 (6.0)	19	25.3	19 (6.5)	35	24.0	5 (3.7)	6	8.8
Influenza like illness	5 (3.5)	7	9.9	2 (1.3)	2	2.7	7 (2.4)	9	6.2	1 (0.7)	1	1.5

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Adverse events by system organ class and preferred term - treatment emergent - summary - carbohydrate counting - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Injection site haematoma	1 (0.7)	1	1.4	2 (1.3)	4	5.3	3 (1.0)	5	3.4	0		
Injection site bruising	1 (0.7)	2	2.8	2 (1.3)	2	2.7	3 (1.0)	4	2.7	0		
Fatigue	0			2 (1.3)	3	4.0	2 (0.7)	3	2.1	0		
Injection site pain	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	1 (0.7)	1	1.5
Chest pain	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	1 (0.7)	1	1.5
Malaise	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	1 (0.7)	1	1.5
Pyrexia	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	0		
Asthenia	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Chest discomfort	0			0			0			1 (0.7)	1	1.5
Drug therapeutic incompatibility	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Inflammation	0			0			0			1 (0.7)	1	1.5
Injection site reaction	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Injection site swelling	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Oedema	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Oedema peripheral	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Pain	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Peripheral swelling	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Respiratory, thoracic and mediastinal disorders	11 (7.7)	12	17.0	10 (6.7)	11	14.6	21 (7.2)	23	15.8	10 (7.4)	11	16.2
Oropharyngeal pain	3 (2.1)	3	4.3	1 (0.7)	1	1.3	4 (1.4)	4	2.7	4 (2.9)	5	7.4
Sinus congestion	3 (2.1)	3	4.3	2 (1.3)	2	2.7	5 (1.7)	5	3.4	0		
Asthma	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	2 (1.5)	2	2.9
Rhinorrhoea	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	1 (0.7)	1	1.5
Dyspnoea	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	0		
Nasal congestion	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	0		
Upper respiratory tract inflammation	0			1 (0.7)	2	2.7	1 (0.3)	2	1.4	0		
Cough	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Epistaxis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Paranasal sinus discomfort	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Pleurisy	0			0			0			1 (0.7)	1	1.5
Respiratory disorder	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Throat irritation	0			0			0			1 (0.7)	1	1.5
Tonsillar hypertrophy	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Upper respiratory tract congestion	0			0			0			1 (0.7)	1	1.5
Eye disorders	8 (5.6)	9	12.8	11 (7.3)	14	18.6	19 (6.5)	23	15.8	8 (5.9)	10	14.7
Diabetic retinopathy	2 (1.4)	2	2.8	4 (2.7)	4	5.3	6 (2.1)	6	4.1	2 (1.5)	2	2.9
Retinopathy	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	2 (1.5)	2	2.9
Macular oedema	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	1 (0.7)	1	1.5
Retinal tear	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	1 (0.7)	1	1.5
Retinopathy hypertensive	0			2 (1.3)	2	2.7	2 (0.7)	2	1.4	0		
Astigmatism	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Cataract nuclear	0			0			0			1 (0.7)	1	1.5
Chalazion	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Cystoid macular oedema	0			0			0			1 (0.7)	1	1.5
Dry eye	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Eye ulcer	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Eyelid oedema	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Glaucoma	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Maculopathy	0			0			0			1 (0.7)	1	1.5
Myopia	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Normal tension glaucoma	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Ocular hypertension	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Retinal haemorrhage	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Retinopathy proliferative	0			0			0			1 (0.7)	1	1.5
Vitreous detachment	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Metabolism and nutrition disorders	10 (7.0)	10	14.2	8 (5.3)	11	14.6	18 (6.2)	21	14.4	10 (7.4)	11	16.2
Hypoglycaemia	5 (3.5)	5	7.1	2 (1.3)	2	2.7	7 (2.4)	7	4.8	5 (3.7)	5	7.4

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Hyperglycaemia	2 (1.4)	2	2.8	1 (0.7)	1	1.3	3 (1.0)	3	2.1	1 (0.7)	2	2.9
Hyperlipidaemia	0			2 (1.3)	2	2.7	2 (0.7)	2	1.4	2 (1.5)	2	2.9
Vitamin D deficiency	0			3 (2.0)	3	4.0	3 (1.0)	3	2.1	0		
Dehydration	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	0		
Hypoglycaemia unawareness	0			2 (1.3)	2	2.7	2 (0.7)	2	1.4	0		
Decreased appetite	0			0			0			1 (0.7)	1	1.5
Fluid retention	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Gout	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Hypokalaemia	0			0			0			1 (0.7)	1	1.5
Skin and subcutaneous tissue disorders	9 (6.3)	9	12.8	9 (6.0)	10	13.3	18 (6.2)	19	13.0	8 (5.9)	8	11.8
Lipohypertrophy	2 (1.4)	2	2.8	1 (0.7)	1	1.3	3 (1.0)	3	2.1	0		
Skin ulcer	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	1 (0.7)	1	1.5
Urticaria	0			2 (1.3)	2	2.7	2 (0.7)	2	1.4	1 (0.7)	1	1.5
Dry skin	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	1 (0.7)	1	1.5
Pruritus	0			2 (1.3)	2	2.7	2 (0.7)	2	1.4	0		
Alopecia	0			0			0			1 (0.7)	1	1.5
Blood blister	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Dermatitis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Dermatitis atopic	0			0			0			1 (0.7)	1	1.5
Dermatitis contact	0			0			0			1 (0.7)	1	1.5
Nail bed inflammation	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Papule	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Parapsoriasis	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Rash	0			0			0			1 (0.7)	1	1.5
Rash erythematous	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Rash papular	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Rash pruritic	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Skin exfoliation	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Skin fissures	0			0			0			1 (0.7)	1	1.5

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Psychiatric disorders	4 (2.8)	5	7.1	7 (4.7)	8	10.6	11 (3.8)	13	8.9	0		
Depression	2 (1.4)	2	2.8	3 (2.0)	3	4.0	5 (1.7)	5	3.4	0		
Anxiety	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	0		
Insomnia	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	0		
Stress	0			2 (1.3)	2	2.7	2 (0.7)	2	1.4	0		
Affective disorder	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Sleep disorder	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Immune system disorders	1 (0.7)	1	1.4	2 (1.3)	4	5.3	3 (1.0)	5	3.4	2 (1.5)	2	2.9
Hypersensitivity	0			1 (0.7)	3	4.0	1 (0.3)	3	2.1	1 (0.7)	1	1.5
Multiple allergies	0			0			0			1 (0.7)	1	1.5
Mycotic allergy	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Seasonal allergy	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Renal and urinary disorders	1 (0.7)	1	1.4	5 (3.3)	5	6.6	6 (2.1)	6	4.1	1 (0.7)	1	1.5
Haematuria	1 (0.7)	1	1.4	2 (1.3)	2	2.7	3 (1.0)	3	2.1	0		
Bladder pain	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Dysuria	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Microalbuminuria	0			0			0			1 (0.7)	1	1.5
Renal failure	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Reproductive system and breast disorders	3 (2.1)	3	4.3	2 (1.3)	4	5.3	5 (1.7)	7	4.8	0		
Dysmenorrhoea	0			1 (0.7)	2	2.7	1 (0.3)	2	1.4	0		
Priapism	0			1 (0.7)	2	2.7	1 (0.3)	2	1.4	0		
Breast tenderness	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Gynaecomastia	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Testicular swelling	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Blood and lymphatic system disorders	4 (2.8)	4	5.7	0			4 (1.4)	4	2.7	2 (1.5)	2	2.9

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	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Iron deficiency anaemia	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	1 (0.7)	1	1.5
Lymphadenopathy	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	0		
Anaemia	0			0			0			1 (0.7)	1	1.5
Leukopenia	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Ear and labyrinth disorders	2 (1.4)	2	2.8	2 (1.3)	2	2.7	4 (1.4)	4	2.7	1 (0.7)	1	1.5
Ear discomfort	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	0		
Ear pain	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	0		
Vertigo	0			0			0			1 (0.7)	1	1.5
Vascular disorders	2 (1.4)	2	2.8	2 (1.3)	2	2.7	4 (1.4)	4	2.7	1 (0.7)	1	1.5
Hypertension	0			2 (1.3)	2	2.7	2 (0.7)	2	1.4	0		
Hypotension	0			0			0			1 (0.7)	1	1.5
Peripheral arterial occlusive disease	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Thrombophlebitis superficial	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Endocrine disorders	1 (0.7)	1	1.4	2 (1.3)	2	2.7	3 (1.0)	3	2.1	1 (0.7)	1	1.5
Hypothyroidism	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	0		
Goitre	0			0			0			1 (0.7)	1	1.5
Hyperadrenalism	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Cardiac disorders	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	1 (0.7)	1	1.5
Coronary artery disease	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Palpitations	0			0			0			1 (0.7)	1	1.5
Sinus bradycardia	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.7)	1	1.4	1 (0.7)	1	1.3	2 (0.7)	2	1.4	1 (0.7)	1	1.5
Haemangioma of liver	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	1 (0.7)	1	1.5
Skin papilloma	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Surgical and medical procedures	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	2 (1.5)	2	2.9
Cataract operation	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Inguinal hernia repair	0			0			0			1 (0.7)	1	1.5
Tooth extraction	0			0			0			1 (0.7)	1	1.5
Hepatobiliary disorders	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	1 (0.7)	1	1.5
Cholecystitis	0			0			0			1 (0.7)	1	1.5
Gallbladder polyp	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Pregnancy, puerperium and perinatal conditions	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Subchorionic haemorrhage	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		

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Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.20. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインの年齢が 18 歳以上 65 歳未満の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	322			319			641			323		
Total exposure (yrs)	161.4			159.5			321.0			160.6		
Total events	18 (5.6)	22	13.6	17 (5.3)	23	14.4	35 (5.5)	45	14.0	16 (5.0)	18	11.2
Metabolism and nutrition disorders	9 (2.8)	9	5.6	5 (1.6)	8	5.0	14 (2.2)	17	5.3	7 (2.2)	7	4.4
Hypoglycaemia	8 (2.5)	8	5.0	3 (0.9)	6	3.8	11 (1.7)	14	4.4	6 (1.9)	6	3.7
Diabetic metabolic decompensation	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	1 (0.3)	1	0.6
Hypoglycaemia unawareness	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Nervous system disorders	4 (1.2)	4	2.5	7 (2.2)	7	4.4	11 (1.7)	11	3.4	3 (0.9)	3	1.9
Hypoglycaemic unconsciousness	2 (0.6)	2	1.2	3 (0.9)	3	1.9	5 (0.8)	5	1.6	2 (0.6)	2	1.2
Hypoglycaemic seizure	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Polyneuropathy	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Cerebrovascular accident	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Diabetic neuropathy	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Hypoglycaemic coma	0			0			0			1 (0.3)	1	0.6
Injury, poisoning and procedural complications	2 (0.6)	3	1.9	2 (0.6)	3	1.9	4 (0.6)	6	1.9	3 (0.9)	3	1.9
Wrong drug administered	0			0			0			2 (0.6)	2	1.2
Extradural haematoma	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Femoral neck fracture	0			0			0			1 (0.3)	1	0.6
Forearm fracture	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Postoperative ileus	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Road traffic accident	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Skull fractured base	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Tendon rupture	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - 18 <= age at baseline < 65 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Musculoskeletal and connective tissue disorders	1 (0.3)	2	1.2	2 (0.6)	2	1.3	3 (0.5)	4	1.2	1 (0.3)	1	0.6
Bursitis	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Collagen disorder	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Intervertebral disc disorder	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Intervertebral disc protrusion	0			0			0			1 (0.3)	1	0.6
Trigger finger	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Infections and infestations	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	2 (0.6)	2	1.2
Cellulitis	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Diverticulitis	0			0			0			1 (0.3)	1	0.6
Pilonidal cyst	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Urinary tract infection	0			0			0			1 (0.3)	1	0.6
Gastrointestinal disorders	2 (0.6)	2	1.2	0			2 (0.3)	2	0.6	0		
Gastritis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Gastrooesophageal reflux disease	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
General disorders and administration site conditions	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Chest pain	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Hepatobiliary disorders	0			0			0			1 (0.3)	1	0.6
Cholecystitis	0			0			0			1 (0.3)	1	0.6
Investigations	0			0			0			1 (0.3)	1	0.6
Blood glucose fluctuation	0			0			0			1 (0.3)	1	0.6
Psychiatric disorders	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Depression	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - 18 <= age at baseline < 65 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Surgical and medical procedures	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Haemorrhoid operation	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.21. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインの年齢が 65 歳以上の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	20			22			42			19		
Total exposure (yrs)	9.8			10.7			20.5			9.6		
Total events	2 (10.0)	5	50.8	0			2 (4.8)	5	24.4	1 (5.3)	1	10.5
Injury, poisoning and procedural complications	1 (5.0)	3	30.5	0			1 (2.4)	3	14.6	0		
Fall	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Radius fracture	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Ulna fracture	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Bladder transitional cell carcinoma	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Nervous system disorders	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Hypoglycaemic seizure	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9	0		
Surgical and medical procedures	0			0			0			1 (5.3)	1	10.5
Inguinal hernia repair	0			0			0			1 (5.3)	1	10.5

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.22. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- 女性被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	158				155				313				163			
Total exposure (yrs)	78.7				77.5				156.3				80.1			
Total events	6	(3.8)	9	11.4	8	(5.2)	8	10.3	14	(4.5)	17	10.9	9	(5.5)	10	12.5
Metabolism and nutrition disorders	3	(1.9)	3	3.8	3	(1.9)	3	3.9	6	(1.9)	6	3.8	2	(1.2)	2	2.5
Hypoglycaemia	3	(1.9)	3	3.8	1	(0.6)	1	1.3	4	(1.3)	4	2.6	2	(1.2)	2	2.5
Diabetic metabolic decompensation	0				1	(0.6)	1	1.3	1	(0.3)	1	0.6	0			
Hypoglycaemia unawareness	0				1	(0.6)	1	1.3	1	(0.3)	1	0.6	0			
Nervous system disorders	1	(0.6)	1	1.3	4	(2.6)	4	5.2	5	(1.6)	5	3.2	3	(1.8)	3	3.7
Hypoglycaemic unconsciousness	0				2	(1.3)	2	2.6	2	(0.6)	2	1.3	2	(1.2)	2	2.5
Cerebrovascular accident	0				1	(0.6)	1	1.3	1	(0.3)	1	0.6	0			
Diabetic neuropathy	1	(0.6)	1	1.3	0				1	(0.3)	1	0.6	0			
Hypoglycaemic coma	0				0				0				1	(0.6)	1	1.2
Polyneuropathy	0				1	(0.6)	1	1.3	1	(0.3)	1	0.6	0			
Injury, poisoning and procedural complications	1	(0.6)	3	3.8	1	(0.6)	1	1.3	2	(0.6)	4	2.6	2	(1.2)	2	2.5
Fall	1	(0.6)	1	1.3	0				1	(0.3)	1	0.6	0			
Femoral neck fracture	0				0				0				1	(0.6)	1	1.2
Postoperative ileus	0				1	(0.6)	1	1.3	1	(0.3)	1	0.6	0			
Radius fracture	1	(0.6)	1	1.3	0				1	(0.3)	1	0.6	0			
Ulna fracture	1	(0.6)	1	1.3	0				1	(0.3)	1	0.6	0			
Wrong drug administered	0				0				0				1	(0.6)	1	1.2
Musculoskeletal and connective tissue disorders	1	(0.6)	2	2.5	0				1	(0.3)	2	1.3	1	(0.6)	1	1.2
Collagen disorder	1	(0.6)	1	1.3	0				1	(0.3)	1	0.6	0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - female - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Intervertebral disc protrusion	0			0			0			1 (0.6)	1	1.2
Trigger finger	1 (0.6)	1	1.3	0			1 (0.3)	1	0.6	0		
Hepatobiliary disorders	0			0			0			1 (0.6)	1	1.2
Cholecystitis	0			0			0			1 (0.6)	1	1.2
Investigations	0			0			0			1 (0.6)	1	1.2
Blood glucose fluctuation	0			0			0			1 (0.6)	1	1.2

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.23. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- 男性被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	184				186				370				179			
Total exposure (yrs)	92.5				92.7				185.2				90.1			
Total events	14	(7.6)	18	19.5	9	(4.8)	15	16.2	23	(6.2)	33	17.8	8	(4.5)	9	10.0
Metabolism and nutrition disorders	6	(3.3)	6	6.5	2	(1.1)	5	5.4	8	(2.2)	11	5.9	5	(2.8)	5	5.6
Hypoglycaemia	5	(2.7)	5	5.4	2	(1.1)	5	5.4	7	(1.9)	10	5.4	4	(2.2)	4	4.4
Diabetic metabolic decompensation	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	1	(0.6)	1	1.1
Nervous system disorders	4	(2.2)	4	4.3	3	(1.6)	3	3.2	7	(1.9)	7	3.8	0			
Hypoglycaemic seizure	2	(1.1)	2	2.2	1	(0.5)	1	1.1	3	(0.8)	3	1.6	0			
Hypoglycaemic unconsciousness	2	(1.1)	2	2.2	1	(0.5)	1	1.1	3	(0.8)	3	1.6	0			
Polyneuropathy	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Injury, poisoning and procedural complications	2	(1.1)	3	3.2	1	(0.5)	2	2.2	3	(0.8)	5	2.7	1	(0.6)	1	1.1
Extradural haematoma	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Forearm fracture	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Road traffic accident	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Skull fractured base	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Tendon rupture	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Wrong drug administered	0				0				0				1	(0.6)	1	1.1
Infections and infestations	0				2	(1.1)	2	2.2	2	(0.5)	2	1.1	2	(1.1)	2	2.2
Cellulitis	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Diverticulitis	0				0				0				1	(0.6)	1	1.1
Pilonidal cyst	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Urinary tract infection	0				0				0				1	(0.6)	1	1.1

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - male - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Gastrointestinal disorders	2 (1.1)	2	2.2	0			2 (0.5)	2	1.1	0		
Gastritis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Gastrooesophageal reflux disease	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Musculoskeletal and connective tissue disorders	0			2 (1.1)	2	2.2	2 (0.5)	2	1.1	0		
Bursitis	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Intervertebral disc disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Surgical and medical procedures	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.1
Haemorrhoid operation	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Inguinal hernia repair	0			0			0			1 (0.6)	1	1.1
General disorders and administration site conditions	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Chest pain	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Bladder transitional cell carcinoma	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Psychiatric disorders	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Depression	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.24. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインの BMI（kg/m^2）が 25 未満の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	190				185				375				194			
Total exposure (yrs)	95.1				92.7				187.8				95.6			
Total events	8	(4.2)	12	12.6	9	(4.9)	10	10.8	17	(4.5)	22	11.7	10	(5.2)	11	11.5
Metabolism and nutrition disorders	4	(2.1)	4	4.2	3	(1.6)	3	3.2	7	(1.9)	7	3.7	4	(2.1)	4	4.2
Hypoglycaemia	4	(2.1)	4	4.2	1	(0.5)	1	1.1	5	(1.3)	5	2.7	4	(2.1)	4	4.2
Diabetic metabolic decompensation	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Hypoglycaemia unawareness	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Nervous system disorders	1	(0.5)	1	1.1	4	(2.2)	4	4.3	5	(1.3)	5	2.7	2	(1.0)	2	2.1
Hypoglycaemic unconsciousness	0				2	(1.1)	2	2.2	2	(0.5)	2	1.1	2	(1.0)	2	2.1
Diabetic neuropathy	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Hypoglycaemic seizure	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Polyneuropathy	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Injury, poisoning and procedural complications	2	(1.1)	3	3.2	1	(0.5)	2	2.2	3	(0.8)	5	2.7	1	(0.5)	1	1.0
Extradural haematoma	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Femoral neck fracture	0				0				0				1	(0.5)	1	1.0
Forearm fracture	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Road traffic accident	0				1	(0.5)	1	1.1	1	(0.3)	1	0.5	0			
Skull fractured base	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Tendon rupture	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Musculoskeletal and connective tissue disorders	1	(0.5)	2	2.1	0				1	(0.3)	2	1.1	1	(0.5)	1	1.0
Collagen disorder	1	(0.5)	1	1.1	0				1	(0.3)	1	0.5	0			
Intervertebral disc protrusion	0				0				0				1	(0.5)	1	1.0

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - BMI at baseline < 25 kg/m^2 - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Trigger finger	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Gastrointestinal disorders	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Gastritis	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
General disorders and administration site conditions	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Chest pain	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Hepatobiliary disorders	0			0			0			1 (0.5)	1	1.0
Cholecystitis	0			0			0			1 (0.5)	1	1.0
Investigations	0			0			0			1 (0.5)	1	1.0
Blood glucose fluctuation	0			0			0			1 (0.5)	1	1.0
Psychiatric disorders	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Depression	1 (0.5)	1	1.1	0			1 (0.3)	1	0.5	0		
Surgical and medical procedures	0			0			0			1 (0.5)	1	1.0
Inguinal hernia repair	0			0			0			1 (0.5)	1	1.0

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.25. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインの BMI（kg/m^2）が 25 以上 30 未満の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	105			104			209			99		
Total exposure (yrs)	52.7			51.3			104.0			50.2		
Total events	10 (9.5)	13	24.7	7 (6.7)	12	23.4	17 (8.1)	25	24.0	4 (4.0)	5	10.0
Metabolism and nutrition disorders	5 (4.8)	5	9.5	2 (1.9)	5	9.8	7 (3.3)	10	9.6	2 (2.0)	2	4.0
Hypoglycaemia	4 (3.8)	4	7.6	2 (1.9)	5	9.8	6 (2.9)	9	8.7	2 (2.0)	2	4.0
Diabetic metabolic decompensation	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Nervous system disorders	2 (1.9)	2	3.8	3 (2.9)	3	5.9	5 (2.4)	5	4.8	1 (1.0)	1	2.0
Hypoglycaemic seizure	2 (1.9)	2	3.8	0			2 (1.0)	2	1.9	0		
Cerebrovascular accident	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Hypoglycaemic coma	0			0			0			1 (1.0)	1	2.0
Hypoglycaemic unconsciousness	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Polyneuropathy	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Injury, poisoning and procedural complications	1 (1.0)	3	5.7	1 (1.0)	1	2.0	2 (1.0)	4	3.8	1 (1.0)	1	2.0
Fall	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Postoperative ileus	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Radius fracture	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Ulna fracture	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Wrong drug administered	0			0			0			1 (1.0)	1	2.0
Infections and infestations	0			2 (1.9)	2	3.9	2 (1.0)	2	1.9	1 (1.0)	1	2.0
Cellulitis	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Diverticulitis	0			0			0			1 (1.0)	1	2.0
Pilonidal cyst	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - 25 <= BMI at baseline < 30 kg/m^2 - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Gastrointestinal disorders	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Gastrooesophageal reflux disease	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Musculoskeletal and connective tissue disorders	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Bursitis	0			1 (1.0)	1	2.0	1 (0.5)	1	1.0	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Bladder transitional cell carcinoma	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Surgical and medical procedures	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		
Haemorrhoid operation	1 (1.0)	1	1.9	0			1 (0.5)	1	1.0	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.26. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインの BMI（kg/m^2）が 30 以上の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	47			52			99			49		
Total exposure (yrs)	23.4			26.3			49.7			24.4		
Total events	2 (4.3)	2	8.5	1 (1.9)	1	3.8	3 (3.0)	3	6.0	3 (6.1)	3	12.3
Nervous system disorders	2 (4.3)	2	8.5	0			2 (2.0)	2	4.0	0		
Hypoglycaemic unconsciousness	2 (4.3)	2	8.5	0			2 (2.0)	2	4.0	0		
Infections and infestations	0			0			0			1 (2.0)	1	4.1
Urinary tract infection	0			0			0			1 (2.0)	1	4.1
Injury, poisoning and procedural complications	0			0			0			1 (2.0)	1	4.1
Wrong drug administered	0			0			0			1 (2.0)	1	4.1
Metabolism and nutrition disorders	0			0			0			1 (2.0)	1	4.1
Diabetic metabolic decompensation	0			0			0			1 (2.0)	1	4.1
Musculoskeletal and connective tissue disorders	0			1 (1.9)	1	3.8	1 (1.0)	1	2.0	0		
Intervertebral disc disorder	0			1 (1.9)	1	3.8	1 (1.0)	1	2.0	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.27. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインの HbA1c が 8%未満の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	265				280				545				276			
Total exposure (yrs)	132.7				139.7				272.4				137.1			
Total events	14	(5.3)	21	15.8	13	(4.6)	19	13.6	27	(5.0)	40	14.7	13	(4.7)	15	10.9
Metabolism and nutrition disorders	6	(2.3)	6	4.5	3	(1.1)	6	4.3	9	(1.7)	12	4.4	6	(2.2)	6	4.4
Hypoglycaemia	5	(1.9)	5	3.8	3	(1.1)	6	4.3	8	(1.5)	11	4.0	5	(1.8)	5	3.6
Diabetic metabolic decompensation	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	1	(0.4)	1	0.7
Nervous system disorders	5	(1.9)	5	3.8	5	(1.8)	5	3.6	10	(1.8)	10	3.7	3	(1.1)	3	2.2
Hypoglycaemic unconsciousness	2	(0.8)	2	1.5	3	(1.1)	3	2.1	5	(0.9)	5	1.8	2	(0.7)	2	1.5
Hypoglycaemic seizure	2	(0.8)	2	1.5	1	(0.4)	1	0.7	3	(0.6)	3	1.1	0			
Diabetic neuropathy	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Hypoglycaemic coma	0				0				0				1	(0.4)	1	0.7
Polyneuropathy	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Injury, poisoning and procedural complications	2	(0.8)	5	3.8	2	(0.7)	3	2.1	4	(0.7)	8	2.9	2	(0.7)	2	1.5
Extradural haematoma	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Fall	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Femoral neck fracture	0				0				0				1	(0.4)	1	0.7
Forearm fracture	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Postoperative ileus	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Radius fracture	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Road traffic accident	0				1	(0.4)	1	0.7	1	(0.2)	1	0.4	0			
Skull fractured base	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Ulna fracture	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Wrong drug administered	0				0				0				1	(0.4)	1	0.7

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline < 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Musculoskeletal and connective tissue disorders	1 (0.4)	2	1.5	2 (0.7)	2	1.4	3 (0.6)	4	1.5	1 (0.4)	1	0.7
Bursitis	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Collagen disorder	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Intervertebral disc disorder	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Intervertebral disc protrusion	0			0			0			1 (0.4)	1	0.7
Trigger finger	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Infections and infestations	0			2 (0.7)	2	1.4	2 (0.4)	2	0.7	1 (0.4)	1	0.7
Cellulitis	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Diverticulitis	0			0			0			1 (0.4)	1	0.7
Pilonidal cyst	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Gastrointestinal disorders	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Gastrooesophageal reflux disease	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
General disorders and administration site conditions	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Chest pain	0			1 (0.4)	1	0.7	1 (0.2)	1	0.4	0		
Hepatobiliary disorders	0			0			0			1 (0.4)	1	0.7
Cholecystitis	0			0			0			1 (0.4)	1	0.7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Bladder transitional cell carcinoma	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Psychiatric disorders	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		
Depression	1 (0.4)	1	0.8	0			1 (0.2)	1	0.4	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline < 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Surgical and medical procedures	0				0				0				1	(0.4)	1	0.7
Inguinal hernia repair	0				0				0				1	(0.4)	1	0.7

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.28. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインの HbA1c が 8%以上の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	77			61			138			66		
Total exposure (yrs)	38.6			30.5			69.1			33.1		
Total events	6 (7.8)	6	15.6	4 (6.6)	4	13.1	10 (7.2)	10	14.5	4 (6.1)	4	12.1
Metabolism and nutrition disorders	3 (3.9)	3	7.8	2 (3.3)	2	6.6	5 (3.6)	5	7.2	1 (1.5)	1	3.0
Hypoglycaemia	3 (3.9)	3	7.8	0			3 (2.2)	3	4.3	1 (1.5)	1	3.0
Diabetic metabolic decompensation	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Hypoglycaemia unawareness	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Injury, poisoning and procedural complications	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	1 (1.5)	1	3.0
Tendon rupture	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Wrong drug administered	0			0			0			1 (1.5)	1	3.0
Nervous system disorders	0			2 (3.3)	2	6.6	2 (1.4)	2	2.9	0		
Cerebrovascular accident	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Polyneuropathy	0			1 (1.6)	1	3.3	1 (0.7)	1	1.4	0		
Gastrointestinal disorders	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Gastritis	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		
Infections and infestations	0			0			0			1 (1.5)	1	3.0
Urinary tract infection	0			0			0			1 (1.5)	1	3.0
Investigations	0			0			0			1 (1.5)	1	3.0
Blood glucose fluctuation	0			0			0			1 (1.5)	1	3.0
Surgical and medical procedures	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - HbA1c at baseline >= 8% - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Haemorrhoid operation	1 (1.3)	1	2.6	0			1 (0.7)	1	1.4	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.29. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインの糖尿病罹病期間が 15 年未満の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	177			190			367			175		
Total exposure (yrs)	88.6			93.9			182.5			86.8		
Total events	7 (4.0)	10	11.3	10 (5.3)	12	12.8	17 (4.6)	22	12.1	8 (4.6)	9	10.4
Metabolism and nutrition disorders	3 (1.7)	3	3.4	3 (1.6)	3	3.2	6 (1.6)	6	3.3	4 (2.3)	4	4.6
Hypoglycaemia	2 (1.1)	2	2.3	1 (0.5)	1	1.1	3 (0.8)	3	1.6	3 (1.7)	3	3.5
Diabetic metabolic decompensation	1 (0.6)	1	1.1	1 (0.5)	1	1.1	2 (0.5)	2	1.1	1 (0.6)	1	1.2
Hypoglycaemia unawareness	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Injury, poisoning and procedural complications	2 (1.1)	3	3.4	2 (1.1)	3	3.2	4 (1.1)	6	3.3	1 (0.6)	1	1.2
Extradural haematoma	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Femoral neck fracture	0			0			0			1 (0.6)	1	1.2
Forearm fracture	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Postoperative ileus	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Road traffic accident	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Skull fractured base	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Tendon rupture	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Nervous system disorders	0			5 (2.6)	5	5.3	5 (1.4)	5	2.7	1 (0.6)	1	1.2
Hypoglycaemic unconsciousness	0			2 (1.1)	2	2.1	2 (0.5)	2	1.1	1 (0.6)	1	1.2
Polyneuropathy	0			2 (1.1)	2	2.1	2 (0.5)	2	1.1	0		
Cerebrovascular accident	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Gastrointestinal disorders	2 (1.1)	2	2.3	0			2 (0.5)	2	1.1	0		
Gastritis	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Gastrooesophageal reflux disease	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - duration of diabetes at baseline < 15 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Surgical and medical procedures	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	1 (0.6)	1	1.2
Haemorrhoid operation	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Inguinal hernia repair	0			0			0			1 (0.6)	1	1.2
Hepatobiliary disorders	0			0			0			1 (0.6)	1	1.2
Cholecystitis	0			0			0			1 (0.6)	1	1.2
Infections and infestations	0			0			0			1 (0.6)	1	1.2
Urinary tract infection	0			0			0			1 (0.6)	1	1.2
Musculoskeletal and connective tissue disorders	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Intervertebral disc disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Psychiatric disorders	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		
Depression	1 (0.6)	1	1.1	0			1 (0.3)	1	0.5	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.30. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインの糖尿病罹病期間が 15 年以上の被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	165			151			316			167		
Total exposure (yrs)	82.7			76.3			159.0			83.4		
Total events	13 (7.9)	17	20.6	7 (4.6)	11	14.4	20 (6.3)	28	17.6	9 (5.4)	10	12.0
Metabolism and nutrition disorders	6 (3.6)	6	7.3	2 (1.3)	5	6.5	8 (2.5)	11	6.9	3 (1.8)	3	3.6
Hypoglycaemia	6 (3.6)	6	7.3	2 (1.3)	5	6.5	8 (2.5)	11	6.9	3 (1.8)	3	3.6
Nervous system disorders	5 (3.0)	5	6.0	2 (1.3)	2	2.6	7 (2.2)	7	4.4	2 (1.2)	2	2.4
Hypoglycaemic unconsciousness	2 (1.2)	2	2.4	1 (0.7)	1	1.3	3 (0.9)	3	1.9	1 (0.6)	1	1.2
Hypoglycaemic seizure	2 (1.2)	2	2.4	1 (0.7)	1	1.3	3 (0.9)	3	1.9	0		
Diabetic neuropathy	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Hypoglycaemic coma	0			0			0			1 (0.6)	1	1.2
Injury, poisoning and procedural complications	1 (0.6)	3	3.6	0			1 (0.3)	3	1.9	2 (1.2)	2	2.4
Wrong drug administered	0			0			0			2 (1.2)	2	2.4
Fall	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Radius fracture	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Ulna fracture	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Musculoskeletal and connective tissue disorders	1 (0.6)	2	2.4	1 (0.7)	1	1.3	2 (0.6)	3	1.9	1 (0.6)	1	1.2
Bursitis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Collagen disorder	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Intervertebral disc protrusion	0			0			0			1 (0.6)	1	1.2
Trigger finger	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Infections and infestations	0			2 (1.3)	2	2.6	2 (0.6)	2	1.3	1 (0.6)	1	1.2

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - duration of diabetes at baseline >= 15 years - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Cellulitis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Diverticulitis	0			0			0			1 (0.6)	1	1.2
Pilonidal cyst	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
General disorders and administration site conditions	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Chest pain	0			1 (0.7)	1	1.3	1 (0.3)	1	0.6	0		
Investigations	0			0			0			1 (0.6)	1	1.2
Blood glucose fluctuation	0			0			0			1 (0.6)	1	1.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		
Bladder transitional cell carcinoma	1 (0.6)	1	1.2	0			1 (0.3)	1	0.6	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.31. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインで正常肝機能を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	318			320			638			318		
Total exposure (yrs)	159.0			159.6			318.6			158.1		
Total events	16 (5.0)	22	13.8	16 (5.0)	22	13.8	32 (5.0)	44	13.8	15 (4.7)	17	10.8
Metabolism and nutrition disorders	7 (2.2)	7	4.4	5 (1.6)	8	5.0	12 (1.9)	15	4.7	5 (1.6)	5	3.2
Hypoglycaemia	6 (1.9)	6	3.8	3 (0.9)	6	3.8	9 (1.4)	12	3.8	5 (1.6)	5	3.2
Diabetic metabolic decompensation	1 (0.3)	1	0.6	1 (0.3)	1	0.6	2 (0.3)	2	0.6	0		
Hypoglycaemia unawareness	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Nervous system disorders	4 (1.3)	4	2.5	7 (2.2)	7	4.4	11 (1.7)	11	3.5	3 (0.9)	3	1.9
Hypoglycaemic unconsciousness	1 (0.3)	1	0.6	3 (0.9)	3	1.9	4 (0.6)	4	1.3	2 (0.6)	2	1.3
Hypoglycaemic seizure	2 (0.6)	2	1.3	1 (0.3)	1	0.6	3 (0.5)	3	0.9	0		
Polyneuropathy	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	0		
Cerebrovascular accident	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Diabetic neuropathy	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Hypoglycaemic coma	0			0			0			1 (0.3)	1	0.6
Injury, poisoning and procedural complications	3 (0.9)	6	3.8	2 (0.6)	3	1.9	5 (0.8)	9	2.8	3 (0.9)	3	1.9
Wrong drug administered	0			0			0			2 (0.6)	2	1.3
Extradural haematoma	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Fall	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Femoral neck fracture	0			0			0			1 (0.3)	1	0.6
Forearm fracture	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Postoperative ileus	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Radius fracture	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Road traffic accident	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Skull fractured base	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - hepatic impairment at baseline: no - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Tendon rupture	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Ulna fracture	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Infections and infestations	0			2 (0.6)	2	1.3	2 (0.3)	2	0.6	2 (0.6)	2	1.3
Cellulitis	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Diverticulitis	0			0			0			1 (0.3)	1	0.6
Pilonidal cyst	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Urinary tract infection	0			0			0			1 (0.3)	1	0.6
Gastrointestinal disorders	2 (0.6)	2	1.3	0			2 (0.3)	2	0.6	0		
Gastritis	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Gastrooesophageal reflux disease	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Musculoskeletal and connective tissue disorders	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	1 (0.3)	1	0.6
Bursitis	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Intervertebral disc protrusion	0			0			0			1 (0.3)	1	0.6
Surgical and medical procedures	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	1 (0.3)	1	0.6
Haemorrhoid operation	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Inguinal hernia repair	0			0			0			1 (0.3)	1	0.6
General disorders and administration site conditions	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Chest pain	0			1 (0.3)	1	0.6	1 (0.2)	1	0.3	0		
Hepatobiliary disorders	0			0			0			1 (0.3)	1	0.6
Cholecystitis	0			0			0			1 (0.3)	1	0.6
Investigations	0			0			0			1 (0.3)	1	0.6

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - hepatic impairment at baseline: no - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Blood glucose fluctuation	0			0			0			1 (0.3)	1	0.6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Bladder transitional cell carcinoma	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Psychiatric disorders	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		
Depression	1 (0.3)	1	0.6	0			1 (0.2)	1	0.3	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.32. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインで肝機能障害を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	24			21			45			24		
Total exposure (yrs)	12.3			10.6			22.9			12.1		
Total events	4 (16.7)	5	40.7	1 (4.8)	1	9.4	5 (11.1)	6	26.2	2 (8.3)	2	16.6
Metabolism and nutrition disorders	2 (8.3)	2	16.3	0			2 (4.4)	2	8.7	2 (8.3)	2	16.6
Hypoglycaemia	2 (8.3)	2	16.3	0			2 (4.4)	2	8.7	1 (4.2)	1	8.3
Diabetic metabolic decompensation	0			0			0			1 (4.2)	1	8.3
Musculoskeletal and connective tissue disorders	1 (4.2)	2	16.3	1 (4.8)	1	9.4	2 (4.4)	3	13.1	0		
Collagen disorder	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Intervertebral disc disorder	0			1 (4.8)	1	9.4	1 (2.2)	1	4.4	0		
Trigger finger	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Nervous system disorders	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		
Hypoglycaemic unconsciousness	1 (4.2)	1	8.1	0			1 (2.2)	1	4.4	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.33. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインで正常腎機能を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	272			263			535			277		
Total exposure (yrs)	136.2			131.5			267.7			138.1		
Total events	15 (5.5)	18	13.2	10 (3.8)	14	10.6	25 (4.7)	32	12.0	14 (5.1)	15	10.9
Metabolism and nutrition disorders	8 (2.9)	8	5.9	4 (1.5)	7	5.3	12 (2.2)	15	5.6	6 (2.2)	6	4.3
Hypoglycaemia	7 (2.6)	7	5.1	3 (1.1)	6	4.6	10 (1.9)	13	4.9	5 (1.8)	5	3.6
Diabetic metabolic decompensation	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	1 (0.4)	1	0.7
Hypoglycaemia unawareness	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Nervous system disorders	4 (1.5)	4	2.9	5 (1.9)	5	3.8	9 (1.7)	9	3.4	3 (1.1)	3	2.2
Hypoglycaemic unconsciousness	2 (0.7)	2	1.5	2 (0.8)	2	1.5	4 (0.7)	4	1.5	2 (0.7)	2	1.4
Hypoglycaemic seizure	1 (0.4)	1	0.7	1 (0.4)	1	0.8	2 (0.4)	2	0.7	0		
Cerebrovascular accident	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Diabetic neuropathy	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Hypoglycaemic coma	0			0			0			1 (0.4)	1	0.7
Polyneuropathy	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Injury, poisoning and procedural complications	1 (0.4)	2	1.5	0			1 (0.2)	2	0.7	2 (0.7)	2	1.4
Extradural haematoma	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Femoral neck fracture	0			0			0			1 (0.4)	1	0.7
Skull fractured base	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Wrong drug administered	0			0			0			1 (0.4)	1	0.7
Infections and infestations	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	2 (0.7)	2	1.4
Diverticulitis	0			0			0			1 (0.4)	1	0.7
Pilonidal cyst	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Urinary tract infection	0			0			0			1 (0.4)	1	0.7

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - renal impairment at baseline: normal - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Gastrointestinal disorders	2 (0.7)	2	1.5	0			2 (0.4)	2	0.7	0		
Gastritis	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Gastrooesophageal reflux disease	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Hepatobiliary disorders	0			0			0			1 (0.4)	1	0.7
Cholecystitis	0			0			0			1 (0.4)	1	0.7
Investigations	0			0			0			1 (0.4)	1	0.7
Blood glucose fluctuation	0			0			0			1 (0.4)	1	0.7
Musculoskeletal and connective tissue disorders	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Intervertebral disc disorder	0			1 (0.4)	1	0.8	1 (0.2)	1	0.4	0		
Psychiatric disorders	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Depression	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Surgical and medical procedures	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		
Haemorrhoid operation	1 (0.4)	1	0.7	0			1 (0.2)	1	0.4	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.34. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインで軽度腎機能障害を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	69				68				137				58			
Total exposure (yrs)	34.6				34.1				68.7				28.5			
Total events	5	(7.2)	9	26.0	7	(10.3)	9	26.4	12	(8.8)	18	26.2	3	(5.2)	4	14.0
Injury, poisoning and procedural complications	2	(2.9)	4	11.6	2	(2.9)	3	8.8	4	(2.9)	7	10.2	1	(1.7)	1	3.5
Fall	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Forearm fracture	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Postoperative ileus	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Radius fracture	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Road traffic accident	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Tendon rupture	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Ulna fracture	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Wrong drug administered	0				0				0				1	(1.7)	1	3.5
Musculoskeletal and connective tissue disorders	1	(1.4)	2	5.8	1	(1.5)	1	2.9	2	(1.5)	3	4.4	1	(1.7)	1	3.5
Bursitis	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Collagen disorder	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Intervertebral disc protrusion	0				0				0				1	(1.7)	1	3.5
Trigger finger	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			
Metabolism and nutrition disorders	1	(1.4)	1	2.9	1	(1.5)	1	2.9	2	(1.5)	2	2.9	1	(1.7)	1	3.5
Hypoglycaemia	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	1	(1.7)	1	3.5
Diabetic metabolic decompensation	0				1	(1.5)	1	2.9	1	(0.7)	1	1.5	0			
Nervous system disorders	1	(1.4)	1	2.9	2	(2.9)	2	5.9	3	(2.2)	3	4.4	0			
Hypoglycaemic seizure	1	(1.4)	1	2.9	0				1	(0.7)	1	1.5	0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - renal impairment at baseline: mild - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Hypoglycaemic unconsciousness	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Polyneuropathy	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
General disorders and administration site conditions	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Chest pain	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Infections and infestations	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Cellulitis	0			1 (1.5)	1	2.9	1 (0.7)	1	1.5	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Bladder transitional cell carcinoma	1 (1.4)	1	2.9	0			1 (0.7)	1	1.5	0		
Surgical and medical procedures	0			0			0			1 (1.7)	1	3.5
Inguinal hernia repair	0			0			0			1 (1.7)	1	3.5

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:06:40 - t_ae_on.sas/t_sae_sum_ren_mild_on_sas.txt

2.7.4.7.3.2.35. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインで中等度腎機能障害を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

There are no data for this output.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:06:41 - t_ae_on.sas/t_sae_sum_ren_mod_on_sas.txt

2.7.4.7.3.2.36. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- ベースラインで重度腎機能障害を有する被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

There are no data for this output.

2.7.4.7.3.2.37. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- Bolus インスリン投与量調節アルゴリズムを用いた被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	200			191			391			206		
Total exposure (yrs)	100.7			95.0			195.7			102.4		
Total events	14 (7.0)	20	19.9	13 (6.8)	18	18.9	27 (6.9)	38	19.4	10 (4.9)	11	10.7
Metabolism and nutrition disorders	7 (3.5)	7	7.0	4 (2.1)	7	7.4	11 (2.8)	14	7.2	4 (1.9)	4	3.9
Hypoglycaemia	6 (3.0)	6	6.0	3 (1.6)	6	6.3	9 (2.3)	12	6.1	3 (1.5)	3	2.9
Diabetic metabolic decompensation	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	1 (0.5)	1	1.0
Nervous system disorders	3 (1.5)	3	3.0	7 (3.7)	7	7.4	10 (2.6)	10	5.1	3 (1.5)	3	2.9
Hypoglycaemic unconsciousness	1 (0.5)	1	1.0	3 (1.6)	3	3.2	4 (1.0)	4	2.0	2 (1.0)	2	2.0
Hypoglycaemic seizure	1 (0.5)	1	1.0	1 (0.5)	1	1.1	2 (0.5)	2	1.0	0		
Polyneuropathy	0			2 (1.0)	2	2.1	2 (0.5)	2	1.0	0		
Cerebrovascular accident	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Diabetic neuropathy	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Hypoglycaemic coma	0			0			0			1 (0.5)	1	1.0
Injury, poisoning and procedural complications	2 (1.0)	5	5.0	2 (1.0)	3	3.2	4 (1.0)	8	4.1	1 (0.5)	1	1.0
Extradural haematoma	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Fall	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Femoral neck fracture	0			0			0			1 (0.5)	1	1.0
Forearm fracture	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Postoperative ileus	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Radius fracture	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Road traffic accident	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Skull fractured base	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Ulna fracture	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - bolus dosing algorithm - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Faster aspart (meal+post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Gastrointestinal disorders	2 (1.0)	2	2.0	0			2 (0.5)	2	1.0	0		
Gastritis	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Gastrooesophageal reflux disease	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Musculoskeletal and connective tissue disorders	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	1 (0.5)	1	1.0
Intervertebral disc disorder	0			1 (0.5)	1	1.1	1 (0.3)	1	0.5	0		
Intervertebral disc protrusion	0			0			0			1 (0.5)	1	1.0
Infections and infestations	0			0			0			1 (0.5)	1	1.0
Diverticulitis	0			0			0			1 (0.5)	1	1.0
Investigations	0			0			0			1 (0.5)	1	1.0
Blood glucose fluctuation	0			0			0			1 (0.5)	1	1.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Bladder transitional cell carcinoma	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Psychiatric disorders	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Depression	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Surgical and medical procedures	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		
Haemorrhoid operation	1 (0.5)	1	1.0	0			1 (0.3)	1	0.5	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.3.2.38. 治験薬投与下で発現した重篤な有害事象の要約（器官別大分類別及び基本語別）- カーボカウントを用いた被験者 - on-treatment 観察期間 - 安全性解析対象集団（4131 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	142			150			292			136		
Total exposure (yrs)	70.6			75.2			145.8			67.8		
Total events	6 (4.2)	7	9.9	4 (2.7)	5	6.6	10 (3.4)	12	8.2	7 (5.1)	8	11.8
Metabolism and nutrition disorders	2 (1.4)	2	2.8	1 (0.7)	1	1.3	3 (1.0)	3	2.1	3 (2.2)	3	4.4
Hypoglycaemia	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	3 (2.2)	3	4.4
Hypoglycaemia unawareness	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Infections and infestations	0			2 (1.3)	2	2.7	2 (0.7)	2	1.4	1 (0.7)	1	1.5
Cellulitis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Pilonidal cyst	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Urinary tract infection	0			0			0			1 (0.7)	1	1.5
Injury, poisoning and procedural complications	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	2 (1.5)	2	2.9
Wrong drug administered	0			0			0			2 (1.5)	2	2.9
Tendon rupture	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Musculoskeletal and connective tissue disorders	1 (0.7)	2	2.8	1 (0.7)	1	1.3	2 (0.7)	3	2.1	0		
Bursitis	0			1 (0.7)	1	1.3	1 (0.3)	1	0.7	0		
Collagen disorder	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Trigger finger	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Nervous system disorders	2 (1.4)	2	2.8	0			2 (0.7)	2	1.4	0		
Hypoglycaemic seizure	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		
Hypoglycaemic unconsciousness	1 (0.7)	1	1.4	0			1 (0.3)	1	0.7	0		

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

Serious adverse events by system organ class and preferred term - treatment emergent - summary - carbohydrate counting - trial 4131 - on-treatment - safety analysis set

	Faster aspart (meal)				Faster aspart (post)				Faster aspart (meal+post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
General disorders and administration site conditions	0				1	(0.7)	1	1.3	1	(0.3)	1	0.7	0			
Chest pain	0				1	(0.7)	1	1.3	1	(0.3)	1	0.7	0			
Hepatobiliary disorders	0				0				0				1	(0.7)	1	1.5
Cholecystitis	0				0				0				1	(0.7)	1	1.5
Surgical and medical procedures	0				0				0				1	(0.7)	1	1.5
Inguinal hernia repair	0				0				0				1	(0.7)	1	1.5

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.4.7 付録
4. 過量投与

ノボ ノルディスク ファーマ株式会社

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	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	Faster aspart (meal+post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects	342	341	683	342
Total exposure (yrs)	171.3	170.2	341.5	170.2
Total events	0	1 (0.3) 1 0.6	1 (0.1) 1 0.3	0
Injury, poisoning and procedural complications	0	1 (0.3) 1 0.6	1 (0.1) 1 0.3	0
Accidental overdose	0	1 (0.3) 1 0.6	1 (0.1) 1 0.3	0

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.4.2. 治験薬投与下で発現した過量投与に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4131 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 110008/ Faster aspart (post)/ 69/M/25.5	1	Injury, poisoning and procedural complications/ Accidental overdose/ Accidental Administration Of Higher Dose Than Intended	13NOV2016	Y/ Y	Japan

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.4.3. 治験薬投与下で発現した過量投与に関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4101 試験）

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	Faster aspart (meal+post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	261			258			519			258		
Total exposure (yrs)	128.4			127.7			256.0			127.7		
Total events	2 (0.8)	2	1.6	2 (0.8)	2	1.6	4 (0.8)	4	1.6	1 (0.4)	1	0.8
Injury, poisoning and procedural complications	2 (0.8)	2	1.6	2 (0.8)	2	1.6	4 (0.8)	4	1.6	1 (0.4)	1	0.8
Accidental overdose	2 (0.8)	2	1.6	2 (0.8)	2	1.6	4 (0.8)	4	1.6	1 (0.4)	1	0.8

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.4.4. 治験薬投与下で発現した過量投与に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4101 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4101/ 119009/ Faster aspart (post)/ 8/M/18.2	6	Injury, poisoning and procedural complications/ Accidental overdose/ Medication Error/Accidental Overdose	22MAY2017	Y/ Y	North America
NN1218-4101/ 131001/ Faster aspart (meal)/ 6/M/16.9	4	Injury, poisoning and procedural complications/ Accidental overdose/ Accidental Overdose	25JAN2017	Y/ Y	North America
NN1218-4101/ 147008/ NovoRapid (meal)/ 15/M/30.9	4	Injury, poisoning and procedural complications/ Accidental overdose/ Wrong Dose/Accidental Overdose	09JUL2017	Y/ Y	North America
NN1218-4101/ 527004/ Faster aspart (post)/ 11/M/16.3	2	Injury, poisoning and procedural complications/ Accidental overdose/ Accidental Overdose	21JUL2017	Y/ Y	Japan

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Overdose adverse events - treatment emergent – listing – trial 4101 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4101/ 551004/ Faster aspart (meal)/ 9/F/20.3	11	Injury, poisoning and procedural complications/ Accidental overdose/ Accidental Overdose Adminstered	27FEB2017	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.4.5. 治験薬投与下で発現した過量投与に関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（3854 試験）

	Faster aspart N	(%)	E	R	NovoRapid N	(%)	E	R
Number of subjects	236				236			
Total exposure (yrs)	72.8				71.7			
Total events	0				1	(0.4)	2	2.8
Injury, poisoning and procedural complications	0				1	(0.4)	2	2.8
Accidental overdose	0				1	(0.4)	2	2.8

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:08:11 - t_ae_te_3854_sum.sas/t_over_ae_sum_3854_on_sas.txt

2.7.4.7.4.6. 治験薬投与下で発現した過量投与に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（3854 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-3854/ 405001/ NovoRapid/ 45/F/24.1	4	Injury, poisoning and procedural complications/ Accidental overdose/ Accidental Overdose	01SEP2016	Y/ Y	Europe
	5	Injury, poisoning and procedural complications/ Accidental overdose/ Accidental Overdose	05SEP2016	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.4.7. 過量投与に関連する有害事象の検索に用いた基本語の一覧

Adverse event class	System organ class	Preferred term
Overdose	General disorders and administration site conditions	Completed suicide
	Injury, poisoning and procedural complications	Accidental overdose
		Intentional overdose
		Overdose
		Prescribed overdose
	Psychiatric disorders	Completed suicide
		Suicide attempt

MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda_20180709_er
23JUL2018:21:05:38 - l_pt.sas/l_ae_pt_over.txt

フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.4.7. 付録
5. 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

ノボ ノルディスク ファーマ株式会社

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	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	342				341				683				342			
Total exposure (yrs)	171.3				170.2				341.5				170.2			
Total events	7	(2.0)	7	4.1	17	(5.0)	19	11.2	24	(3.5)	26	7.6	7	(2.0)	8	4.7
Nervous system disorders	4	(1.2)	4	2.3	6	(1.8)	7	4.1	10	(1.5)	11	3.2	6	(1.8)	7	4.1
Dizziness	2	(0.6)	2	1.2	4	(1.2)	5	2.9	6	(0.9)	7	2.0	3	(0.9)	4	2.4
Lethargy	1	(0.3)	1	0.6	0				1	(0.1)	1	0.3	1	(0.3)	1	0.6
Presyncope	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	1	(0.3)	1	0.6
Syncope	1	(0.3)	1	0.6	0				1	(0.1)	1	0.3	1	(0.3)	1	0.6
Cerebrovascular accident	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	0			
Injury, poisoning and procedural complications	2	(0.6)	2	1.2	5	(1.5)	5	2.9	7	(1.0)	7	2.0	0			
Fall	2	(0.6)	2	1.2	3	(0.9)	3	1.8	5	(0.7)	5	1.5	0			
Road traffic accident	0				2	(0.6)	2	1.2	2	(0.3)	2	0.6	0			
General disorders and administration site conditions	1	(0.3)	1	0.6	4	(1.2)	5	2.9	5	(0.7)	6	1.8	0			
Fatigue	1	(0.3)	1	0.6	2	(0.6)	3	1.8	3	(0.4)	4	1.2	0			
Asthenia	0				2	(0.6)	2	1.2	2	(0.3)	2	0.6	0			
Ear and labyrinth disorders	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	1	(0.3)	1	0.6
Vertigo	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	1	(0.3)	1	0.6
Eye disorders	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	0			
Visual impairment	0				1	(0.3)	1	0.6	1	(0.1)	1	0.3	0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.5.2. 治験薬投与下で発現した自動車運転及び機械操作の能力又は精神機能の障害に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4131 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 103005/ NovoRapid (meal)/ 49/M/22.3	4	Ear and labyrinth disorders/ Vertigo/ Vertigo	20DEC2016	Y/ Y	Japan
NN1218-4131/ 105004/ Faster aspart (meal)/ 73/F/26.1	2	Injury, poisoning and procedural complications/ Fall/ Fall	17SEP2016	Y/ Y	Japan
NN1218-4131/ 106007/ NovoRapid (meal)/ 37/M/25.2	1	Nervous system disorders/ Presyncope/ Vagal Reflex	27FEB2017	Y/ Y	Japan
NN1218-4131/ 109012/ NovoRapid (meal)/ 64/M/29.8	3	Nervous system disorders/ Dizziness/ Dizziness	25DEC2016	Y/ Y	Japan

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 4131 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 111004/ NovoRapid (meal)/ 27/F/24.3	3	Nervous system disorders/ Dizziness/ Dizziness	09DEC2016	Y/ Y	Japan
NN1218-4131/ 113001/ Faster aspart (post)/ 59/M/21.2	4	Nervous system disorders/ Dizziness/ Dizzy	19OCT2016	Y/ Y	Japan
NN1218-4131/ 124006/ Faster aspart (post)/ 72/F/21.5	2	Ear and labyrinth disorders/ Vertigo/ Vertigo Attack	25AUG2016	Y/ Y	Japan
NN1218-4131/ 204001/ Faster aspart (post)/ 44/F/26.3	2	Nervous system disorders/ Cerebrovascular accident/ Cerebro Vascular Accident Right Hemiparesis	03APR2017	Y/ Y	Asia (Excluding Japan)

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 4131 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 402006/ Faster aspart (post)/ 20/F/19.6	7	Nervous system disorders/ Dizziness/ Dizziness	01DEC2016	Y/ Y	Europe
	8	Nervous system disorders/ Dizziness/ Dizziness	29DEC2016	Y/ Y	Europe
NN1218-4131/ 405001/ Faster aspart (post)/ 64/F/26.7	8	Nervous system disorders/ Dizziness/ Dizziness	19DEC2016	Y/ Y	Europe
NN1218-4131/ 451011/ Faster aspart (post)/ 25/F/28.1	1	Nervous system disorders/ Dizziness/ Dizziness	20JUL2016	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 4131 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 455001/ Faster aspart (post)/ 20/F/23.1	2	General disorders and administration site conditions/ Asthenia/ Weakness	11SEP2016	Y/ Y	Europe
NN1218-4131/ 455005/ Faster aspart (meal)/ 57/F/28.7	1	Nervous system disorders/ Dizziness/ Dizziness	01AUG2016	Y/ Y	Europe
NN1218-4131/ 553011/ Faster aspart (meal)/ 50/F/30.1	4	Injury, poisoning and procedural complications/ Fall/ Left Hand Is Swollen After Fall	25MAY2017	Y/ Y	Europe
NN1218-4131/ 555007/ Faster aspart (post)/ 41/F/33.0	3	Injury, poisoning and procedural complications/ Fall/ Distortion Lumbar Spine (Due To Fall)	19JAN2017	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 4131 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 606002/ Faster aspart (meal)/ 45/M/26.4	2	Nervous system disorders/ Dizziness/ Dizziness	07FEB2017	Y/ Y	Europe
NN1218-4131/ 606007/ Faster aspart (post)/ 22/M/23.0	2	Injury, poisoning and procedural complications/ Road traffic accident/ Contusions In The Level Of The Cervical Spine Due To Road Accident	15DEC2016	Y/ Y	Europe
NN1218-4131/ 652003/ Faster aspart (post)/ 52/F/32.3	6	Injury, poisoning and procedural complications/ Fall/ Fall	01FEB2017	Y/ Y	Europe
NN1218-4131/ 703007/ Faster aspart (post)/ 27/M/19.6	1	Injury, poisoning and procedural complications/ Road traffic accident/ Car Accident	05APR2017	Y/ Y	Asia (Excluding Japan)

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 4131 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 751004/ Faster aspart (meal)/ 66/M/32.1	3	General disorders and administration site conditions/ Fatigue/ Fatigue (Post Immunoglobuline Therapy)	01NOV2016	Y/ Y	North America
NN1218-4131/ 751005/ Faster aspart (post)/ 63/M/23.4	3	Eye disorders/ Visual impairment/ Reduced Vision (Spot) Left Eye	05FEB2017	Y/ Y	North America
NN1218-4131/ 752002/ Faster aspart (post)/ 71/M/26.9	4	Injury, poisoning and procedural complications/ Fall/ Left Shoulder Pain Secondary To Fall On Ice	13DEC2016	Y/ Y	North America
NN1218-4131/ 755006/ Faster aspart (post)/ 56/M/28.3	2	General disorders and administration site conditions/ Fatigue/ Tiredness	06DEC2016	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 4131 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 755006/ Faster aspart (post)/ 56/M/28.3	4	General disorders and administration site conditions/ Fatigue/ Tireness	17JAN2017	Y/ Y	North America
NN1218-4131/ 756001/ NovoRapid (meal)/ 24/F/29.4	6	Nervous system disorders/ Dizziness/ Occasional Dizziness	22SEP2016	Y/ Y	North America
	8	Nervous system disorders/ Dizziness/ Occasionnal Dizziness	01NOV2016	Y/ Y	North America
NN1218-4131/ 814003/ Faster aspart (meal)/ 49/M/35.0	7	Nervous system disorders/ Lethargy/ Lethargy	01FEB2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 4131 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 815009/ Faster aspart (post)/ 66/F/26.9	4	General disorders and administration site conditions/ Asthenia/ General Weakness	11APR2017	Y/ Y	North America
NN1218-4131/ 830002/ NovoRapid (meal)/ 53/F/20.6	3	Nervous system disorders/ Lethargy/ Lethargy	17MAR2017	Y/ Y	North America
NN1218-4131/ 832001/ NovoRapid (meal)/ 43/F/34.9	2	Nervous system disorders/ Syncope/ Fainted	28AUG2016	Y/ Y	North America
NN1218-4131/ 848003/ Faster aspart (post)/ 31/M/26.2	6	Nervous system disorders/ Presyncope/ Presyncopol Event	03JAN2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 4131 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4131/ 858013/ Faster aspart (meal)/ 40/M/26.6	3	Nervous system disorders/ Syncope/ Syncope	29JUN2017	Y/ Y	North America
NN1218-4131/ 861006/ Faster aspart (post)/ 32/M/29.2	3	General disorders and administration site conditions/ Fatigue/ Fatigue	04DEC2016	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.5.3. 治験薬投与下で発現した自動車運転及び機械操作の能力又は精神機能の障害に関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（4101 試験）

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	Faster aspart (meal+post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	261				258				519				258			
Total exposure (yrs)	128.4				127.7				256.0				127.7			
Total events	7	(2.7)	7	5.5	5	(1.9)	5	3.9	12	(2.3)	12	4.7	4	(1.6)	5	3.9
General disorders and administration site conditions	1	(0.4)	1	0.8	5	(1.9)	5	3.9	6	(1.2)	6	2.3	1	(0.4)	1	0.8
Fatigue	1	(0.4)	1	0.8	4	(1.6)	4	3.1	5	(1.0)	5	2.0	0			
Asthenia	0				1	(0.4)	1	0.8	1	(0.2)	1	0.4	1	(0.4)	1	0.8
Nervous system disorders	3	(1.1)	3	2.3	0				3	(0.6)	3	1.2	2	(0.8)	3	2.3
Syncope	2	(0.8)	2	1.6	0				2	(0.4)	2	0.8	1	(0.4)	2	1.6
Dizziness	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Presyncope	0				0				0				1	(0.4)	1	0.8
Injury, poisoning and procedural complications	3	(1.1)	3	2.3	0				3	(0.6)	3	1.2	0			
Fall	2	(0.8)	2	1.6	0				2	(0.4)	2	0.8	0			
Road traffic accident	1	(0.4)	1	0.8	0				1	(0.2)	1	0.4	0			
Ear and labyrinth disorders	0				0				0				1	(0.4)	1	0.8
Vertigo	0				0				0				1	(0.4)	1	0.8

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
MedDRA version 20.0.

2.7.4.7.5.4. 治験薬投与下で発現した自動車運転及び機械操作の能力又は精神機能の障害に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（4101 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4101/ 111007/ Faster aspart (post)/ 13/M/21.9	5	General disorders and administration site conditions/ Fatigue/ Fatigue	25DEC2016	Y/ Y	North America
NN1218-4101/ 111101/ Faster aspart (post)/ 10/F/24.6	1	General disorders and administration site conditions/ Fatigue/ Fatigue	06NOV2016	Y/ Y	North America
NN1218-4101/ 123001/ Faster aspart (meal)/ 16/F/24.1	4	General disorders and administration site conditions/ Fatigue/ Fatigue	15SEP2017	Y/ Y	North America
NN1218-4101/ 124002/ Faster aspart (meal)/ 13/F/21.7	7	Nervous system disorders/ Syncope/ Syncope	07AUG2016	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 4101 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4101/ 134003/ Faster aspart (post)/ 17/M/23.5	4	General disorders and administration site conditions/ Fatigue/ Fatigue	16NOV2017	Y/ Y	North America
NN1218-4101/ 147004/ NovoRapid (meal)/ 17/F/26.0	3	Nervous system disorders/ Presyncope/ Pre-Syncope	06MAR2017	Y/ Y	North America
NN1218-4101/ 149004/ Faster aspart (post)/ 14/F/21.9	12	General disorders and administration site conditions/ Fatigue/ Fatigue	21JAN2018	Y/ Y	North America
NN1218-4101/ 152001/ Faster aspart (meal)/ 17/F/28.5	3	Nervous system disorders/ Syncope/ Vasovagal Response	08AUG2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 4101 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4101/ 253004/ Faster aspart (meal)/ 6/F/16.0	9	Injury, poisoning and procedural complications/ Fall/ Fallen At Daycare. Small Scratch On Upper Lip, On Nose. A Very Small Piece From One Upper Tooth Loosened.	10APR2017	Y/ Y	Europe
NN1218-4101/ 451003/ NovoRapid (meal)/ 14/M/29.0	5	Ear and labyrinth disorders/ Vertigo/ Vertigo	21MAY2017	Y/ Y	Europe
NN1218-4101/ 515001/ NovoRapid (meal)/ 9/M/16.6	8	General disorders and administration site conditions/ Asthenia/ Physical Deconditioning	11JUN2017	Y/ Y	Japan
NN1218-4101/ 601004/ NovoRapid (meal)/ 14/F/27.2	10	Nervous system disorders/ Syncope/ Faint	07APR2017	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 4101 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4101/ 601004/ NovoRapid (meal)/ 14/F/27.2	12	Nervous system disorders/ Syncope/ Faint	21APR2017	Y/ Y	Europe
NN1218-4101/ 602011/ Faster aspart (meal)/ 16/M/20.2	2	Nervous system disorders/ Dizziness/ Felt From Bike Due To Dizziness	24MAR2017	Y/ Y	Europe
NN1218-4101/ 851002/ Faster aspart (post)/ 14/M/26.1	2	General disorders and administration site conditions/ Asthenia/ Weakness	16AUG2016	Y/ Y	Europe
NN1218-4101/ 903007/ Faster aspart (meal)/ 14/M/25.4	2	Injury, poisoning and procedural complications/ Road traffic accident/ Mild Trauma From Motor Vehicle Accident- Chin Laceration Sature S/P	25AUG2017	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 4101 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-4101/ 963019/ Faster aspart (meal)/ 13/M/15.8	2	Injury, poisoning and procedural complications/ Fall/ Had A Fall While Getting Down The Staircase. Had Abrasions On Legs.	07OCT2017	Y/ Y	Asia (Excluding Japan)

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.5.5. 治験薬投与下で発現した自動車運転及び機械操作の能力又は精神機能の障害に関連する有害事象の要約（器官別大分類別及び基本語別） - on-treatment 観察期間 - 安全性解析対象集団（3854 試験）

	Faster aspart N	(%)	E	R	NovoRapid N	(%)	E	R
Number of subjects	236				236			
Total exposure (yrs)	72.8				71.7			
Total events	5	(2.1)	5	6.9	11	(4.7)	11	15.3
General disorders and administration site conditions	4	(1.7)	4	5.5	3	(1.3)	3	4.2
Fatigue	2	(0.8)	2	2.7	3	(1.3)	3	4.2
Asthenia	2	(0.8)	2	2.7	0			
Nervous system disorders	1	(0.4)	1	1.4	6	(2.5)	6	8.4
Dizziness	1	(0.4)	1	1.4	3	(1.3)	3	4.2
Presyncope	0				1	(0.4)	1	1.4
Somnolence	0				1	(0.4)	1	1.4
Syncope	0				1	(0.4)	1	1.4
Eye disorders	0				2	(0.8)	2	2.8
Vision blurred	0				2	(0.8)	2	2.8

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

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23JUL2018:21:08:12 - t_ae_te_3854_sum.sas/t_abil_ae_sum_3854_on_sas.txt

2.7.4.7.5.6. 治験薬投与下で発現した自動車運転及び機械操作の能力又は精神機能の障害に関連する有害事象の一覧 - in-trial 観察期間 - 安全性解析対象集団（3854 試験）

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-3854/ 103001/ NovoRapid/ 48/M/27.3	10	General disorders and administration site conditions/ Fatigue/ Fatigue	12NOV2016	Y/ Y	Europe
NN1218-3854/ 103002/ Faster aspart/ 30/F/20.8	4	General disorders and administration site conditions/ Fatigue/ Fatigue	30OCT2016	Y/ Y	Europe
NN1218-3854/ 103005/ NovoRapid/ 58/F/22.9	5	General disorders and administration site conditions/ Fatigue/ Fatigue	05OCT2016	Y/ Y	Europe
NN1218-3854/ 205005/ NovoRapid/ 26/F/24.9	1	Nervous system disorders/ Presyncope/ Vasovagal Episode At Start Of Meal Test	29NOV2016	Y/ Y	North America
NN1218-3854/ 301003/ Faster aspart/ 62/M/20.0	2	Nervous system disorders/ Dizziness/ Light-Headed Sensation	16NOV2016	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 3854 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-3854/ 305006/ Faster aspart/ 49/F/23.9	2	General disorders and administration site conditions/ Asthenia/ Asthenia	09JAN2017	Y/ Y	Europe
NN1218-3854/ 308001/ Faster aspart/ 66/F/21.0	5	General disorders and administration site conditions/ Asthenia/ Asthenia	09MAR2017	Y/ Y	Europe
NN1218-3854/ 500003/ Faster aspart/ 55/M/25.0	4	General disorders and administration site conditions/ Fatigue/ Tiredness	05JAN2017	Y/ Y	Europe
NN1218-3854/ 505004/ NovoRapid/ 26/F/26.9	4	Nervous system disorders/ Syncope/ Syncope	09JUN2017	Y/ Y	Europe
NN1218-3854/ 607001/ NovoRapid/ 34/F/24.2	1	Nervous system disorders/ Dizziness/ Dizziness	20FEB2017	Y/ Y	Europe

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 3854 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-3854/ 801003/ NovoRapid/ 60/F/23.8	11	Eye disorders/ Vision blurred/ Blurry Vision	14MAR2017	Y/ Y	Europe
NN1218-3854/ 904007/ NovoRapid/ 52/F/31.5	12	Nervous system disorders/ Somnolence/ State Of Being Sleepy	23FEB2017	Y/ Y	North America
NN1218-3854/ 904010/ NovoRapid/ 46/F/25.9	4	Nervous system disorders/ Dizziness/ Sporadic Lightheadedness	20FEB2017	Y/ Y	North America
NN1218-3854/ 919004/ NovoRapid/ 56/M/29.1	4	Eye disorders/ Vision blurred/ Intermittent Blurry Vision Bilateral Eyes	11DEC2016	Y/ Y	North America
NN1218-3854/ 919013/ NovoRapid/ 56/M/24.6	1	General disorders and administration site conditions/ Fatigue/ Fatigue	24MAR2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Ability to drive/operate machinery adverse events - treatment emergent – listing – trial 3854 - in-trial - safety analysis set

Trial ID/ Subject ID/ Treatment/ Age(yrs)/ Sex/BMI	AE no.	System organ class/ Preferred term/ Reported term	Onset date	in-trial/ on-treatment	Region
NN1218-3854/ 922003/ NovoRapid/ 57/F/28.6	1	Nervous system disorders/ Dizziness/ Dizziness	02JAN2017	Y/ Y	North America

AE: Adverse event, BMI: Body mass index (kg/m^2), F: Female, M: Male, N: No, Y: Yes, no: Number, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

2.7.4.7.5.7. 自動車運転及び機械操作の能力又は精神機能の障害に関連する有害事象の検索に用いた基本語の一覧

Adverse event class	System organ class	Preferred term
Ability to drive	Cardiac disorders	Dizziness
		Dizziness postural
		Presyncope
		Syncope
	Ear and labyrinth disorders	Vertigo
		Vestibular disorder
	Eye disorders	Metamorphopsia
		Vision blurred
		Visual impairment
	General disorders and administration site conditions	Asthenia
		Fatigue
		Lethargy
	Injury, poisoning and procedural complications	Fall
		Road traffic accident
	Nervous system disorders	Balance disorder
		Cerebrovascular accident
		Clonic convulsion
		Confusional state
		Disorientation
		Dizziness
		Dizziness postural
		Generalised tonic-clonic seizure
		Lethargy
		Loss of consciousness
		Metamorphopsia
		Presyncope
		Seizure
		Sensory disturbance
		Sensory loss
		Somnolence
		Syncope
		Tonic convulsion
		Transient ischaemic attack
		Vertigo
		Vestibular disorder
		Vision blurred
	Psychiatric disorders	Confusional state
		Disorientation
		Lethargy
		Somnolence
	Vascular disorders	Cerebrovascular accident
		Dizziness
		Dizziness postural
		Presyncope
		Syncope
		Transient ischaemic attack

MedDRA version 20.0.

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フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.4.7 付録
6. 公表文献の検索方法

ノボ ノルディスク ファーマ株式会社

Databases/Sources:
Proquest database (Medline, Embase, Embase alert, Current Content, Biosis)

Search details:

((DEGLUDEC OR TRESIBA OR IDEG OR NN1250 OR RYZODEG OR IDEGASP OR NN5401 OR LEVEMIR OR DETEMIR OR NN304 OR LANTUS OR GLARGINE OR (LISPRO NEAR/1 PROTAMINE NEAR/1 SUSPENSION) OR ((LONG-ACTING OR (LONG PRE/0 ACTING) OR BASAL) PRE/0 INSULIN)) OR (NOVORAPID OR NOVOLOG OR ASPART OR HUMALOG OR LISPRO OR APIDRA OR GLULISINE OR ((FAST-ACTING OR (FAST PRE/0 ACTING) OR RAPID-ACTING OR (RAPID PRE/0 ACTING) OR SHORT-ACTING OR (SHORT PRE/0 ACTING) OR BOLUS OR PRANDIAL) PRE/0 INSULIN)) OR ((BIPHASIC PRE/0 INSULIN PRE/0 ASPART) OR NOVOMIX OR (NOVOLOG PRE/0 MIX) OR (BIPHASIC PRE/0 INSULIN PRE/0 LISPRO) OR (HUMALOG PRE/0 MIX) OR ((BIPHASIC OR PREMIX* OR DUAL-ACTING OR (DUAL PRE/0 ACTING)) PRE/0 INSULIN) OR (INSULIN PRE/0 ANALOG*)) OR ((HUMAN PRE/0 INSULIN) OR (NPH NEAR/2 INSULIN) OR ((NEUTRAL PRE/0 PROTAMINE PRE/0 HAGEDORN) NEAR/2 INSULIN) OR ACTRAPID OR BIOHULIN OR NOVOLIN OR VELASULIN OR VELOSULIN OR ULTRAPHANE OR INSULATARD OR NOVOLIN OR BIOHULIN OR PROTAPHAN*) OR (MONOTARD OR NOVOLET OR ULTRATARD OR ((INTERMEDIATE PRE/0 ACTING) PRE/1 INSULIN) OR MIXTARD OR NOVOLIN OR ACTRAPHANE OR PENMIX OR AFREZZA))

フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.4.7 付録
7. 海外併合データにおける
有害事象の検索方法

ノボ ノルディスク ファーマ株式会社

Title for search	Search – all in MedDRA version 17.0
Cardiovascular disorders	No MedDRA search – cardiovascular events were adjudicated and the evaluation based on positively adjudicated events
Medication errors	HLGT_Medication errors HLGT_Device issues HLGT_Product Quality Issue HLT_Complications associated with device NEC. Including both primary and secondary PTs
Immunogenicity-related events (allergic reactions)	SMQ_Anaphylactic reaction (narrow terms) SMQ_Angioedema (narrow terms) SMQ_Severe cutaneous reactions (narrow terms) SMQ_Anaphylactic/anaphylactoid shock conditions (narrow terms) SMQ_Hypersensiticity (narrow terms)
Injection/infusion site and lipodystrophy	HLT_Application and installation site reactions HLT_Administration site reactions NEC HLT_Infusion site reactions HLT_Injection site reactions HLT_lipodystrophies Including both primary and secondary PTs
Peripheral oedema	PT_generalised oedema PT_oedema PT_oedema peripheral PT_gravitational oedema
Eye disorder – diabetic retinopathy	List of PTs: 'Amaurosis' 'Diabetic blindness' 'Diabetic eye disease' 'Diabetic glaucoma' 'Diabetic retinal oedema' 'Diabetic retinopathy' 'Diabetic uveitis' 'Exudative retinopathy' 'Macular oedema' 'Macular opacity' 'Maculopathy' 'Night blindness' 'Papilloedema' 'Retinal deposits' 'Retinal detachment' 'Retinal exudates' 'Retinal haemorrhage' 'Retinal ischaemia' 'Retinal oedema' 'Retinal pallor' 'Retinal vascular occlusion' 'Retinopathy' 'Retinopathy proliferative' 'Sudden visual loss' 'Visual acuity reduced' 'Visual acuity reduced transiently' 'Vitreous detachment' 'Vitreous haemorrhage' 'Vitreous opacities' 'Retinal neovascularisation' 'Cystoid macular oedema' 'Macular pseudohole' 'Papillophlebitis' 'Macular ischaemia' 'Vitreal cells'
Eye disorder – refraction disorders	HLT_Refractive and accomodative disorders Excluding secondary terms

Title for search	Search – all in MedDRA version 17.0
Peripheral neuropathy	SMQ_peripheral neuropathy (broad and narrow terms) PT_Diabetic neuropathy PT_Diabetic mononeuropathy PT_Diabetic autonomin neuropathy
Rare events	SMQ_Acute renal failure (narrow terms) SMQ_Agranulocytosis (narrow terms) SMQ_Anaphylactic reaction (narrow terms) SMQ_Cardiac arrhythmias (broad and narrow terms) SMQ_Cholestasis and jaundice of hepatic origin (broad and narrow terms) SMQ_Guillain-Barre syndrome (narrow terms) SMQ_Haematopoietic cytopenias affecting more than one type of blood cell (broad and narrow) SMQ_Haematopoietic leukopenia (broad and narrow terms) SMQ_Haematopoietic thrombocytopenia (narrow terms) SMQ_Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow terms) SMQ_Hepatitis, non-infectious (broad and narrow terms) SMQ_Severe cutaneous adverse reactions (narrow terms) SMQ_Interstitial lung disease (narrow terms) SMQ_Neuroleptic malignant syndrome (narrow terms) SMQ_Pseudomembranous colitis (narrow terms) SMQ_Retroperitoneal fibrosis (narrow terms) SOC_Congenital, familial and genetic disorders (primary and secondary routed PTs) HLT_Acute and chronic pancreatitis (primary and secondary routed PTs) HLT_Angioedemas (primary and secondary routed PTs) HLT_Glomerulonephritis and nephrotic syndrome (primary and secondary routed PTs) HLT_Nephritis NEC (primary and secondary routed PTs) PT_disseminated intravascular coagulation PT_Multi-organ failure
Suspected transmission of infectious agent via trial product	HLT_Infectious dirsorders carrier HLT_Infectious transmission (only primary terms)

フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.4.7 付録
8. 4131、4101 及び 3854 試験における
有害事象の検索方法

ノボ ノルディスク ファーマ株式会社

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2.7.4.7.8.1. 心血管系事象、糖尿病網膜症、屈折障害、末梢性ニューロパチー、稀な事象及び治験薬による病原体感染の疑いに関連する有害事象の検索に用いた基本語の一覧

Adverse event class	System organ class	Preferred term
Cardiovascular	Cardiac disorders	Acute coronary syndrome
		Acute myocardial infarction
		Angina pectoris
		Angina unstable
		Anginal equivalent
		Arteriosclerosis coronary artery
		Arteriospasm coronary
		Coronary artery disease
		Coronary artery dissection
		Coronary artery embolism
		Coronary artery insufficiency
		Coronary artery occlusion
		Coronary artery reocclusion
		Coronary artery restenosis
		Coronary artery stenosis
		Coronary artery thrombosis
		Coronary bypass stenosis
		Coronary bypass thrombosis
		Coronary no-reflow phenomenon
		Coronary ostial stenosis
		Coronary vascular graft occlusion
		Coronary vascular graft stenosis
		Dissecting coronary artery aneurysm
		Haemorrhage coronary artery
		Ischaemic cardiomyopathy
		Ischaemic mitral regurgitation
		Kounis syndrome
		Microvascular coronary artery disease
		Myocardial hypoxia
		Myocardial infarction
		Myocardial ischaemia
		Myocardial necrosis
		Myocardial reperfusion injury
		Myocardial stunning
		Papillary muscle infarction
		Periprocedural myocardial infarction
		Post cardiac arrest syndrome
		Post procedural myocardial infarction
		Postinfarction angina
		Prinzmetal angina
		Silent myocardial infarction
		Stress cardiomyopathy
		Subclavian coronary steal syndrome
		Subendocardial ischaemia
	Congenital, familial and genetic disorders	Cerebral arteriovenous malformation haemorrhagic
		Congenital hemiparesis
		Vein of Galen aneurysmal malformation
	Ear and labyrinth disorders	Inner ear infarction
	Endocrine disorders	Pituitary haemorrhage
	Eye disorders	Amaurosis fugax
		Balint's syndrome

MedDRA version 20.0.

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Cardiovascular	Eye disorders	Millard-Gubler syndrome
	General disorders and administration site conditions	Basilar artery perforation
		Carotid artery perforation
		Carotid artery restenosis
		Cerebral artery perforation
		Cerebral artery restenosis
		Coronary artery restenosis
		Post cardiac arrest syndrome
		Vertebral artery perforation
	Immune system disorders	Kounis syndrome
		Vasculitis cerebral
	Infections and infestations	Cerebral aneurysm ruptured syphilitic
		Cerebral septic infarct
	Injury, poisoning and procedural complications	Basilar artery perforation
		Carotid artery perforation
		Carotid artery restenosis
		Cerebral aneurysm perforation
		Cerebral artery perforation
		Cerebral artery restenosis
		Cerebral hypoperfusion
		Cerebral microembolism
		Cerebral reperfusion injury
		Cerebral ventricular rupture
		Coronary artery reocclusion
		Coronary artery restenosis
		Coronary bypass stenosis
		Coronary bypass thrombosis
		Coronary vascular graft occlusion
		Coronary vascular graft stenosis
		Epidural haemorrhage
		Extra-axial haemorrhage
		Extradural haematoma
		Meningorrhagia
		Myocardial reperfusion injury
		Periprocedural myocardial infarction
		Post procedural myocardial infarction
		Post procedural stroke
		Spinal cord haematoma
		Spinal cord haemorrhage
		Spinal epidural haematoma
		Spinal epidural haemorrhage
		Spinal subarachnoid haemorrhage
		Spinal subdural haematoma
		Spinal subdural haemorrhage
		Subarachnoid haematoma
		Subarachnoid haemorrhage
		Subarachnoid haemorrhage neonatal
		Subdural haematoma
		Subdural haemorrhage

MedDRA version 20.0.

Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Cardiovascular	Injury, poisoning and procedural complications	Vertebral artery perforation
	Investigations	Blood creatine phosphokinase MB abnormal
		Blood creatine phosphokinase MB increased
		CSF bilirubin positive
		ECG signs of myocardial ischaemia
		Troponin I increased
		Troponin T increased
		Troponin increased
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Intracranial tumour haemorrhage
	Nervous system disorders	Amaurosis fugax
		Balint's syndrome
		Basal ganglia haematoma
		Basal ganglia haemorrhage
		Basal ganglia infarction
		Basal ganglia stroke
		Basilar artery aneurysm
		Basilar artery occlusion
		Basilar artery perforation
		Basilar artery stenosis
		Basilar artery thrombosis
		Brain hypoxia
		Brain stem embolism
		Brain stem haematoma
		Brain stem haemorrhage
		Brain stem infarction
		Brain stem ischaemia
		Brain stem microhaemorrhage
		Brain stem stroke
		Brain stem thrombosis
		Capsular warning syndrome
		Carotid aneurysm rupture
		Carotid arterial embolus
		Carotid arteriosclerosis
		Carotid artery aneurysm
		Carotid artery calcification
		Carotid artery disease
		Carotid artery dissection
		Carotid artery insufficiency
		Carotid artery occlusion
		Carotid artery perforation
		Carotid artery restenosis
		Carotid artery stenosis
		Carotid artery thrombosis
		Central nervous system haemorrhage
		Cerebellar artery occlusion
		Cerebellar artery thrombosis
		Cerebellar embolism
		Cerebellar haematoma

MedDRA version 20.0.

nn1218/nn1218-summary/pmda_nda
25MAY2018:08:16:20 - l_pt.sas/l_ae_soc_pt.txt

Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Cardiovascular	Nervous system disorders	Cerebellar haemorrhage
		Cerebellar infarction
		Cerebellar ischaemia
		Cerebellar microhaemorrhage
		Cerebellar stroke
		Cerebral aneurysm perforation
		Cerebral aneurysm ruptured syphilitic
		Cerebral arteriosclerosis
		Cerebral arteriovenous malformation haemorrhagic
		Cerebral arteritis
		Cerebral artery embolism
		Cerebral artery occlusion
		Cerebral artery perforation
		Cerebral artery restenosis
		Cerebral artery stenosis
		Cerebral artery thrombosis
		Cerebral capillary telangiectasia
		Cerebral circulatory failure
		Cerebral congestion
		Cerebral gas embolism
		Cerebral haematoma
		Cerebral haemorrhage
		Cerebral haemorrhage foetal
		Cerebral haemorrhage neonatal
		Cerebral hypoperfusion
		Cerebral infarction
		Cerebral infarction foetal
		Cerebral ischaemia
		Cerebral microembolism
		Cerebral microhaemorrhage
		Cerebral reperfusion injury
		Cerebral septic infarct
		Cerebral small vessel ischaemic disease
		Cerebral thrombosis
		Cerebral vascular occlusion
		Cerebral vasoconstriction
		Cerebral venous thrombosis
		Cerebral ventricular rupture
		Cerebrovascular accident
		Cerebrovascular disorder
		Cerebrovascular insufficiency
		Cerebrovascular stenosis
		Charcot-Bouchard microaneurysms
		Congenital hemiparesis
		Delayed ischaemic neurological deficit
		Dural arteriovenous fistula
		Embolic cerebral infarction
		Embolic stroke
		Epidural haemorrhage
		Extra-axial haemorrhage
		Extradural haematoma
		Haemorrhage intracranial

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Cardiovascular	Nervous system disorders	Haemorrhagic cerebral infarction
		Haemorrhagic stroke
		Haemorrhagic transformation stroke
		Hemianaesthesia
		Hemiasomatognosia
		Hemiparaesthesia
		Hemiparesis
		Hemiplegia
		Hypoxic-ischaemic encephalopathy
		Inner ear infarction
		Intracranial aneurysm
		Intracranial haematoma
		Intracranial tumour haemorrhage
		Intracranial venous sinus thrombosis
		Intraventricular haemorrhage
		Intraventricular haemorrhage neonatal
		Ischaemic cerebral infarction
		Ischaemic stroke
		Lacunar infarction
		Lacunar stroke
		Lateral medullary syndrome
		Meningorrhagia
		Migrainous infarction
		Millard-Gubler syndrome
		Moyamoya disease
		Perinatal stroke
		Periventricular haemorrhage neonatal
		Pituitary haemorrhage
		Post cardiac arrest syndrome
		Post procedural stroke
		Post stroke depression
		Precerebral arteriosclerosis
		Precerebral artery occlusion
		Putamen haemorrhage
		Reversible cerebral vasoconstriction syndrome
		Reversible ischaemic neurological deficit
		Ruptured cerebral aneurysm
		Spinal artery embolism
		Spinal artery thrombosis
		Spinal cord haematoma
		Spinal cord haemorrhage
		Spinal epidural haematoma
		Spinal epidural haemorrhage
		Spinal subarachnoid haemorrhage
		Spinal subdural haematoma
		Spinal subdural haemorrhage
		Stroke in evolution
		Subarachnoid haematoma
		Subarachnoid haemorrhage
		Subarachnoid haemorrhage neonatal
		Subclavian steal syndrome

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Cardiovascular	Nervous system disorders	Subdural haematoma
		Subdural haemorrhage
		Subdural haemorrhage neonatal
		Superior sagittal sinus thrombosis
		Thalamic infarction
		Thalamus haemorrhage
		Thrombotic cerebral infarction
		Thrombotic stroke
		Transient ischaemic attack
		Transverse sinus thrombosis
		Vascular encephalopathy
		Vasculitis cerebral
		Vein of Galen aneurysmal malformation
		Vertebral artery aneurysm
		Vertebral artery dissection
		Vertebral artery occlusion
		Vertebral artery perforation
		Vertebral artery stenosis
		Vertebral artery thrombosis
		Vertebrobasilar insufficiency
	Pregnancy, puerperium and perinatal conditions	Cerebral haemorrhage foetal
		Cerebral haemorrhage neonatal
		Cerebral infarction foetal
		Intraventricular haemorrhage neonatal
		Perinatal stroke
		Periventricular haemorrhage neonatal
		Reversible cerebral vasoconstriction syndrome
		Subarachnoid haemorrhage neonatal
		Subdural haemorrhage neonatal
	Psychiatric disorders	Hemiasomatognosia
		Post stroke depression
		Vascular encephalopathy
	Respiratory, thoracic and mediastinal disorders	Brain hypoxia
		Hypoxic-ischaemic encephalopathy
	Surgical and medical procedures	Carotid angioplasty
		Carotid artery bypass
		Carotid artery stent insertion
		Carotid artery stent removal
		Carotid endarterectomy
		Carotid revascularisation
		Cerebral endovascular aneurysm repair
		Cerebral revascularisation
		Cerebrovascular accident prophylaxis
		Coronary angioplasty
		Coronary arterial stent insertion
		Coronary artery bypass
		Coronary brachytherapy
		Coronary endarterectomy
		Coronary revascularisation

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Adverse event class	System organ class	Preferred term
Cardiovascular	Surgical and medical procedures	External counterpulsation
		Intra-cerebral aneurysm operation
		Intracerebral haematoma evacuation
		Percutaneous coronary intervention
		Subdural haematoma evacuation
	Vascular disorders	Acute coronary syndrome
		Acute myocardial infarction
		Amaurosis fugax
		Angina pectoris
		Angina unstable
		Anginal equivalent
		Arteriosclerosis coronary artery
		Arteriospasm coronary
		Basal ganglia haematoma
		Basal ganglia haemorrhage
		Basal ganglia infarction
		Basal ganglia stroke
		Basilar artery aneurysm
		Basilar artery occlusion
		Basilar artery perforation
		Basilar artery stenosis
		Basilar artery thrombosis
		Brachiocephalic arteriosclerosis
		Brachiocephalic artery occlusion
		Brachiocephalic artery stenosis
		Brain hypoxia
		Brain stem embolism
		Brain stem haematoma
		Brain stem haemorrhage
		Brain stem infarction
		Brain stem ischaemia
		Brain stem microhaemorrhage
		Brain stem stroke
		Brain stem thrombosis
		Capsular warning syndrome
		Carotid aneurysm rupture
		Carotid arterial embolus
		Carotid arteriosclerosis
		Carotid artery aneurysm
		Carotid artery calcification
		Carotid artery disease
		Carotid artery dissection
		Carotid artery insufficiency
		Carotid artery occlusion
		Carotid artery perforation
		Carotid artery restenosis
		Carotid artery stenosis
		Carotid artery thrombosis
		Central nervous system haemorrhage
		Cerebellar artery occlusion
		Cerebellar artery thrombosis
		Cerebellar embolism

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Cardiovascular	Vascular disorders	Cerebellar haematoma
		Cerebellar haemorrhage
		Cerebellar infarction
		Cerebellar ischaemia
		Cerebellar microhaemorrhage
		Cerebellar stroke
		Cerebral aneurysm perforation
		Cerebral aneurysm ruptured syphilitic
		Cerebral arteriosclerosis
		Cerebral arteriovenous malformation haemorrhagic
		Cerebral arteritis
		Cerebral artery embolism
		Cerebral artery occlusion
		Cerebral artery perforation
		Cerebral artery restenosis
		Cerebral artery stenosis
		Cerebral artery thrombosis
		Cerebral capillary telangiectasia
		Cerebral circulatory failure
		Cerebral congestion
		Cerebral gas embolism
		Cerebral haematoma
		Cerebral haemorrhage
		Cerebral haemorrhage foetal
		Cerebral haemorrhage neonatal
		Cerebral hypoperfusion
		Cerebral infarction
		Cerebral infarction foetal
		Cerebral ischaemia
		Cerebral microembolism
		Cerebral microhaemorrhage
		Cerebral reperfusion injury
		Cerebral septic infarct
		Cerebral small vessel ischaemic disease
		Cerebral thrombosis
		Cerebral vascular occlusion
		Cerebral vasoconstriction
		Cerebral venous thrombosis
		Cerebrovascular accident
		Cerebrovascular disorder
		Cerebrovascular insufficiency
		Cerebrovascular stenosis
		Charcot-Bouchard microaneurysms
		Coronary artery disease
		Coronary artery dissection
		Coronary artery embolism
		Coronary artery insufficiency
		Coronary artery occlusion
		Coronary artery reocclusion
		Coronary artery restenosis
		Coronary artery stenosis
		Coronary artery thrombosis

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Adverse event class	System organ class	Preferred term
Cardiovascular	Vascular disorders	Coronary bypass stenosis
		Coronary bypass thrombosis
		Coronary no-reflow phenomenon
		Coronary ostial stenosis
		Coronary vascular graft occlusion
		Coronary vascular graft stenosis
		Delayed ischaemic neurological deficit
		Dissecting coronary artery aneurysm
		Dural arteriovenous fistula
		Embolic cerebral infarction
		Embolic stroke
		Epidural haemorrhage
		Extra-axial haemorrhage
		Extradural haematoma
		Haemorrhage coronary artery
		Haemorrhage intracranial
		Haemorrhagic cerebral infarction
		Haemorrhagic stroke
		Haemorrhagic transformation stroke
		Hypoxic-ischaemic encephalopathy
		Inner ear infarction
		Intracranial aneurysm
		Intracranial haematoma
		Intracranial tumour haemorrhage
		Intracranial venous sinus thrombosis
		Intraventricular haemorrhage
		Intraventricular haemorrhage neonatal
		Ischaemic cardiomyopathy
		Ischaemic cerebral infarction
		Ischaemic stroke
		Kounis syndrome
		Lacunar infarction
		Lacunar stroke
		Lateral medullary syndrome
		Meningorrhagia
		Microvascular coronary artery disease
		Migrainous infarction
		Millard-Gubler syndrome
		Moyamoya disease
		Myocardial infarction
		Myocardial ischaemia
		Myocardial necrosis
		Myocardial reperfusion injury
		Myocardial stunning
		Papillary muscle infarction
		Perinatal stroke
		Periventricular haemorrhage neonatal
		Pituitary haemorrhage
		Post cardiac arrest syndrome
		Post procedural stroke
		Postinfarction angina
		Precerebral arteriosclerosis
		Precerebral artery occlusion

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Cardiovascular	Vascular disorders	Prinzmetal angina
		Putamen haemorrhage
		Reversible cerebral vasoconstriction syndrome
		Reversible ischaemic neurological deficit
		Ruptured cerebral aneurysm
		Silent myocardial infarction
		Spinal artery embolism
		Spinal artery thrombosis
		Spinal cord haematoma
		Spinal cord haemorrhage
		Spinal epidural haematoma
		Spinal epidural haemorrhage
		Spinal subarachnoid haemorrhage
		Spinal subdural haematoma
		Spinal subdural haemorrhage
		Stress cardiomyopathy
		Stroke in evolution
		Subarachnoid haematoma
		Subarachnoid haemorrhage
		Subarachnoid haemorrhage neonatal
		Subclavian coronary steal syndrome
		Subclavian steal syndrome
		Subdural haematoma
		Subdural haemorrhage
		Subdural haemorrhage neonatal
		Subendocardial ischaemia
		Superior sagittal sinus thrombosis
		Thalamic infarction
		Thalamus haemorrhage
		Thrombotic cerebral infarction
		Thrombotic stroke
		Transient ischaemic attack
		Transverse sinus thrombosis
		Vascular encephalopathy
		Vasculitis cerebral
		Vein of Galen aneurysmal malformation
		Vertebral artery aneurysm
		Vertebral artery dissection
		Vertebral artery occlusion
		Vertebral artery perforation
		Vertebral artery stenosis
		Vertebral artery thrombosis
		Vertebrobasilar insufficiency
Diabetic retinopathy	Endocrine disorders	Diabetic blindness
		Diabetic eye disease
		Diabetic glaucoma
		Diabetic retinal oedema
		Diabetic retinopathy
		Diabetic uveitis
		Retinal neovascularisation

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Diabetic retinopathy	Endocrine disorders	Retinopathy proliferative
	Eye disorders	Amaurosis
		Cystoid macular oedema
		Diabetic blindness
		Diabetic eye disease
		Diabetic glaucoma
		Diabetic retinal oedema
		Diabetic retinopathy
		Diabetic uveitis
		Exudative retinopathy
		Macular ischaemia
		Macular oedema
		Macular opacity
		Macular pseudohole
		Maculopathy
		Night blindness
		Papilloedema
		Papillophlebitis
		Retinal deposits
		Retinal detachment
		Retinal exudates
		Retinal haemorrhage
		Retinal ischaemia
		Retinal neovascularisation
		Retinal oedema
		Retinal pallor
		Retinal vascular occlusion
		Retinopathy
		Retinopathy proliferative
		Sudden visual loss
		Visual acuity reduced
		Visual acuity reduced transiently
		Vitreal cells
		Vitreous detachment
		Vitreous haemorrhage
		Vitreous opacities
	Injury, poisoning and procedural complications	Cystoid macular oedema
		Retinal detachment
		Vitreous detachment
	Metabolism and nutrition disorders	Diabetic blindness
		Diabetic eye disease
		Diabetic glaucoma
		Diabetic retinal oedema
		Diabetic retinopathy
		Diabetic uveitis
		Night blindness
		Retinal neovascularisation
		Retinopathy proliferative
	Nervous system disorders	Papilloedema
		Sudden visual loss
		Visual acuity reduced

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Diabetic retinopathy	Nervous system disorders	Visual acuity reduced transiently
	Vascular disorders	Diabetic retinopathy
		Exudative retinopathy
		Macular ischaemia
		Papilloedema
		Papillophlebitis
		Retinal exudates
		Retinal haemorrhage
		Retinal ischaemia
		Retinal neovascularisation
		Retinal oedema
		Retinal vascular occlusion
		Retinopathy
		Retinopathy proliferative
		Vitreous haemorrhage
Peripheral neuropathy	Congenital, familial and genetic disorders	Hereditary motor and sensory neuropathy
	Ear and labyrinth disorders	Paraesthesia ear
	Endocrine disorders	Acute painful neuropathy of rapid glycaemic control
		Diabetic autonomic neuropathy
		Diabetic mononeuropathy
		Diabetic neuropathy
		Small fibre neuropathy
	Eye disorders	Miller Fisher syndrome
	Gastrointestinal disorders	Autonomic failure syndrome
	General disorders and administration site conditions	Burning sensation
		Gait disturbance
	Immune system disorders	Angiopathic neuropathy
		Anti-myelin-associated glycoprotein associated polyneuropathy
		Autoimmune neuropathy
		Demyelinating polyneuropathy
		Guillain-Barre syndrome
		Multifocal motor neuropathy
	Infections and infestations	Guillain-Barre syndrome
		Tick paralysis
	Injury, poisoning and procedural complications	Neuromuscular toxicity
		Neurotoxicity
		Radiation neuropathy
		Tick paralysis
		Toxic neuropathy
	Investigations	Anti-ganglioside antibody positive
		Anti-myelin-associated glycoprotein antibodies positive
		Biopsy peripheral nerve abnormal

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Peripheral neuropathy	Investigations	Electromyogram abnormal
		Nerve conduction studies abnormal
		Peripheral nervous system function test abnormal
		Temperature perception test decreased
	Metabolism and nutrition disorders	Acute painful neuropathy of rapid glycaemic control
		Diabetic autonomic neuropathy
		Diabetic mononeuropathy
		Diabetic neuropathy
		Neuropathy vitamin B6 deficiency
		Small fibre neuropathy
	Musculoskeletal and connective tissue disorders	Amyotrophy
		Burning feet syndrome
		Decreased nasolabial fold
		Hypotonia
		Motor dysfunction
		Muscle atrophy
		Muscular weakness
		Neuromuscular pain
		Neuromyopathy
		Neuropathic muscular atrophy
	Nervous system disorders	Acute painful neuropathy of rapid glycaemic control
		Acute polyneuropathy
		Amyotrophy
		Angiopathic neuropathy
		Anti-myelin-associated glycoprotein associated polyneuropathy
		Areflexia
		Autoimmune neuropathy
		Autonomic failure syndrome
		Autonomic neuropathy
		Axonal neuropathy
		Burning feet syndrome
		Burning sensation
		Decreased nasolabial fold
		Decreased vibratory sense
		Demyelinating polyneuropathy
		Diabetic autonomic neuropathy
		Diabetic mononeuropathy
		Diabetic neuropathy
		Dysaesthesia
		Formication
		Gait disturbance
		Genital hypoaesthesia
		Guillain-Barre syndrome
		Hereditary motor and sensory neuropathy
		Hypoaesthesia
		Hyporeflexia

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Adverse event class	System organ class	Preferred term
Peripheral neuropathy	Nervous system disorders	Hypotonia
		Ischaemic neuropathy
		Loss of proprioception
		Miller Fisher syndrome
		Mononeuritis
		Mononeuropathy
		Mononeuropathy multiplex
		Motor dysfunction
		Multifocal motor neuropathy
		Muscle atrophy
		Muscular weakness
		Myelopathy
		Nerve degeneration
		Neuralgia
		Neuritis
		Neuromuscular pain
		Neuromuscular toxicity
		Neuromyopathy
		Neuronal neuropathy
		Neuropathic muscular atrophy
		Neuropathy peripheral
		Neuropathy vitamin B6 deficiency
		Neurotoxicity
		Notalgia paraesthetica
		Paraesthesia
		Paraesthesia ear
		Peripheral motor neuropathy
		Peripheral nerve lesion
		Peripheral nerve palsy
		Peripheral nerve paresis
		Peripheral sensorimotor neuropathy
		Peripheral sensory neuropathy
		Peroneal nerve palsy
		Phrenic nerve paralysis
		Polyneuropathy
		Polyneuropathy chronic
		Polyneuropathy idiopathic progressive
		Radiation neuropathy
		Sensorimotor disorder
		Sensory disturbance
		Sensory loss
		Skin burning sensation
		Small fibre neuropathy
		Synkinesis
		Tick paralysis
		Tinel's sign
		Toxic neuropathy
		Ulnar neuritis
		Vulvovaginal hypoaesthesia
	Psychiatric disorders	Formication
	Reproductive system and breast disorders	Genital hypoaesthesia

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Adverse event class	System organ class	Preferred term
Peripheral neuropathy	Reproductive system and breast disorders	Vulvovaginal hypoaesthesia
	Skin and subcutaneous tissue disorders	Burning feet syndrome
		Notalgia paraesthetica
		Skin burning sensation
	Vascular disorders	Angiopathic neuropathy
		Autonomic failure syndrome
		Ischaemic neuropathy
Rare	Blood and lymphatic system disorders	ABO haemolytic disease of newborn
		Aase syndrome
		Accessory spleen
		Acquired amegakaryocytic thrombocytopenia
		Agranulocytosis
		Amegakaryocytic thrombocytopenia
		Antithrombin III deficiency
		Aplastic anaemia
		Asplenia
		Autoimmune aplastic anaemia
		Autoimmune lymphoproliferative syndrome
		B-lymphocyte abnormalities
		Basophilopenia
		Bicytopenia
		Blood disorder
		Blood incompatibility haemolytic anaemia of newborn
		Bone marrow disorder
		Bone marrow failure
		Bone marrow infiltration
		Bone marrow necrosis
		Bone marrow toxicity
		CANDLE syndrome
		Cardiac lymphangioma
		Chediak-Higashi syndrome
		Chronic granulomatous disease
		Coagulation factor mutation
		Complement deficiency disease
		Congenital anaemia
		Congenital aplastic anaemia
		Congenital coagulopathy
		Congenital dysfibrinogenaemia
		Congenital dyskeratosis
		Congenital haematological disorder
		Congenital hypercoagulation
		Congenital lymphoedema
		Congenital malaria
		Congenital methaemoglobinaemia
		Congenital thrombocyte disorder
		Congenital thrombocytopenia
		Congenital thymus absence

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Adverse event class	System organ class	Preferred term
Rare	Blood and lymphatic system disorders	Congenital white blood cell disorder
		Cutaneovisceral angiomatosis with thrombocytopenia
		Cyclic neutropenia
		Cystic lymphangioma
		Cytopenia
		Delta-beta thalassaemia
		Disseminated intravascular coagulation
		Double heterozygous sickling disorders
		Dubowitz syndrome
		Elliptocytosis hereditary
		Eosinopenia
		Erythroblastosis foetalis
		Factor I deficiency
		Factor II deficiency
		Factor II mutation
		Factor III deficiency
		Factor IX deficiency
		Factor V Leiden mutation
		Factor V deficiency
		Factor VII deficiency
		Factor VIII deficiency
		Factor X deficiency
		Factor XI deficiency
		Factor XII deficiency
		Factor XIII deficiency
		Familial haemophagocytic lymphohistiocytosis
		Familial polycythaemia
		Febrile bone marrow aplasia
		Febrile neutropenia
		Gelatinous transformation of the bone marrow
		Gleich's syndrome
		Glucose-6-phosphate dehydrogenase deficiency
		Glutathione synthetase deficiency
		Granulocytes maturation arrest
		Granulocytopenia
		Granulocytopenia neonatal
		Haematotoxicity
		Haemoglobin C disease
		Haemoglobin C trait
		Haemoglobin D disease
		Haemoglobin D trait
		Haemoglobin E disease
		Haemoglobin E trait
		Haemoglobin E-thalassaemia disease
		Haemoglobinopathy
		Haemophilia
		Haemophilia A with anti factor VIII
		Haemophilia A without inhibitors

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Adverse event class	System organ class	Preferred term
Rare	Blood and lymphatic system disorders	Haemophilia B with anti factor IX
		Haemophilia B without inhibitors
		Henoch-Schonlein purpura nephritis
		Hepatic infiltration eosinophilic
		Hereditary haemolytic anaemia
		Hereditary sideroblastic anaemia
		Hereditary spherocytosis
		Hereditary stomatocytosis
		Hermansky-Pudlak syndrome
		Hexokinase deficiency anaemia
		Hyperbilirubinaemia
		Hypersplenism congenital
		Idiopathic neutropenia
		Infantile genetic agranulocytosis
		Jaundice
		Leukopenia
		Leukopenia neonatal
		Lymphangiectasia intestinal congenital
		Lymphocytopenia neonatal
		Lymphopenia
		MLASA syndrome
		MYH9-related disease
		Methylenetetrahydrofolate reductase deficiency
		Monocytopenia
		Myelodysplastic syndrome
		Myelodysplastic syndrome transformation
		Myelofibrosis
		Myeloid maturation arrest
		Myeloid metaplasia
		Myeloperoxidase deficiency
		Neonatal alloimmune thrombocytopenia
		Neonatal leukaemia
		Neutropenia
		Neutropenia neonatal
		Neutropenic colitis
		Neutropenic infection
		Neutropenic sepsis
		Ocular icterus
		Omenn syndrome
		Pancytopenia
		Panmyelopathy
		Pearson's syndrome
		Plasma cell disorder
		Platelet glycoprotein gene mutation
		Platelet maturation arrest
		Platelet production decreased
		Platelet toxicity
		Primary myelofibrosis
		Protein C deficiency
		Protein S deficiency
		Pulmonary lymphangiectasia

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Adverse event class	System organ class	Preferred term
Rare	Blood and lymphatic system disorders	Pure white cell aplasia
		Pyruvate kinase deficiency anaemia
		Radiation leukopenia
		Red blood cell enzymes abnormal
		Rhesus haemolytic disease of newborn
		Shwachman-Diamond syndrome
		Sickle cell anaemia
		Sickle cell trait
		Spleen malformation
		Splenic hamartoma
		Splenic varices
		Splenic varices haemorrhage
		Sticky platelet syndrome
		Thalassaemia
		Thalassaemia alpha
		Thalassaemia beta
		Thalassaemia sickle cell
		Thrombocytopenia
		Thrombocytopenia-absent radius syndrome
		Thymus hypoplasia
		Trisomy 12
		Von Willebrand's disease
		White blood cell disorder
		Wiskott-Aldrich syndrome
		X-linked lymphoproliferative syndrome
	Cardiac disorders	Acardia
		Accelerated idioventricular rhythm
		Accessory cardiac pathway
		Adams-Stokes syndrome
		Agonal rhythm
		Anomalous atrioventricular excitation
		Anomalous pulmonary venous connection
		Aortic valve atresia
		Arrhythmia
		Arrhythmia neonatal
		Arrhythmia supraventricular
		Arrhythmogenic right ventricular dysplasia
		Ascites
		Atrial conduction time prolongation
		Atrial fibrillation
		Atrial flutter
		Atrial parasystole
		Atrial septal defect
		Atrial tachycardia
		Atrioventricular block
		Atrioventricular block complete
		Atrioventricular block first degree
		Atrioventricular block second degree
		Atrioventricular conduction time shortened
		Atrioventricular dissociation

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Adverse event class	System organ class	Preferred term
Rare	Cardiac disorders	Atrioventricular node dispersion
		Atrioventricular septal defect
		Baseline foetal heart rate variability disorder
		Bezold-Jarisch reflex
		Bicuspid aortic valve
		Bicuspid pulmonary valve
		Bifascicular block
		Bradyarrhythmia
		Bradycardia
		Bradycardia foetal
		Bradycardia neonatal
		Brugada syndrome
		Bundle branch block
		Bundle branch block bilateral
		Bundle branch block left
		Bundle branch block right
		CHARGE syndrome
		Cardiac arrest
		Cardiac arrest neonatal
		Cardiac death
		Cardiac fibrillation
		Cardiac flutter
		Cardiac lymphangioma
		Cardiac malposition
		Cardiac septal defect
		Cardio-respiratory arrest
		Cardio-respiratory arrest neonatal
		Carney complex
		Central bradycardia
		Chiari network
		Chronotropic incompetence
		Conduction disorder
		Congenital aortic valve incompetence
		Congenital aortic valve stenosis
		Congenital cardiovascular anomaly
		Congenital great vessel anomaly
		Congenital heart valve disorder
		Congenital heart valve incompetence
		Congenital mitral valve incompetence
		Congenital mitral valve stenosis
		Congenital pulmonary valve atresia
		Congenital pulmonary valve disorder
		Congenital tricuspid valve atresia
		Congenital tricuspid valve incompetence
		Congenital tricuspid valve stenosis
		Cor biloculare
		Cor triatriatum
		Corrected transposition of great vessels
		Defect conduction intraventricular
		Dextrocardia
		DiGeorge's syndrome
		Double outlet right ventricle

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Adverse event class	System organ class	Preferred term
Rare	Cardiac disorders	Ductus arteriosus premature closure
		Ebstein's anomaly
		Ectopia cordis
		Emanuel syndrome
		Endocardial fibroelastosis
		Extrasystoles
		Fallot's pentalogy
		Fallot's tetralogy
		Fallot's trilogy
		Foetal arrhythmia
		Foetal heart rate acceleration abnormality
		Foetal heart rate deceleration abnormality
		Foetal heart rate disorder
		Foetal tachyarrhythmia
		Glycogen storage disease type II
		Heart alternation
		Heart block congenital
		Heart disease congenital
		Holt-Oram syndrome
		Hypertrophic cardiomyopathy
		Hypoplastic left heart syndrome
		Hypoplastic right heart syndrome
		Inherited cardiac conduction disorder
		Junctional ectopic tachycardia
		Kabuki make-up syndrome
		Kearns-Sayre syndrome
		Kleefstra syndrome
		Kounis syndrome
		Laevocardia
		Larsen syndrome
		Left ventricle outflow tract obstruction
		Left-to-right cardiac shunt
		Lenegre's disease
		Long QT syndrome
		Long QT syndrome congenital
		Lown-Ganong-Levine syndrome
		Mitral valve atresia
		Mitral valve hypoplasia
		Multiple cardiac defects
		Multiple lentigines syndrome
		Myocardial bridging
		Neonatal tachycardia
		Nodal arrhythmia
		Nodal rhythm
		Non-compaction cardiomyopathy
		Nonreassuring foetal heart rate pattern
		Noonan syndrome
		Pacemaker generated arrhythmia
		Pacemaker syndrome
		Palpitations
		Parachute mitral valve

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Adverse event class	System organ class	Preferred term
Rare	Cardiac disorders	Parasystole
		Paroxysmal arrhythmia
		Paroxysmal atrioventricular block
		Patent ductus arteriosus
		Persistent foetal circulation
		Primary ciliary dyskinesia
		Pulmonary artery atresia
		Pulmonary valve stenosis congenital
		Pulseless electrical activity
		Rebound tachycardia
		Reperfusion arrhythmia
		Rhythm idioventricular
		Right ventricle outflow tract obstruction
		Rubinstein-Taybi syndrome
		Shone complex
		Sinoatrial block
		Sinus arrest
		Sinus arrhythmia
		Sinus bradycardia
		Sinus node dysfunction
		Sinus tachycardia
		Sudden cardiac death
		Sudden death
		Supraventricular extrasystoles
		Supraventricular tachyarrhythmia
		Supraventricular tachycardia
		Syncope
		Tachyarrhythmia
		Tachycardia
		Tachycardia foetal
		Tachycardia paroxysmal
		Timothy syndrome
		Torsade de pointes
		Transposition of the great vessels
		Trifascicular block
		Trisomy 11
		Trisomy 13
		Trisomy 14
		Trisomy 17
		Trisomy 18
		Trisomy 21
		Trisomy 22
		Trisomy 9
		Truncus arteriosus persistent
		Twin reversed arterial perfusion sequence malformation
		Uhl's anomaly
		Univentricular heart
		VACTERL syndrome
		Velo-cardio-facial syndrome
		Ventricular arrhythmia
		Ventricular asystole

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Adverse event class	System organ class	Preferred term
Rare	Cardiac disorders	Ventricular dyssynchrony
		Ventricular extrasystoles
		Ventricular fibrillation
		Ventricular flutter
		Ventricular hypoplasia
		Ventricular parasystole
		Ventricular pre-excitation
		Ventricular septal defect
		Ventricular tachyarrhythmia
		Ventricular tachycardia
		Wandering pacemaker
		Williams syndrome
		Withdrawal arrhythmia
		Wolff-Parkinson-White syndrome
		Wolff-Parkinson-White syndrome congenital
	Congenital, familial and genetic disorders	11-beta-hydroxylase deficiency
		17,20-desmolase deficiency
		17-alpha-hydroxylase deficiency
		18q minus syndrome
		2-Hydroxyglutaric aciduria
		20,22-desmolase deficiency
		21-hydroxylase deficiency
		3-hydroxyacetyl-coenzyme A dehydrogenase deficiency
		5-alpha-reductase deficiency
		ABO haemolytic disease of newborn
		Aase syndrome
		Abdominal transposition
		Abdominal wall anomaly
		Abnormal palmar/plantar creases
		Acardia
		Accessory auricle
		Accessory breast
		Accessory carpal bone
		Accessory kidney
		Accessory liver lobe
		Accessory muscle
		Accessory navicular syndrome
		Accessory salivary gland
		Accessory spleen
		Acetylcholinesterase deficiency
		Achromotrichia congenital
		Acral peeling skin syndrome
		Acrodermatitis enteropathica
		Acrokeratosis verruciformis
		Activated PI3 kinase delta syndrome
		Adactyly
		Adams-Oliver syndrome
		Adenine phosphoribosyl transferase deficiency
		Adenomatous polyposis coli

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Adrenal insufficiency neonatal
		Adrenogenital syndrome
		Adrenoleukodystrophy
		Adult polyglucosan body disease
		Aglossia
		Aicardi's syndrome
		Alagille syndrome
		Albinism
		Albright's disease
		Alkaptonuria
		Allan-Herndon-Dudley syndrome
		Alpers' disease
		Alpha-1 anti-trypsin deficiency
		Alport's syndrome
		Alstroem syndrome
		Alternating hemiplegia of childhood
		Alveolar capillary dysplasia
		Amblyopia congenital
		Amegakaryocytic thrombocytopenia
		Aminoaciduria
		Amniotic band syndrome
		Amyotrophic lateral sclerosis gene carrier
		Anal atresia
		Androgen insensitivity syndrome
		Anencephaly
		Angelman's syndrome
		Angiotensin converting enzyme inhibitor foetopathy
		Aniridia
		Ankyloglossia congenital
		Annular pancreas
		Anodontia
		Anomalous arrangement of pancreaticobiliary duct
		Anomalous pulmonary venous connection
		Anomaly of external ear congenital
		Anomaly of middle ear congenital
		Anomaly of orbit, congenital
		Anophthalmos
		Anorchism
		Anorectal agenesis
		Anotia
		Anterior chamber cleavage syndrome
		Anterior displaced anus
		Antithrombin III deficiency
		Aorta hypoplasia
		Aortic valve atresia
		Aorticopulmonary septal defect
		Apert's syndrome
		Aphakia congenital
		Aplasia

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Aplasia cutis congenita
		Arachnodactyly
		Arcuate foramen
		Arginase deficiency
		Argininosuccinate lyase deficiency
		Argininosuccinate synthetase deficiency
		Arnold-Chiari malformation
		Arrhythmogenic right ventricular dysplasia
		Arteriovenous malformation
		Ash leaf macule
		Aspartate-glutamate-transporter deficiency
		Aspartylglucosaminuria
		Asphyxiating thoracic dystrophy
		Asplenia
		Asymptomatic gene carrier
		Ataxia telangiectasia
		Atrial septal defect
		Atrioventricular node dispersion
		Atrioventricular septal defect
		Auditory neuropathy spectrum disorder
		Autoimmune lymphoproliferative syndrome
		Autosomal chromosome anomaly
		Azygos lobe
		Baltic myoclonic epilepsy
		Baraitser Rodeck Garner syndrome
		Barakat syndrome
		Barth syndrome
		Bartter's syndrome
		Basal cell naevus syndrome
		Becker's muscular dystrophy
		Beckwith-Wiedemann syndrome
		Benign congenital hypotonia
		Benign familial haematuria
		Benign familial neonatal convulsions
		Benign familial pemphigus
		Berdon's syndrome
		Beta ketothiolase deficiency
		Bicuspid aortic valve
		Bicuspid pulmonary valve
		Biliary hamartoma
		Biotinidase deficiency
		Birt-Hogg-Dube syndrome
		Birth mark
		Bladder agenesis
		Blau syndrome
		Blepharophimosis congenital
		Blindness congenital
		Bloch-Sulzberger syndrome
		Blood incompatibility haemolytic anaemia of newborn

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Bloom syndrome
		Brachycephaly
		Brachydactyly
		Brain malformation
		Branchial cleft sinus
		Branchial cyst
		Branchio-oto-renal syndrome
		Branchiogenic syndrome
		Breast malformation
		Bronchogenic cyst
		Bruton's agammaglobulinaemia
		Bulbospinal muscular atrophy congenital
		Buried penis syndrome
		CANDLE syndrome
		CHARGE syndrome
		Camptodactyly congenital
		Camptomelia
		Canavan disease
		Cancer gene carrier
		Carbamoyl phosphate synthetase deficiency
		Carbohydrate metabolism disorder
		Carcinogenic effect in offspring
		Cardiac lymphangioma
		Cardiac malposition
		Cardiac septal defect
		Carney complex
		Carnitine palmitoyltransferase deficiency
		Carnitine-acylcarnitine translocase deficiency
		Carpus curvus
		Cartilage-hair hypoplasia
		Cataract congenital
		Caudal regression syndrome
		Central core disease
		Central nervous system dermoid tumour
		Cerebellar dysplasia
		Cerebellar hypoplasia
		Cerebral arteriovenous malformation haemorrhagic
		Cerebral atrophy congenital
		Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
		Cerebral dysgenesis
		Cerebral palsy
		Cerebrohepatorenal syndrome
		Cerebrovascular arteriovenous malformation
		Cervical auricle
		Cervical rib

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Chediak-Higashi syndrome
		Chiari network
		Chimerism
		Choanal atresia
		Choanal stenosis
		Cholangiectasis congenital
		Choledochal cyst
		Chondrodystrophy
		Chondroectodermal dysplasia
		Chordee
		Chorioretinal degeneration congenital
		Choroidal coloboma
		Chromosomal deletion
		Chromosomal mutation
		Chronic granulomatous disease
		Chronic infantile neurological cutaneous and articular syndrome
		Citrate transporter deficiency
		Cleft foot
		Cleft lip
		Cleft lip and palate
		Cleft palate
		Cleft uvula
		Cleidocranial dysostosis
		Clinodactyly
		Cloacal exstrophy
		Coagulation factor mutation
		Coarctation of the aorta
		Cobb syndrome
		Cockayne's syndrome
		Cohen syndrome
		Collodion baby
		Coloboma
		Colour blindness
		Combined immunodeficiency
		Complement deficiency disease
		Congenital Eustachian tube anomaly
		Congenital HIV infection
		Congenital Horner's syndrome
		Congenital abdominal hernia
		Congenital absence of bile ducts
		Congenital absence of cranial vault
		Congenital absence of vertebra
		Congenital acrochordon
		Congenital adrenal gland hypoplasia
		Congenital anaemia
		Congenital androgen deficiency
		Congenital anomalies of ear ossicles
		Congenital anomaly
		Congenital anomaly in offspring
		Congenital anomaly of adrenal gland
		Congenital anomaly of inner ear

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Congenital aortic anomaly
		Congenital aortic atresia
		Congenital aortic dilatation
		Congenital aortic stenosis
		Congenital aortic valve incompetence
		Congenital aortic valve stenosis
		Congenital aplastic anaemia
		Congenital aqueductal stenosis
		Congenital arterial malformation
		Congenital arteriovenous fistula
		Congenital astigmatism
		Congenital aural fistula
		Congenital benign neoplasm
		Congenital bladder anomaly
		Congenital bladder diverticulum
		Congenital bladder neck obstruction
		Congenital bowing of long bones
		Congenital brain damage
		Congenital bronchiectasis
		Congenital bronchomalacia
		Congenital calyceal diverticulum
		Congenital cardiovascular anomaly
		Congenital carnitine deficiency
		Congenital central diabetes insipidus
		Congenital central hypoventilation syndrome
		Congenital central nervous system anomaly
		Congenital cerebellar agenesis
		Congenital cerebral cyst
		Congenital cerebral haemangioma
		Congenital cerebrovascular anomaly
		Congenital choroid plexus cyst
		Congenital choroidal anomaly
		Congenital chylothorax
		Congenital clavicular agenesis
		Congenital claw toe
		Congenital cleft hand
		Congenital coagulopathy
		Congenital condyloma
		Congenital corneal anomaly
		Congenital coronary artery malformation
		Congenital cranial nerve paralysis
		Congenital cutis laxa
		Congenital cyst
		Congenital cystic disease of liver
		Congenital cystic kidney disease
		Congenital cystic lung
		Congenital cytomegalovirus infection
		Congenital deformity of clavicle
		Congenital dermal sinus
		Congenital diaphragmatic anomaly

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Congenital diaphragmatic eventration
		Congenital diaphragmatic hernia
		Congenital disorder of glycosylation
		Congenital dysfibrinogenaemia
		Congenital dyskeratosis
		Congenital ectodermal dysplasia
		Congenital ectopic bladder
		Congenital ectopic pancreas
		Congenital elevation of scapula
		Congenital emphysema
		Congenital endocrine anomaly
		Congenital epiblepharon
		Congenital epiglottal anomaly
		Congenital eye disorder
		Congenital eye naevus
		Congenital eyelid malformation
		Congenital facial nerve hypoplasia
		Congenital fallopian tube anomaly
		Congenital fibrosarcoma
		Congenital flaccid paralysis
		Congenital flat feet
		Congenital floppy infant
		Congenital foot malformation
		Congenital gastric anomaly
		Congenital gastrointestinal vessel anomaly
		Congenital generalised lipodystrophy
		Congenital genital malformation
		Congenital genital malformation female
		Congenital genital malformation male
		Congenital genitourinary abnormality
		Congenital great vessel anomaly
		Congenital haematological disorder
		Congenital hair disorder
		Congenital hand malformation
		Congenital hearing disorder
		Congenital heart valve disorder
		Congenital heart valve incompetence
		Congenital hemiparesis
		Congenital hepatic fibrosis
		Congenital hepatitis B infection
		Congenital hepatobiliary anomaly
		Congenital hepatomegaly
		Congenital herpes simplex infection
		Congenital hiatus hernia
		Congenital high airway obstruction syndrome
		Congenital hydrocele renalis
		Congenital hydrocephalus
		Congenital hydronephrosis
		Congenital hypercoagulation
		Congenital hyperextension of knee

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Congenital hyperextension of spine
		Congenital hyperthyroidism
		Congenital hypertrichosis
		Congenital hypogammaglobulinaemia
		Congenital hypoparathyroidism
		Congenital hypothyroidism
		Congenital infection
		Congenital inguinal hernia
		Congenital intestinal malformation
		Congenital intestinal obstruction
		Congenital intrinsic factor deficiency
		Congenital iris anomaly
		Congenital jaw malformation
		Congenital joint malformation
		Congenital knee deformity
		Congenital knee dislocation
		Congenital kyphoscoliosis
		Congenital labia pudendi adhesions
		Congenital lacrimal gland anomaly
		Congenital lacrimal passage anomaly
		Congenital large intestinal atresia
		Congenital laryngeal stridor
		Congenital lenticonus
		Congenital limb hyperextension
		Congenital lip fistula
		Congenital lymphoedema
		Congenital malaria
		Congenital malignant neoplasm
		Congenital megacolon
		Congenital megaureter
		Congenital melanocytic naevus
		Congenital melanosis
		Congenital methaemoglobinaemia
		Congenital mitochondrial cytopathy
		Congenital mitral valve incompetence
		Congenital mitral valve stenosis
		Congenital monorchidism
		Congenital multiplex arthrogryposis
		Congenital muscle absence
		Congenital musculoskeletal anomaly
		Congenital myopathy
		Congenital myopia
		Congenital naevus
		Congenital nail disorder
		Congenital neoplasm
		Congenital nephrogenic diabetes insipidus
		Congenital nephrotic syndrome
		Congenital neurological degeneration
		Congenital neurological disorder
		Congenital neuropathy
		Congenital night blindness

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Congenital nose malformation
		Congenital nystagmus
		Congenital oculomotor apraxia
		Congenital oesophageal anomaly
		Congenital oesophageal stenosis
		Congenital oesophageal web
		Congenital optic nerve anomaly
		Congenital oral malformation
		Congenital osteodystrophy
		Congenital ovarian anomaly
		Congenital oxalosis
		Congenital pancreatic anomaly
		Congenital perforated nasal septum
		Congenital pharyngeal anomaly
		Congenital pigmentation disorder
		Congenital pneumonia
		Congenital poikiloderma
		Congenital pseudarthrosis
		Congenital pulmonary artery anomaly
		Congenital pulmonary hypertension
		Congenital pulmonary valve atresia
		Congenital pulmonary valve disorder
		Congenital pyelocaliectasis
		Congenital renal cyst
		Congenital renal disorder
		Congenital retinoblastoma
		Congenital rubella infection
		Congenital salivary gland anomaly
		Congenital scleral disorder
		Congenital scoliosis
		Congenital scrotal hypertrophy
		Congenital skin dimples
		Congenital skin disorder
		Congenital small intestinal atresia
		Congenital spinal cord anomaly
		Congenital spinal fusion
		Congenital spinal stenosis
		Congenital spondylolisthesis
		Congenital spondylolysis
		Congenital syphilis
		Congenital syphilitic encephalitis
		Congenital syphilitic meningitis
		Congenital syphilitic osteochondritis
		Congenital teratoma
		Congenital thrombocyte disorder
		Congenital thrombocytopenia
		Congenital thymus absence
		Congenital thyroid disorder
		Congenital tongue anomaly
		Congenital torticollis
		Congenital toxoplasmosis
		Congenital tracheomalacia

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Congenital trichomegaly
		Congenital tricuspid valve atresia
		Congenital tricuspid valve incompetence
		Congenital tricuspid valve stenosis
		Congenital tuberculosis
		Congenital umbilical hernia
		Congenital ureteric anomaly
		Congenital ureterocele
		Congenital ureterovesical junction anomaly
		Congenital urethral anomaly
		Congenital urinary tract obstruction
		Congenital uterine anomaly
		Congenital vaginal cyst
		Congenital varicella infection
		Congenital varicocele
		Congenital vas deferens absence
		Congenital vesicoureteric reflux
		Congenital visual acuity reduced
		Congenital vitreous anomaly
		Congenital white blood cell disorder
		Conjoined twins
		Conjunctivitis gonococcal neonatal
		Constricted ear deformity
		Cor biloculare
		Cor triatriatum
		Corneal dystrophy
		Corneal opacity congenital
		Cornelia de Lange syndrome
		Corrected transposition of great vessels
		Cortical dysplasia
		Costello syndrome
		Cowden's disease
		Craniofacial deformity
		Craniofacial dysostosis
		Craniolacunia
		Craniorachischisis
		Craniosynostosis
		Craniotabes
		Cri du Chat syndrome
		Crigler-Najjar syndrome
		Cryopyrin associated periodic syndrome
		Cryptophthalmos
		Cryptorchism
		Cutaneovisceral angiomatosis with thrombocytopenia
		Cyclopia
		Cystathionine beta-synthase deficiency
		Cystic angiomatosis
		Cystic eyeball, congenital
		Cystic fibrosis
		Cystic fibrosis carrier

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Cystic fibrosis gastrointestinal disease
		Cystic fibrosis hepatic disease
		Cystic fibrosis lung
		Cystic fibrosis pancreatic
		Cystic fibrosis related diabetes
		Cystic lymphangioma
		Cystinosis
		Cystinuria
		Cytogenetic abnormality
		DNA mismatch repair protein gene mutation
		Dacryostenosis congenital
		Dandy-Walker syndrome
		Deaf mutism
		Deafness congenital
		Deficiency of the interleukin-1 receptor antagonist
		Deficiency of the interleukin-36 receptor antagonist
		Delta-beta thalassaemia
		Dent's disease
		Dentatorubral-pallidoluysian atrophy
		Dentinogenesis imperfecta
		Dentofacial anomaly
		Denys-Drash syndrome
		Dermatofibrosis lenticularis disseminata
		Dermatoglyphic anomaly
		Dermoid cyst
		Developmental glaucoma
		Developmental hip dysplasia
		Dextrocardia
		DiGeorge's syndrome
		Diabetic foetopathy
		Diaphragmatic aplasia
		Diastematomyelia
		Diencephalic syndrome of infancy
		Diethylstilboestrol syndrome
		Dihydropyrimidine dehydrogenase deficiency
		Dilatation intrahepatic duct congenital
		Disorder of sex development
		Distichiasis
		Diverticulitis Meckel's
		Diverticulum of pharynx, congenital
		Dolichocolon
		Double cortex syndrome
		Double heterozygous sickling disorders
		Double outlet right ventricle
		Double ureter
		Dowling-Degos disease
		Duane's syndrome
		Dubin-Johnson syndrome

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Dubowitz syndrome
		Duchenne muscular dystrophy
		Duchenne muscular dystrophy gene carrier
		Ductus arteriosus premature closure
		Ductus arteriosus stenosis foetal
		Ductus venosus agenesis
		Duodenal atresia
		Duplex appendix
		Dyschondrosteosis
		Dysgnathia
		Dysmorphism
		Dysmyelination
		Dysplastic naevus syndrome
		Eagle Barrett syndrome
		Ear malformation
		Early onset familial Alzheimer's disease
		Early onset primary dystonia
		Ebstein's anomaly
		Ectopia cordis
		Ectopic kidney
		Ectopic ovary
		Ectopic posterior pituitary gland
		Ectopic thyroid
		Ectopic ureter
		Ehlers-Danlos syndrome
		Elliptocytosis hereditary
		Ellis-van Creveld syndrome
		Emanuel syndrome
		Encephalocele
		Encephalocutaneous angiomatosis
		Endocardial fibroelastosis
		Enteric duplication
		Entropion congenital
		Epidermal naevus
		Epidermal naevus syndrome
		Epidermolysis
		Epidermolysis bullosa
		Epilepsy congenital
		Epispadias
		Erythroblastosis foetalis
		Erythrokeratodermia variabilis
		Essential fructosuria
		Exomphalos
		Exophthalmos congenital
		External auditory canal atresia
		Extrarenal pelvis
		Eye anterior chamber congenital anomaly
		Eyelid ptosis congenital
		Fabry's disease
		Faciodigitogenital dysplasia
		Facioscapulohumeral muscular dystrophy
		Factor I deficiency

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Factor II deficiency
		Factor II mutation
		Factor III deficiency
		Factor IX deficiency
		Factor V Leiden carrier
		Factor V Leiden mutation
		Factor V deficiency
		Factor VII deficiency
		Factor VIII deficiency
		Factor X deficiency
		Factor XI deficiency
		Factor XII deficiency
		Factor XIII deficiency
		Fallot's pentalogy
		Fallot's tetralogy
		Fallot's trilogy
		Familial amyloidosis
		Familial amyotrophic lateral sclerosis
		Familial cold autoinflammatory syndrome
		Familial haemophagocytic lymphohistiocytosis
		Familial hemiplegic migraine
		Familial high density lipoprotein deficiency
		Familial hypertriglyceridaemia
		Familial hypocalciuric hypercalcaemia
		Familial infantile bilateral striatal necrosis
		Familial mediterranean fever
		Familial medullary thyroid cancer
		Familial periodic paralysis
		Familial polycythaemia
		Familial renal glycosuria
		Familial scaphocephaly syndrome
		Familial tremor
		Fanconi syndrome
		Fatal familial insomnia
		Fatty acid oxidation disorder
		Femoral anteversion
		Femoral retroversion
		Femur-fibula-ulna complex
		Fibrodysplasia ossificans progressiva
		Fibrous dysplasia of bone
		Fibrous dysplasia of jaw
		Fibula agenesis
		Fissure of tongue, congenital
		Foetal alcohol syndrome
		Foetal anticonvulsant syndrome
		Foetal chromosome abnormality
		Foetal cystic hygroma
		Foetal malformation
		Foetal megacystis

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Foetal methotrexate syndrome
		Foetal retinoid syndrome
		Foetal warfarin syndrome
		Foramen magnum stenosis
		Fragile X carrier
		Fragile X syndrome
		Freeman-Sheldon syndrome
		Frenulum breve
		Friedreich's ataxia
		Fryns syndrome
		GNE myopathy
		Galactosaemia
		Gallbladder agenesis
		Gallbladder anomaly congenital
		Gastrointestinal arteriovenous malformation
		Gastrointestinal disorder congenital
		Gastrointestinal malformation
		Gastroschisis
		Gaucher's disease
		Gaucher's disease type I
		Gaucher's disease type II
		Gaucher's disease type III
		Gene mutation
		Generalised resistance to thyroid hormone
		Genitalia external ambiguous
		Gilbert's syndrome
		Gitelman's syndrome
		Glucose transporter type 1 deficiency syndrome
		Glucose-6-phosphate dehydrogenase deficiency
		Glucose-galactose malabsorption
		Glutathione synthetase deficiency
		Glycogen storage disease type I
		Glycogen storage disease type II
		Glycogen storage disease type III
		Glycogen storage disease type IV
		Glycogen storage disease type V
		Glycogen storage disease type VI
		Glycogen storage disease type VII
		Glycogen storage disease type VIII
		Glycogen storage disorder
		Gnathoschisis
		Goitre congenital
		Gonadal dysgenesis
		Gorham's disease
		Greig's syndrome
		Haemangioma congenital
		Haemangioma of retina
		Haemochromatosis trait

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Haemoglobin C disease
		Haemoglobin C trait
		Haemoglobin D disease
		Haemoglobin D trait
		Haemoglobin E disease
		Haemoglobin E trait
		Haemoglobin E-thalassaemia disease
		Haemoglobinopathy
		Haemophilia
		Haemophilia A with anti factor VIII
		Haemophilia A without inhibitors
		Haemophilia B with anti factor IX
		Haemophilia B without inhibitors
		Haemophilia carrier
		Haemorrhagic arteriovenous malformation
		Hamartoma
		Hamartoma vascular
		Hand-foot-genital syndrome
		Harlequin foetus
		Hartnup disease
		Heart block congenital
		Heart disease congenital
		Hemihypertrophy
		Hemimegalencephaly
		Hemivertebra
		Hepatic arteriovenous malformation
		Hepato-lenticular degeneration
		Hereditary angioedema
		Hereditary areflexic dystasia
		Hereditary cerebral degeneration
		Hereditary choroidal dystrophy
		Hereditary disorder
		Hereditary fructose intolerance
		Hereditary haemochromatosis
		Hereditary haemolytic anaemia
		Hereditary haemorrhagic telangiectasia
		Hereditary hypophosphataemic rickets
		Hereditary leiomyomatosis renal cell carcinoma
		Hereditary motor and sensory neuropathy
		Hereditary motor neurone disease
		Hereditary multiple osteochondromas
		Hereditary neuropathic amyloidosis
		Hereditary neuropathy with liability to pressure palsies
		Hereditary non-polyposis colorectal cancer syndrome
		Hereditary optic atrophy
		Hereditary palmoplantar keratoderma
		Hereditary pancreatitis
		Hereditary papillary renal carcinoma
		Hereditary retinal dystrophy

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Hereditary sideroblastic anaemia
		Hereditary spastic paraplegia
		Hereditary spherocytosis
		Hereditary stomatocytosis
		Hermansky-Pudlak syndrome
		Hermaphroditism
		Hernia congenital
		Heterochromia iridis
		Heterotaxia
		Hexokinase deficiency anaemia
		High arched palate
		Hollow visceral myopathy
		Holoprosencephaly
		Holt-Oram syndrome
		Homocystinaemia
		Homocystinuria
		Hooded prepuce
		Huntington's disease
		Hydranencephaly
		Hydrocele
		Hydroxyprolinaemia
		Hyper IgD syndrome
		Hyper IgE syndrome
		Hyper IgM syndrome
		Hyperexplexia
		Hyperinsulinism syndrome
		Hypermethioninaemia
		Hypermethioniuria
		Hyperprolinaemia
		Hypersplenism congenital
		Hypertelorism of orbit
		Hypertrophic cardiomyopathy
		Hypocalvaria
		Hypochondroplasia
		Hypodontia
		Hypomelanosis of Ito
		Hypophosphatasia
		Hypopituitarism foetal
		Hypoplastic left heart syndrome
		Hypoplastic nasal cartilage
		Hypoplastic right heart syndrome
		Hypospadias
		Hypotelorism of orbit
		Hypothalamic hamartoma
		Hypoxanthine-guanine phosphoribosyl transferase deficiency
		Ichthyosis
		Ileal atresia
		Immunodeficiency congenital
		Imperforate hymen
		Imperforate oesophagus

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Inborn error in primary bile acid synthesis
		Inborn error of bilirubin metabolism
		Inborn error of lipid metabolism
		Inborn error of metabolism
		Infantile cortical hyperostosis
		Infantile genetic agranulocytosis
		Infantile septic granulomatosis
		Inherited cardiac conduction disorder
		Iniencephaly
		Interferon gamma receptor deficiency
		Interruption of aortic arch
		Intestinal atresia
		Intestinal malrotation
		Intestinal neuronal dysplasia
		Intestinal transposition
		Intracranial arterial fenestration
		Intracranial lipoma
		Iris coloboma
		Johanson-Blizzard syndrome
		Joubert syndrome
		Juvenile Paget's disease
		Kabuki make-up syndrome
		Kaufman-McKusick syndrome
		Kearns-Sayre syndrome
		Kenny-Caffey syndrome
		Keratitis-ichthyosis-deafness syndrome
		Keratolysis exfoliativa congenital
		Keratosis follicular
		Kidney duplex
		Kidney malformation
		Kidney malrotation
		Kimmerle's anomaly
		Kinematic imbalances due to suboccipital strain
		Kleefstra syndrome
		Klinefelter's syndrome
		Klippel-Feil syndrome
		Klippel-Trenaunay syndrome
		Krabbe's disease
		Kyphosis congenital
		LDLR mutation
		Labial tie
		Lacrimal punctum agenesis
		Laevocardia
		Lafora's myoclonic epilepsy
		Lamin A/C gene mutation
		Langer-Giedion syndrome
		Laron syndrome
		Larsen syndrome
		Laryngeal cleft
		Laryngeal web
		Laryngo-onycho-cutaneous syndrome

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Laryngocele
		Laryngomalacia
		Laurence-Moon-Bardet-Biedl syndrome
		Leber's congenital amaurosis
		Lecithin-cholesterol acyltransferase deficiency
		Left ventricle outflow tract obstruction
		Left-to-right cardiac shunt
		Lens abnormality, congenital
		Leukodystrophy
		Li-Fraumeni syndrome
		Lichen spinulosus
		Liddle's syndrome
		Limb hypoplasia congenital
		Limb malformation
		Limb reduction defect
		Lipid proteinosis
		Lipidosis
		Lipodermoid tumour
		Lipomeningocele
		Lissencephaly
		Long QT syndrome congenital
		Long-chain acyl-coenzyme A dehydrogenase deficiency
		Low set ears
		Lown-Ganong-Levine syndrome
		Lowry-Wood syndrome
		Lumbarisation
		Lymphangiectasia intestinal congenital
		Lysinuric protein intolerance
		Lysosomal acid lipase deficiency
		MELAS syndrome
		MLASA syndrome
		MYH9-related disease
		Macrocephaly
		Macrocheilia
		Macrocornea
		Macrodactyly
		Macrogenia
		Macroglossia
		Macrognathia
		Macrostomia
		Macrotia
		Macular dystrophy congenital
		Majeed's syndrome
		Malformation biliary
		Malformation venous
		Mandibulofacial dysostosis
		Maple syrup disease
		Marcus Gunn syndrome
		Marfan's syndrome
		Maxillonasal dysplasia

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Mayer-Rokitansky-Kuster-Hauser syndrome
		Medium-chain acyl-coenzyme A dehydrogenase deficiency
		Meier-Gorlin syndrome
		Melkersson-Rosenthal syndrome
		Membranous lipodystrophy
		Meningocele
		Meningomyelocele
		Menkes' syndrome
		Mesoblastic nephroma
		Mesonephric duct cyst
		Metabolic myopathy
		Metachromatic leukodystrophy
		Metaphyseal dysplasia
		Metatarsus primus varus
		Methylenetetrahydrofolate reductase deficiency
		Methylenetetrahydrofolate reductase gene mutation
		Methylmalonic aciduria
		Mevalonate kinase deficiency
		Mevalonic aciduria
		Microcephaly
		Microcheilia
		Microcolon
		Microcornea
		Microencephaly
		Microgenia
		Microglossia
		Micrognathia
		Micropenis
		Microphthalmos
		Microstomia
		Microtia
		Microvillous inclusion disease
		Mismatch repair cancer syndrome
		Mitochondrial DNA deletion
		Mitochondrial DNA depletion
		Mitochondrial DNA duplication
		Mitochondrial DNA mutation
		Mitochondrial encephalomyopathy
		Mitochondrial enzyme deficiency
		Mitochondrial hepatopathy
		Mitochondrial myopathy
		Mitochondrial neurogastrointestinal encephalopathy
		Mitral valve atresia
		Mitral valve hypoplasia
		Mittendorf dot
		Mobile caecum syndrome
		Moebius II syndrome
		Molybdenum cofactor deficiency

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Monopodia
		Morning glory syndrome
		Morton's syndrome
		Mosaicism
		Mount-Reback syndrome
		Muckle-Wells syndrome
		Mucolipidosis
		Mucolipidosis type I
		Mucolipidosis type II
		Mucolipidosis type III
		Mucolipidosis type IV
		Mucopolysaccharidosis
		Mucopolysaccharidosis I
		Mucopolysaccharidosis II
		Mucopolysaccharidosis III
		Mucopolysaccharidosis IV
		Mucopolysaccharidosis V
		Mucopolysaccharidosis VI
		Mucopolysaccharidosis VII
		Muir-Torre syndrome
		Multiple carboxylase deficiency
		Multiple cardiac defects
		Multiple congenital abnormalities
		Multiple cutaneous and uterine leiomyomatosis
		Multiple endocrine neoplasia
		Multiple endocrine neoplasia Type 1
		Multiple endocrine neoplasia Type 2
		Multiple endocrine neoplasia Type 2A
		Multiple endocrine neoplasia Type 2B
		Multiple epiphyseal dysplasia
		Multiple gastrointestinal atresias
		Multiple lentigines syndrome
		Muscular dystrophy
		Mutagenic effect
		Myeloperoxidase deficiency
		Myocardial bridging
		Myoclonic epilepsy and ragged-red fibres
		Myotonia congenita
		Myotonic dystrophy
		N-acetylglutamate synthase deficiency
		Naevus anaemicus
		Naevus flammeus
		Naevus spider congenital
		Nail-patella syndrome
		Nasopharyngeal atresia
		Neonatal alloimmune thrombocytopenia
		Neonatal haemochromatosis
		Neonatal leukaemia
		Neonatal lupus erythematosus
		Netherton's syndrome
		Neural tube defect

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Neurofibromatosis
		Neuronal ceroid lipofuscinosis
		Neuronal migration disorder
		Neuropathy, ataxia, retinitis pigmentosa syndrome
		Niemann-Pick disease
		Nijmegen breakage syndrome
		Non-compaction cardiomyopathy
		Nonketotic hyperglycinaemia
		Noonan syndrome
		Norrie's disease
		Ocular albinism
		Oculoauriculovertebral dysplasia
		Oculocerebrorenal syndrome
		Oculodentodigital dysplasia
		Oculopharyngeal dystrophy
		Odontogenic cyst
		Oesophageal atresia
		Oesophageal cyst
		Olfacto genital dysplasia
		Olfactory nerve agenesis
		Olmsted syndrome
		Omenn syndrome
		Opitz-G/BBB syndrome
		Optic nerve hypoplasia
		Oral-facial-digital syndrome type II
		Ornithine transcarbamoylase deficiency
		Oroticaciduria congenital
		Os trigonum
		Osteogenesis imperfecta
		Osteopathia striata
		Osteopetrosis
		Osteopoikilosis
		Osteoporosis-pseudoglioma syndrome
		Ota's naevus
		Otocephaly
		Ovarian agenesis
		Ovarian hypoplasia
		PHACES syndrome
		Pachydermoperiostosis
		Pachygyria
		Pancreas divisum
		Parachute mitral valve
		Paranasal sinus aplasia
		Parkes-Weber syndrome
		Patent ductus arteriosus
		Pearson's syndrome
		Pectus carinatum
		Pectus excavatum
		Pelizaeus-Merzbacher disease
		Pelvic kidney
		Penile torsion

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Penoscrotal fusion
		Penoscrotal transposition
		Periodontal congenital anomaly
		Periventricular nodular heterotopia
		Perry syndrome
		Persistent cloaca
		Persistent foetal circulation
		Persistent left superior vena cava
		Persistent pupillary membrane
		Persistent urogenital sinus
		Peutz-Jeghers syndrome
		Phakomatosis
		Phalangeal agenesis
		Phalangeal hypoplasia
		Phenylketonuria
		Phimosis
		Phytosterolaemia
		Pierre Robin syndrome
		Pilonidal cyst congenital
		Plagiocephaly
		Platelet glycoprotein gene mutation
		Platonychia
		Platybasia
		Platyspondylia
		Poland's syndrome
		Polycystic liver disease
		Polydactyly
		Polymicrogyria
		Porencephaly
		Porokeratosis
		Porphyria
		Porphyria acute
		Porphyria non-acute
		Porphyrin metabolism disorder
		Porphyrinuria
		Portal venous system anomaly
		Postauricular fistula
		Posterior segment of eye anomaly congenital
		Potter's syndrome
		Prader-Willi syndrome
		Preauricular cyst
		Preduodenal portal vein
		Preternatural anus
		Primary cerebellar degeneration
		Primary ciliary dyskinesia
		Primary familial brain calcification
		Primary familial hypomagnesaemia
		Primary hypercholesterolaemia
		Primary immunodeficiency syndrome
		Primary insulin like growth factor-1 deficiency

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Progeria
		Progressive cerebellar degeneration
		Progressive external ophthalmoplegia
		Progressive familial intrahepatic cholestasis
		Prominent epicanthal folds
		Protein C deficiency
		Protein S deficiency
		Proteus syndrome
		Protuberant ear
		Proximal focal femoral deficiency
		Pseudocholinesterase deficiency
		Pseudohermaphroditism
		Pseudohermaphroditism female
		Pseudohermaphroditism male
		Pseudohypoparathyroidism
		Pseudotruncus arteriosus
		Pseudoxanthoma elasticum
		Pterygium colli
		Pulmonary aplasia
		Pulmonary arteriovenous fistula
		Pulmonary artery atresia
		Pulmonary artery stenosis congenital
		Pulmonary hypoplasia
		Pulmonary lymphangiectasia
		Pulmonary malformation
		Pulmonary sequestration
		Pulmonary valve stenosis congenital
		Pyloric stenosis
		Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome
		Pyruvate carboxylase deficiency
		Pyruvate kinase deficiency anaemia
		Radioulnar synostosis
		Rathke's cleft cyst
		Rectal atresia
		Red blood cell enzymes abnormal
		Refsum's disease
		Renal aplasia
		Renal arteriovenous malformation
		Renal dysplasia
		Renal fusion anomaly
		Renal hypoplasia
		Renal malposition
		Renal vessel congenital anomaly
		Reproductive tract hypoplasia, male
		Respiratory tract malformation
		Retinal anomaly congenital
		Retinal arteriovenous malformation
		Retinal coloboma
		Retinitis pigmentosa
		Retinopathy congenital

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Retinoschisis congenital
		Rett syndrome
		Rhesus haemolytic disease of newborn
		Rib hypoplasia
		Rib synostosis
		Right aortic arch
		Right ventricle outflow tract obstruction
		Right-to-left cardiac shunt
		Riley-Day syndrome
		Rippling muscle disease
		Rotor's syndrome
		Rubinstein-Taybi syndrome
		Sacral hypoplasia
		Sacralisation
		Sarcosinaemia
		Scaphocephaly
		Schimke immunoosseous dysplasia
		Schinzel-Giedion syndrome
		Schizencephaly
		Scimitar syndrome
		Sclerotylosis
		Sebaceous naevus
		Sensory neuropathy hereditary
		Septate hymen
		Septo-optic dysplasia
		Septum pellucidum agenesis
		Sertoli-cell-only syndrome
		Severe myoclonic epilepsy of infancy
		Sex chromosome abnormality
		Shone complex
		Short-chain acyl-coenzyme A dehydrogenase deficiency
		Shwachman-Diamond syndrome
		Sickle cell anaemia
		Sickle cell trait
		Silver-Russell syndrome
		Single umbilical artery
		Sirenomelia
		Sjogren-Larsson syndrome
		Skeletal dysplasia
		Skin hypoplasia
		Skin malformation
		Skull malformation
		Smith-Lemli-Opitz syndrome
		Sotos' syndrome
		Special senses congenital anomaly
		Spherophakia
		Spina bifida
		Spina bifida cystica
		Spina bifida occulta
		Spinal muscular atrophy

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Spinal vessel congenital anomaly
		Spine malformation
		Spinocerebellar ataxia
		Spleen malformation
		Splenic hamartoma
		Spondyloepiphyseal dysplasia
		Stargardt's disease
		Steatocystoma multiplex
		Stickler's syndrome
		Sticky platelet syndrome
		Strabismus congenital
		Sturge-Weber syndrome
		Subependymal nodular heterotopia
		Sucrase-isomaltase deficiency
		Supernumerary nipple
		Supernumerary vertebra
		Syndactyly
		Synostosis
		Syringomyelia
		Talipes
		Tangier disease
		Tay-Sachs disease
		Telangiectasia congenital
		Teratogenicity
		Testicular dysplasia
		Testotoxicosis
		Tetrahydrobiopterin deficiency
		Thalassaemia
		Thalassaemia alpha
		Thalassaemia beta
		Thalassaemia sickle cell
		Thalidomide embryopathy
		Thanatophoric dwarfism
		Thrombocytopenia-absent radius syndrome
		Thymus hypoplasia
		Thyroglossal cyst
		Thyroglossal fistula
		Thyroid hemiagenesis
		Thyroid malformation
		Tibial torsion
		Tilted disc syndrome
		Timothy syndrome
		Tooth discolouration congenital
		Tooth hypoplasia
		Tooth malformation hereditary
		Tornwaldt cyst
		Tourette's disorder
		Tracheal atresia
		Tracheal web
		Tracheo-oesophageal fistula
		Transitional vertebrae
		Transposition of the great vessels

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Trichorhinophalangeal syndrome
		Trifunctional protein deficiency
		Trimethylaminuria
		Triple A syndrome
		Trisomy 11
		Trisomy 12
		Trisomy 13
		Trisomy 14
		Trisomy 15
		Trisomy 17
		Trisomy 18
		Trisomy 21
		Trisomy 22
		Trisomy 8
		Trisomy 9
		Truncus arteriosus persistent
		Tuberous sclerosis
		Tumour necrosis factor receptor-associated periodic syndrome
		Turner's syndrome
		Twin reversed arterial perfusion sequence malformation
		Type I hyperlipidaemia
		Type II hyperlipidaemia
		Type III hyperlipidaemia
		Type IIa hyperlipidaemia
		Type IIb hyperlipidaemia
		Type IV hyperlipidaemia
		Type V hyperlipidaemia
		Tyrosinaemia
		Uhl's anomaly
		Umbilical artery hypoplasia
		Umbilical malformation
		Univentricular heart
		Urachal abnormality
		Ureteric atresia
		Urethral atresia
		Urethral valves
		Urinary tract malformation
		Usher's syndrome
		Uterine aplasia
		Uterine cervix hypoplasia
		Uterine hypoplasia
		Uvula aplasia
		VACTERL syndrome
		Vaginal atresia
		Vaginal hypoplasia
		Vaginal septum
		Vascular malformation
		Vein of Galen aneurysmal malformation
		Velo-cardio-facial syndrome
		Venous angioma of brain

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Adverse event class	System organ class	Preferred term
Rare	Congenital, familial and genetic disorders	Ventricular hypoplasia
		Ventricular septal defect
		Vertebral artery hypoplasia
		Vertical talus
		Very long-chain acyl-coenzyme A dehydrogenase deficiency
		Virilism foetal
		Vitello-intestinal duct remnant
		Von Hippel-Lindau disease
		Von Willebrand's disease
		Waardenburg syndrome
		Wagner's disease
		Weill-Marchesani syndrome
		Welander distal myopathy
		Werner's syndrome
		Wildervanck syndrome
		Williams syndrome
		Winchester syndrome
		Wiskott-Aldrich syndrome
		Wolf-Hirschhorn syndrome
		Wolff-Parkinson-White syndrome congenital
		Wolfram syndrome
		Wyburn Mason's syndrome
		X-linked chromosomal disorder
		X-linked lymphoproliferative syndrome
		XXX syndrome
		XXXY syndrome
		XXYY syndrome
		XYY syndrome
		Xeroderma pigmentosum
		Y-linked chromosomal disorder
		Young's syndrome
	Ear and labyrinth disorders	Accessory auricle
		Alport's syndrome
		Alstroem syndrome
		Anomaly of external ear congenital
		Anomaly of middle ear congenital
		Anotia
		Auditory neuropathy spectrum disorder
		Barakat syndrome
		Branchio-oto-renal syndrome
		Branchiogenic syndrome
		CHARGE syndrome
		Cockayne's syndrome
		Congenital Eustachian tube anomaly
		Congenital anomalies of ear ossicles
		Congenital anomaly of inner ear
		Congenital aural fistula
		Congenital hearing disorder
		Constricted ear deformity

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Adverse event class	System organ class	Preferred term
Rare	Ear and labyrinth disorders	Deaf mutism
		Deafness congenital
		Ear malformation
		Emanuel syndrome
		External auditory canal atresia
		Johanson-Blizzard syndrome
		Keratitis-ichthyosis-deafness syndrome
		Low set ears
		MYH9-related disease
		Macrotia
		Meier-Gorlin syndrome
		Microtia
		Norrie's disease
		Preauricular cyst
		Protuberant ear
		Usher's syndrome
		Waardenburg syndrome
		Wildervanck syndrome
		Wolfram syndrome
	Endocrine disorders	18q minus syndrome
		Adrenal insufficiency neonatal
		Adrenogenital syndrome
		Adrenoleukodystrophy
		Albright's disease
		Androgen insensitivity syndrome
		Anorchism
		Barakat syndrome
		Bulbospinal muscular atrophy congenital
		Carney complex
		Congenital adrenal gland hypoplasia
		Congenital androgen deficiency
		Congenital anomaly of adrenal gland
		Congenital central diabetes insipidus
		Congenital endocrine anomaly
		Congenital generalised lipodystrophy
		Congenital hyperthyroidism
		Congenital hypoparathyroidism
		Congenital hypothyroidism
		Congenital thyroid disorder
		Cryptorchism
		Cystic fibrosis related diabetes
		Denys-Drash syndrome
		DiGeorge's syndrome
		Diabetic foetopathy
		Diabetic hepatopathy
		Diencephalic syndrome of infancy
		Ectopic posterior pituitary gland
		Ectopic thyroid
		Familial hypocalciuric hypercalcaemia
		Familial medullary thyroid cancer
		Generalised resistance to thyroid hormone

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Adverse event class	System organ class	Preferred term
Rare	Endocrine disorders	Goitre congenital
		Hermaphroditism
		Hyperinsulinism syndrome
		Hypopituitarism foetal
		Hypothalamic hamartoma
		Kenny-Caffey syndrome
		Klinefelter's syndrome
		Laron syndrome
		Multiple endocrine neoplasia
		Multiple endocrine neoplasia Type 1
		Multiple endocrine neoplasia Type 2
		Multiple endocrine neoplasia Type 2A
		Multiple endocrine neoplasia Type 2B
		Myotonic dystrophy
		Ovarian hypoplasia
		Pseudohermaphroditism
		Pseudohermaphroditism female
		Pseudohermaphroditism male
		Septo-optic dysplasia
		Sertoli-cell-only syndrome
		Thyroglossal cyst
		Thyroglossal fistula
		Thyroid hemiagenesis
		Thyroid malformation
		Triple A syndrome
		Turner's syndrome
		Virilism foetal
		Wolfram syndrome
		XXXY syndrome
		XXYY syndrome
	Eye disorders	Alstroem syndrome
		Amblyopia congenital
		Aniridia
		Anomaly of orbit, congenital
		Anophthalmos
		Anterior chamber cleavage syndrome
		Aphakia congenital
		Basal cell naevus syndrome
		Bickerstaff's encephalitis
		Blau syndrome
		Blepharophimosis congenital
		Blindness congenital
		Bloch-Sulzberger syndrome
		CHARGE syndrome
		Cataract congenital
		Chorioretinal degeneration congenital
		Choroidal coloboma
		Cockayne's syndrome
		Cohen syndrome
		Coloboma
		Colour blindness
		Congenital Horner's syndrome
		Congenital astigmatism

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Adverse event class	System organ class	Preferred term
Rare	Eye disorders	Congenital choroidal anomaly
		Congenital corneal anomaly
		Congenital epiblepharon
		Congenital eye disorder
		Congenital eye naevus
		Congenital eyelid malformation
		Congenital iris anomaly
		Congenital lacrimal gland anomaly
		Congenital lacrimal passage anomaly
		Congenital lenticonus
		Congenital myopia
		Congenital night blindness
		Congenital nystagmus
		Congenital oculomotor apraxia
		Congenital optic nerve anomaly
		Congenital retinoblastoma
		Congenital scleral disorder
		Congenital trichomegaly
		Congenital visual acuity reduced
		Congenital vitreous anomaly
		Conjunctivitis gonococcal neonatal
		Corneal dystrophy
		Corneal opacity congenital
		Cri du Chat syndrome
		Cryptophthalmos
		Cyclopia
		Cystic eyeball, congenital
		Dacryostenosis congenital
		Developmental glaucoma
		Distichiasis
		Duane's syndrome
		Emanuel syndrome
		Entropion congenital
		Exophthalmos congenital
		Eye anterior chamber congenital anomaly
		Eyelid oedema
		Eyelid ptosis congenital
		Faciodigitogenital dysplasia
		Haemangioma of retina
		Hepato-lenticular degeneration
		Hereditary choroidal dystrophy
		Hereditary optic atrophy
		Hereditary retinal dystrophy
		Hermansky-Pudlak syndrome
		Heterochromia iridis
		Hypertelorism of orbit
		Hypotelorism of orbit
		Iris coloboma
		Kearns-Sayre syndrome
		Keratitis-ichthyosis-deafness syndrome
		Lacrimal punctum agenesis
		Laurence-Moon-Bardet-Biedl syndrome
		Leber's congenital amaurosis

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Adverse event class	System organ class	Preferred term
Rare	Eye disorders	Lecithin-cholesterol acyltransferase deficiency
		Lens abnormality, congenital
		Lipodermoid tumour
		MYH9-related disease
		Macrocornea
		Macular dystrophy congenital
		Marcus Gunn syndrome
		Marfan's syndrome
		Microcornea
		Microphthalmos
		Miller Fisher syndrome
		Mittendorf dot
		Morning glory syndrome
		Neuropathy, ataxia, retinitis pigmentosa syndrome
		Norrie's disease
		Ocular albinism
		Ocular icterus
		Oculocerebrorenal syndrome
		Oculodentodigital dysplasia
		Oculomucocutaneous syndrome
		Oculopharyngeal dystrophy
		Oculorespiratory syndrome
		Opitz-G/BBB syndrome
		Optic nerve hypoplasia
		Osteoporosis-pseudoglioma syndrome
		Ota's naevus
		PHACES syndrome
		Periorbital oedema
		Persistent pupillary membrane
		Phakomatosis
		Posterior segment of eye anomaly congenital
		Progressive external ophthalmoplegia
		Prominent epicanthal folds
		Pseudoxanthoma elasticum
		Retinal anomaly congenital
		Retinal arteriovenous malformation
		Retinal coloboma
		Retinitis pigmentosa
		Retinopathy congenital
		Retinoschisis congenital
		Septo-optic dysplasia
		Spherophakia
		Stargardt's disease
		Stickler's syndrome
		Strabismus congenital
		Sturge-Weber syndrome
		Tilted disc syndrome
		Triple A syndrome
		Trisomy 13
		Trisomy 22

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Adverse event class	System organ class	Preferred term
Rare	Eye disorders	Tuberous sclerosis
		Tubulointerstitial nephritis and uveitis syndrome
		Usher's syndrome
		Waardenburg syndrome
		Wagner's disease
		Weill-Marchesani syndrome
		Wildervanck syndrome
		Winchester syndrome
		Wolfram syndrome
		Wyburn Mason's syndrome
	Gastrointestinal disorders	Abdominal transposition
		Abdominal wall anomaly
		Accessory salivary gland
		Acrodermatitis enteropathica
		Adenomatous polyposis coli
		Aglossia
		Alcoholic pancreatitis
		Alcoholic pancreopathy
		Anal atresia
		Ankyloglossia congenital
		Annular pancreas
		Anodontia
		Anomalous arrangement of pancreaticobiliary duct
		Anorectal agenesis
		Anterior displaced anus
		Ascites
		Autoimmune pancreatitis
		Bacterascites
		Basal cell naevus syndrome
		Beckwith-Wiedemann syndrome
		Cleft lip
		Cleft lip and palate
		Cleft palate
		Cleft uvula
		Cloacal exstrophy
		Clostridium colitis
		Clostridium difficile colitis
		Congenital abdominal hernia
		Congenital diaphragmatic hernia
		Congenital dyskeratosis
		Congenital ectopic pancreas
		Congenital gastric anomaly
		Congenital gastrointestinal vessel anomaly
		Congenital hiatus hernia
		Congenital inguinal hernia
		Congenital intestinal malformation
		Congenital intestinal obstruction
		Congenital intrinsic factor deficiency
		Congenital large intestinal atresia

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Adverse event class	System organ class	Preferred term
Rare	Gastrointestinal disorders	Congenital lip fistula
		Congenital megacolon
		Congenital oesophageal anomaly
		Congenital oesophageal stenosis
		Congenital oesophageal web
		Congenital oral malformation
		Congenital pancreatic anomaly
		Congenital salivary gland anomaly
		Congenital small intestinal atresia
		Congenital tongue anomaly
		Congenital umbilical hernia
		Cullen's sign
		Cutaneovisceral angiomatosis with thrombocytopenia
		Cystic fibrosis
		Cystic fibrosis gastrointestinal disease
		Cystic fibrosis pancreatic
		Cytomegalovirus pancreatitis
		Dentinogenesis imperfecta
		Dentofacial anomaly
		Diverticulitis Meckel's
		Dolichocolon
		Duodenal atresia
		Duodenal varices
		Duplex appendix
		Encapsulating peritoneal sclerosis
		Enteric duplication
		Exomphalos
		Fissure of tongue, congenital
		Fryns syndrome
		Gastric varices
		Gastric varices haemorrhage
		Gastroenteritis clostridial
		Gastrointestinal arteriovenous malformation
		Gastrointestinal disorder congenital
		Gastrointestinal malformation
		Gastroschisis
		Glucose-galactose malabsorption
		Gnathoschisis
		Grey Turner's sign
		Haemorrhagic necrotic pancreatitis
		Hepatic hydrothorax
		Hereditary haemorrhagic telangiectasia
		Hereditary non-polyposis colorectal cancer syndrome
		Hereditary pancreatitis
		High arched palate
		Hollow visceral myopathy
		Hypodontia
		Ileal atresia
		Imperforate oesophagus

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Adverse event class	System organ class	Preferred term
Rare	Gastrointestinal disorders	Intestinal angioedema
		Intestinal atresia
		Intestinal malrotation
		Intestinal neuronal dysplasia
		Intestinal sepsis
		Intestinal transposition
		Intestinal varices
		Intestinal varices haemorrhage
		Ischaemic pancreatitis
		Johanson-Blizzard syndrome
		Labial tie
		Lip oedema
		Lip swelling
		Lupus pancreatitis
		Lymphangiectasia intestinal congenital
		Macroglossia
		Melkersson-Rosenthal syndrome
		Mesenteric fibrosis
		Microcolon
		Microglossia
		Microvillous inclusion disease
		Mobile caecum syndrome
		Mouth swelling
		Muir-Torre syndrome
		Multiple gastrointestinal atresias
		Neutropenic colitis
		Oculomucocutaneous syndrome
		Odontogenic cyst
		Oedema mouth
		Oedematous pancreatitis
		Oesophageal atresia
		Oesophageal cyst
		Oesophageal varices haemorrhage
		Oropharyngeal oedema
		Oropharyngeal swelling
		Pancreas divisum
		Pancreas infection
		Pancreatic abscess
		Pancreatic haemorrhage
		Pancreatic necrosis
		Pancreatic phlegmon
		Pancreatic pseudocyst
		Pancreatitis
		Pancreatitis acute
		Pancreatitis bacterial
		Pancreatitis chronic
		Pancreatitis fungal
		Pancreatitis haemorrhagic
		Pancreatitis helminthic
		Pancreatitis mumps
		Pancreatitis necrotising
		Pancreatitis relapsing

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Adverse event class	System organ class	Preferred term
Rare	Gastrointestinal disorders	Pancreatitis viral
		Pancreatorenal syndrome
		Pearson's syndrome
		Periodontal congenital anomaly
		Peripancreatic varices
		Persistent cloaca
		Peutz-Jeghers syndrome
		Portal hypertensive colopathy
		Portal hypertensive enteropathy
		Portal hypertensive gastropathy
		Preduodenal portal vein
		Preternatural anus
		Pseudomembranous colitis
		Pyloric stenosis
		Rectal atresia
		Retroperitoneal fibrosis
		Retroperitonitis
		Shwachman-Diamond syndrome
		Sucrase-isomaltase deficiency
		Swollen tongue
		Tongue oedema
		Tooth discolouration congenital
		Tooth hypoplasia
		Tooth malformation hereditary
		Tracheo-oesophageal fistula
		Traumatic pancreatitis
		Triple A syndrome
		Uvula aplasia
		VACTERL syndrome
		Varices oesophageal
		Varicose veins of abdominal wall
		Vitello-intestinal duct remnant
		White nipple sign
	General disorders and administration site conditions	Aplasia
		Cardiac death
		Chronic infantile neurological cutaneous and articular syndrome
		Congenital cyst
		Cryopyrin associated periodic syndrome
		Deficiency of the interleukin-1 receptor antagonist
		Deficiency of the interleukin-36 receptor antagonist
		Dentatorubral-pallidoluysian atrophy
		Face oedema
		Familial cold autoinflammatory syndrome
		Familial mediterranean fever
		Febrile bone marrow aplasia
		Febrile neutropenia
		Friedreich's ataxia

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Adverse event class	System organ class	Preferred term
Rare	General disorders and administration site conditions	Hernia congenital
		Hyper IgD syndrome
		Hyperthermia malignant
		Joubert syndrome
		Majeed's syndrome
		Mevalonate kinase deficiency
		Mevalonic aciduria
		Multiple organ dysfunction syndrome
		Neuroleptic malignant syndrome
		Oedema due to hepatic disease
		Pacemaker generated arrhythmia
		Pacemaker syndrome
		Pelvic fibrosis
		Rebound tachycardia
		Spinocerebellar ataxia
		Sudden cardiac death
		Sudden death
		Tumour necrosis factor receptor-associated periodic syndrome
		Withdrawal arrhythmia
		Yellow skin
	Hepatobiliary disorders	Accessory liver lobe
		Acute graft versus host disease in liver
		Acute hepatic failure
		Acute on chronic liver failure
		Acute yellow liver atrophy
		Alagille syndrome
		Allergic hepatitis
		Alpha-1 anti-trypsin deficiency
		Anomalous arrangement of pancreaticobiliary duct
		Ascites
		Asterixis
		Autoimmune hepatitis
		Bacterascites
		Biliary cirrhosis
		Biliary cirrhosis primary
		Biliary fibrosis
		Biliary hamartoma
		Bilirubin excretion disorder
		Cerebrohepatorenal syndrome
		Cholaemia
		Cholangiectasis congenital
		Cholangitis
		Choledochal cyst
		Cholestasis
		Cholestatic liver injury
		Cholestatic pruritus
		Chronic graft versus host disease in liver
		Chronic hepatic failure

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Adverse event class	System organ class	Preferred term
Rare	Hepatobiliary disorders	Chronic hepatitis
		Coma hepatic
		Congenital absence of bile ducts
		Congenital cystic disease of liver
		Congenital hepatic fibrosis
		Congenital hepatitis B infection
		Congenital hepatobiliary anomaly
		Congenital hepatomegaly
		Crigler-Najjar syndrome
		Cryptogenic cirrhosis
		Cystic fibrosis hepatic disease
		Deficiency of bile secretion
		Diabetic hepatopathy
		Dilatation intrahepatic duct congenital
		Drug-induced liver injury
		Dubin-Johnson syndrome
		Duodenal varices
		Gallbladder agenesis
		Gallbladder anomaly congenital
		Gallbladder varices
		Gastric varices
		Gastric varices haemorrhage
		Gilbert's syndrome
		Glycogen storage disease type I
		Glycogen storage disease type III
		Glycogen storage disease type IV
		Glycogen storage disease type VI
		Graft versus host disease in liver
		Granulomatous liver disease
		Haemochromatosis trait
		Hepatic arteriovenous malformation
		Hepatic atrophy
		Hepatic calcification
		Hepatic cirrhosis
		Hepatic encephalopathy
		Hepatic failure
		Hepatic fibrosis
		Hepatic hydrothorax
		Hepatic infiltration eosinophilic
		Hepatic lesion
		Hepatic necrosis
		Hepatic steato-fibrosis
		Hepatic steatosis
		Hepatitis
		Hepatitis acute
		Hepatitis cholestatic
		Hepatitis chronic active
		Hepatitis chronic persistent
		Hepatitis fulminant
		Hepatitis toxic
		Hepato-lenticular degeneration
		Hepatobiliary disease
		Hepatocellular foamy cell syndrome

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Adverse event class	System organ class	Preferred term
Rare	Hepatobiliary disorders	Hepatocellular injury
		Hepatopulmonary syndrome
		Hepatorenal failure
		Hepatorenal syndrome
		Hepatotoxicity
		Hereditary haemochromatosis
		Hyperbilirubinaemia
		Intestinal varices
		Ischaemic hepatitis
		Jaundice
		Jaundice cholestatic
		Jaundice hepatocellular
		Liver disorder
		Liver injury
		Liver sarcoidosis
		Lupoid hepatic cirrhosis
		Lupus hepatitis
		Lysosomal acid lipase deficiency
		Malformation biliary
		Minimal hepatic encephalopathy
		Mitochondrial hepatopathy
		Mixed liver injury
		Nodular regenerative hyperplasia
		Non-alcoholic fatty liver
		Non-alcoholic steatohepatitis
		Non-cirrhotic portal hypertension
		Ocular icterus
		Oedema due to hepatic disease
		Oesophageal varices haemorrhage
		Parenteral nutrition associated liver disease
		Peripancreatic varices
		Polycystic liver disease
		Porphyria acute
		Porphyria non-acute
		Porphyrin metabolism disorder
		Porphyrinuria
		Portal fibrosis
		Portal hypertension
		Portal hypertensive colopathy
		Portal hypertensive enteropathy
		Portal hypertensive gastropathy
		Portal tract inflammation
		Portal vein cavernous transformation
		Portal vein dilatation
		Portal venous system anomaly
		Portopulmonary hypertension
		Progressive familial intrahepatic cholestasis
		Radiation hepatitis
		Retrograde portal vein flow
		Reye's syndrome
		Reynold's syndrome

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Adverse event class	System organ class	Preferred term
Rare	Hepatobiliary disorders	Rotor's syndrome
		Splenic varices
		Splenic varices haemorrhage
		Steatohepatitis
		Subacute hepatic failure
		Varices oesophageal
		Varicose veins of abdominal wall
		White nipple sign
		Yellow skin
	Immune system disorders	ABO haemolytic disease of newborn
		Acquired amegakaryocytic thrombocytopenia
		Activated PI3 kinase delta syndrome
		Acute graft versus host disease in liver
		Acute motor axonal neuropathy
		Acute motor-sensory axonal neuropathy
		Allergic hepatitis
		Amegakaryocytic thrombocytopenia
		Anaphylactic reaction
		Anaphylactic shock
		Anaphylactic transfusion reaction
		Anaphylactoid reaction
		Anaphylactoid shock
		Angioedema
		Ataxia telangiectasia
		Autoimmune aplastic anaemia
		Autoimmune hepatitis
		Autoimmune lymphoproliferative syndrome
		Autoimmune nephritis
		Autoimmune pancreatitis
		Benign familial pemphigus
		Bickerstaff's encephalitis
		Biliary cirrhosis primary
		Blau syndrome
		Bruton's agammaglobulinaemia
		C3 glomerulopathy
		CANDLE syndrome
		Cartilage-hair hypoplasia
		Chediak-Higashi syndrome
		Chronic autoimmune glomerulonephritis
		Chronic graft versus host disease in liver
		Chronic granulomatous disease
		Chronic infantile neurological cutaneous and articular syndrome
		Chronic inflammatory demyelinating polyradiculoneuropathy
		Circumoral oedema
		Combined immunodeficiency
		Complement deficiency disease
		Congenital HIV infection
		Congenital hypogammaglobulinaemia
		Congenital thrombocytopenia

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Adverse event class	System organ class	Preferred term
Rare	Immune system disorders	Cryopyrin associated periodic syndrome
		Cutaneous vasculitis
		Deficiency of the interleukin-1 receptor antagonist
		Deficiency of the interleukin-36 receptor antagonist
		Demyelinating polyneuropathy
		Dermatitis exfoliative
		Dermatitis exfoliative generalised
		DiGeorge's syndrome
		Dialysis membrane reaction
		Drug reaction with eosinophilia and systemic symptoms
		Erythema multiforme
		Eyelid oedema
		Face oedema
		Familial amyloidosis
		Familial cold autoinflammatory syndrome
		Familial mediterranean fever
		Fibrillary glomerulonephritis
		Gleich's syndrome
		Glomerulonephritis
		Glomerulonephritis rapidly progressive
		Goodpasture's syndrome
		Graft versus host disease in liver
		Granulomatosis with polyangiitis
		Guillain-Barre syndrome
		HIV associated nephropathy
		Henoch-Schonlein purpura nephritis
		Hereditary angioedema
		Hereditary neuropathic amyloidosis
		Hyper IgD syndrome
		Hyper IgE syndrome
		Hyper IgM syndrome
		Idiopathic angioedema
		IgA nephropathy
		IgM nephropathy
		Immunodeficiency congenital
		Interferon gamma receptor deficiency
		Intestinal angioedema
		Kounis syndrome
		Laryngeal oedema
		Laryngotracheal oedema
		Lip oedema
		Lip swelling
		Liver sarcoidosis
		Lupoid hepatic cirrhosis
		Lupus hepatitis
		Lupus nephritis
		Lupus pancreatitis
		Majeed's syndrome
		Mevalonate kinase deficiency
		Mevalonic aciduria

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Adverse event class	System organ class	Preferred term
Rare	Immune system disorders	Microscopic polyangiitis
		Mouth swelling
		Muckle-Wells syndrome
		Myeloperoxidase deficiency
		Neonatal alloimmune thrombocytopenia
		Neonatal lupus erythematosus
		Nephritis allergic
		Oculorespiratory syndrome
		Oedema mouth
		Omenn syndrome
		Oropharyngeal oedema
		Oropharyngeal swelling
		Periorbital oedema
		Pharyngeal oedema
		Primary immunodeficiency syndrome
		Pulmonary renal syndrome
		Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome
		Retroperitoneal fibrosis
		Reynold's syndrome
		Rhesus haemolytic disease of newborn
		Schimke immunoosseous dysplasia
		Stevens-Johnson syndrome
		Swelling face
		Swollen tongue
		Tongue oedema
		Toxic epidermal necrolysis
		Toxic skin eruption
		Tubulointerstitial nephritis and uveitis syndrome
		Tumour necrosis factor receptor-associated periodic syndrome
		Type I hypersensitivity
		Wiskott-Aldrich syndrome
		X-linked lymphoproliferative syndrome
	Infections and infestations	Activated PI3 kinase delta syndrome
		Acute focal bacterial nephritis
		Acute motor axonal neuropathy
		Acute motor-sensory axonal neuropathy
		Bacterascites
		Bickerstaff's encephalitis
		Cataract congenital
		Chronic hepatitis
		Clostridial infection
		Clostridial sepsis
		Clostridium bacteraemia
		Clostridium colitis
		Clostridium difficile colitis
		Clostridium difficile infection
		Congenital HIV infection
		Congenital condyloma
		Congenital cytomegalovirus infection

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Adverse event class	System organ class	Preferred term
Rare	Infections and infestations	Congenital hepatitis B infection
		Congenital herpes simplex infection
		Congenital infection
		Congenital malaria
		Congenital pneumonia
		Congenital rubella infection
		Congenital syphilis
		Congenital syphilitic encephalitis
		Congenital syphilitic meningitis
		Congenital syphilitic osteochondritis
		Congenital toxoplasmosis
		Congenital tuberculosis
		Congenital varicella infection
		Conjunctivitis gonococcal neonatal
		Cytomegalovirus nephritis
		Cytomegalovirus pancreatitis
		Fatal familial insomnia
		Gastroenteritis clostridial
		Guillain-Barre syndrome
		HIV associated nephropathy
		Hepatitis chronic active
		Hepatitis chronic persistent
		Hepatitis fulminant
		Hepatitis virus-associated nephropathy
		Infantile septic granulomatosis
		Intestinal sepsis
		Neutropenic infection
		Neutropenic sepsis
		Pancreas infection
		Pancreatic abscess
		Pancreatitis bacterial
		Pancreatitis fungal
		Pancreatitis helminthic
		Pancreatitis mumps
		Pancreatitis viral
		Pilonidal cyst congenital
		Post infection glomerulonephritis
		Post streptococcal glomerulonephritis
		Pseudomembranous colitis
		Retroperitonitis
		Reye's syndrome
		Shigella sepsis
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
		X-linked lymphoproliferative syndrome
		Young's syndrome
	Injury, poisoning and procedural complications	Acute generalised exanthematous pustulosis
		Acute graft versus host disease in liver
		Anaphylactic transfusion reaction
		Angiotensin converting enzyme inhibitor foetopathy

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Adverse event class	System organ class	Preferred term
Rare	Injury, poisoning and procedural complications	Bacterascites
		Bone marrow toxicity
		Chronic graft versus host disease in liver
		Dialysis membrane reaction
		Diethylstilboestrol syndrome
		Drug-induced liver injury
		Foetal alcohol syndrome
		Foetal anticonvulsant syndrome
		Foetal methotrexate syndrome
		Foetal retinoid syndrome
		Foetal warfarin syndrome
		Graft versus host disease in liver
		Haematotoxicity
		Hepatitis toxic
		Hepatotoxicity
		Junctional ectopic tachycardia
		Liver injury
		Nephritis radiation
		Nephropathy toxic
		Neuroleptic malignant syndrome
		Parenteral nutrition associated liver disease
		Platelet toxicity
		Radiation hepatitis
		Radiation leukopenia
		Serotonin syndrome
		Stevens-Johnson syndrome
		Teratogenicity
		Thalidomide embryopathy
		Toxic epidermal necrolysis
		Traumatic pancreatitis
	Investigations	Aspiration bone marrow abnormal
		B-lymphocyte count abnormal
		B-lymphocyte count decreased
		Band neutrophil count decreased
		Band neutrophil percentage decreased
		Basophil count abnormal
		Basophil count decreased
		Basophil percentage decreased
		Biopsy bone marrow abnormal
		Blood count abnormal
		Bone marrow myelogram abnormal
		Cardiac telemetry abnormal
		Clostridium test positive
		Differential white blood cell count abnormal
		ECG P wave inverted
		Electrocardiogram P wave abnormal
		Electrocardiogram PQ interval prolonged
		Electrocardiogram PQ interval shortened
		Electrocardiogram PR prolongation

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Adverse event class	System organ class	Preferred term
Rare	Investigations	Electrocardiogram PR shortened
		Electrocardiogram QRS complex prolonged
		Electrocardiogram QT prolonged
		Electrocardiogram RR interval prolonged
		Electrocardiogram U-wave abnormality
		Electrocardiogram abnormal
		Electrocardiogram ambulatory abnormal
		Electrocardiogram change
		Electrocardiogram delta waves abnormal
		Electrocardiogram repolarisation abnormality
		Eosinophil count abnormal
		Eosinophil count decreased
		Eosinophil percentage decreased
		Full blood count abnormal
		Full blood count decreased
		Granulocyte count decreased
		Granulocytes abnormal
		Heart rate abnormal
		Heart rate decreased
		Heart rate increased
		Heart rate irregular
		Icterus index increased
		Lymphocyte count abnormal
		Lymphocyte count decreased
		Lymphocyte percentage abnormal
		Lymphocyte percentage decreased
		Megakaryocytes decreased
		Metamyelocyte count decreased
		Monoblast count decreased
		Monocyte count abnormal
		Monocyte count decreased
		Monocyte percentage decreased
		Myeloblast count decreased
		Myeloblast percentage decreased
		Myelocyte count decreased
		Myelocyte percentage decreased
		Neutrophil count abnormal
		Neutrophil count decreased
		Neutrophil percentage decreased
		Plasma cells absent
		Plasmablast count decreased
		Platelet count decreased
		Promyelocyte count decreased
		Respiratory sinus arrhythmia magnitude abnormal
		Respiratory sinus arrhythmia magnitude decreased
		Respiratory sinus arrhythmia magnitude increased
		Retrograde p-waves
		Scan bone marrow abnormal
		T-lymphocyte count abnormal

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Adverse event class	System organ class	Preferred term
Rare	Investigations	T-lymphocyte count decreased
		White blood cell analysis abnormal
		White blood cell count abnormal
		White blood cell count decreased
	Metabolism and nutrition disorders	11-beta-hydroxylase deficiency
		17,20-desmolase deficiency
		17-alpha-hydroxylase deficiency
		2-Hydroxyglutaric aciduria
		20,22-desmolase deficiency
		21-hydroxylase deficiency
		3-hydroxyacetyl-coenzyme A dehydrogenase deficiency
		5-alpha-reductase deficiency
		Acetylcholinesterase deficiency
		Acrodermatitis enteropathica
		Acute phosphate nephropathy
		Adenine phosphoribosyl transferase deficiency
		Adrenal insufficiency neonatal
		Albinism
		Alkaptonuria
		Alpha-1 anti-trypsin deficiency
		Aminoaciduria
		Arginase deficiency
		Argininosuccinate lyase deficiency
		Argininosuccinate synthetase deficiency
		Aspartate-glutamate-transporter deficiency
		Aspartylglucosaminuria
		Barth syndrome
		Bartter's syndrome
		Beta ketothiolase deficiency
		Bilirubin excretion disorder
		Biotinidase deficiency
		CANDLE syndrome
		Canavan disease
		Carbamoyl phosphate synthetase deficiency
		Carbohydrate metabolism disorder
		Carnitine palmitoyltransferase deficiency
		Carnitine-acylcarnitine translocase deficiency
		Citrate transporter deficiency
		Congenital carnitine deficiency
		Congenital central diabetes insipidus
		Congenital disorder of glycosylation
		Congenital generalised lipodystrophy
		Congenital hyperthyroidism
		Congenital hypothyroidism
		Congenital intrinsic factor deficiency
		Congenital mitochondrial cytopathy

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Adverse event class	System organ class	Preferred term
Rare	Metabolism and nutrition disorders	Congenital nephrogenic diabetes insipidus
		Congenital oxalosis
		Craniotabes
		Crigler-Najjar syndrome
		Cystathionine beta-synthase deficiency
		Cystic fibrosis related diabetes
		Cystinosis
		Cystinuria
		Dent's disease
		Diabetic foetopathy
		Diabetic hepatopathy
		Diencephalic syndrome of infancy
		Dihydropyrimidine dehydrogenase deficiency
		Dubin-Johnson syndrome
		Dysmyelination
		Essential fructosuria
		Fabry's disease
		Familial high density lipoprotein deficiency
		Familial hypertriglyceridaemia
		Familial hypocalciuric hypercalcaemia
		Fanconi syndrome
		Fatty acid oxidation disorder
		Galactosaemia
		Gaucher's disease
		Gaucher's disease type I
		Gaucher's disease type II
		Gaucher's disease type III
		Gilbert's syndrome
		Gitelman's syndrome
		Glucose-6-phosphate dehydrogenase deficiency
		Glucose-galactose malabsorption
		Glutathione synthetase deficiency
		Glycogen storage disease type I
		Glycogen storage disease type II
		Glycogen storage disease type III
		Glycogen storage disease type IV
		Glycogen storage disease type V
		Glycogen storage disease type VI
		Glycogen storage disease type VII
		Glycogen storage disease type VIII
		Glycogen storage disorder
		Gorham's disease
		Haemochromatosis trait
		Hartnup disease
		Hepatic steato-fibrosis
		Hepatic steatosis
		Hepato-lenticular degeneration
		Hereditary fructose intolerance
		Hereditary haemochromatosis

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Adverse event class	System organ class	Preferred term
Rare	Metabolism and nutrition disorders	Hereditary hypophosphataemic rickets
		Hermansky-Pudlak syndrome
		Homocystinaemia
		Homocystinuria
		Hydroxyprolinaemia
		Hyper IgD syndrome
		Hyperbilirubinaemia
		Hyperinsulinism syndrome
		Hypermethioninaemia
		Hypermethioniuria
		Hyperprolinaemia
		Hypochondroplasia
		Hyponatriuria
		Hypophosphatasia
		Hypoxanthine-guanine phosphoribosyl transferase deficiency
		Inborn error in primary bile acid synthesis
		Inborn error of bilirubin metabolism
		Inborn error of lipid metabolism
		Inborn error of metabolism
		Krabbe's disease
		Lecithin-cholesterol acyltransferase deficiency
		Leukodystrophy
		Liddle's syndrome
		Lipid proteinosis
		Lipidosis
		Long-chain acyl-coenzyme A dehydrogenase deficiency
		Lysinuric protein intolerance
		Lysosomal acid lipase deficiency
		MELAS syndrome
		MLASA syndrome
		Maple syrup disease
		Medium-chain acyl-coenzyme A dehydrogenase deficiency
		Menkes' syndrome
		Metabolic myopathy
		Metachromatic leukodystrophy
		Methylenetetrahydrofolate reductase deficiency
		Methylenetetrahydrofolate reductase gene mutation
		Methylmalonic aciduria
		Mevalonate kinase deficiency
		Mitochondrial DNA deletion
		Mitochondrial DNA depletion
		Mitochondrial DNA mutation
		Mitochondrial enzyme deficiency
		Molybdenum cofactor deficiency
		Mucolipidosis

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Adverse event class	System organ class	Preferred term
Rare	Metabolism and nutrition disorders	Mucolipidosis type I
		Mucolipidosis type II
		Mucolipidosis type III
		Mucolipidosis type IV
		Mucopolysaccharidosis
		Mucopolysaccharidosis I
		Mucopolysaccharidosis II
		Mucopolysaccharidosis III
		Mucopolysaccharidosis IV
		Mucopolysaccharidosis V
		Mucopolysaccharidosis VI
		Mucopolysaccharidosis VII
		Multiple carboxylase deficiency
		N-acetylglutamate synthase deficiency
		Neonatal haemochromatosis
		Neuronal ceroid lipofuscinosis
		Niemann-Pick disease
		Non-alcoholic fatty liver
		Non-alcoholic steatohepatitis
		Nonketotic hyperglycinaemia
		Ornithine transcarbamoylase deficiency
		Oroticaciduria congenital
		Pelizaeus-Merzbacher disease
		Phenylketonuria
		Phytosterolaemia
		Porphyria
		Porphyria acute
		Porphyria non-acute
		Porphyrin metabolism disorder
		Porphyrinuria
		Prader-Willi syndrome
		Primary familial brain calcification
		Primary familial hypomagnesaemia
		Primary hypercholesterolaemia
		Primary insulin like growth factor-1 deficiency
		Pseudocholinesterase deficiency
		Pseudohypoparathyroidism
		Pyruvate carboxylase deficiency
		Refsum's disease
		Rett syndrome
		Rotor's syndrome
		Sarcosinaemia
		Short-chain acyl-coenzyme A dehydrogenase deficiency
		Steatohepatitis
		Sucrase-isomaltase deficiency
		Tangier disease
		Tay-Sachs disease
		Tetrahydrobiopterin deficiency
		Trifunctional protein deficiency
		Trimethylaminuria

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Adverse event class	System organ class	Preferred term
Rare	Metabolism and nutrition disorders	Type I hyperlipidaemia
		Type II hyperlipidaemia
		Type III hyperlipidaemia
		Type IIa hyperlipidaemia
		Type IIb hyperlipidaemia
		Type IV hyperlipidaemia
		Type V hyperlipidaemia
		Tyrosinaemia
		Very long-chain acyl-coenzyme A dehydrogenase deficiency
		Williams syndrome
		Wolfram syndrome
	Musculoskeletal and connective tissue disorders	18q minus syndrome
		3-hydroxyacetyl-coenzyme A dehydrogenase deficiency
		Aase syndrome
		Accessory carpal bone
		Accessory muscle
		Accessory navicular syndrome
		Adactyly
		Adult polyglucosan body disease
		Albright's disease
		Allan-Herndon-Dudley syndrome
		Amniotic band syndrome
		Apert's syndrome
		Arachnodactyly
		Arcuate foramen
		Asphyxiating thoracic dystrophy
		Becker's muscular dystrophy
		Benign congenital hypotonia
		Blau syndrome
		Bloom syndrome
		Brachycephaly
		Brachydactyly
		Branchial cleft sinus
		Branchial cyst
		Branchiogenic syndrome
		Bulbospinal muscular atrophy congenital
		Camptodactyly congenital
		Camptomelia
		Carpus curvus
		Cartilage-hair hypoplasia
		Caudal regression syndrome
		Central core disease
		Cervical auricle
		Cervical rib
		Chondrodystrophy
		Chondroectodermal dysplasia
		Chronic infantile neurological cutaneous and articular syndrome

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Adverse event class	System organ class	Preferred term
Rare	Musculoskeletal and connective tissue disorders	Cleft foot
		Cleft lip
		Cleidocranial dysostosis
		Clinodactyly
		Cohen syndrome
		Congenital absence of cranial vault
		Congenital absence of vertebra
		Congenital bowing of long bones
		Congenital clavicular agenesis
		Congenital claw toe
		Congenital cleft hand
		Congenital cutis laxa
		Congenital deformity of clavicle
		Congenital elevation of scapula
		Congenital fibrosarcoma
		Congenital flat feet
		Congenital floppy infant
		Congenital foot malformation
		Congenital hand malformation
		Congenital hyperextension of knee
		Congenital hyperextension of spine
		Congenital jaw malformation
		Congenital joint malformation
		Congenital knee deformity
		Congenital knee dislocation
		Congenital kyphoscoliosis
		Congenital limb hyperextension
		Congenital lip fistula
		Congenital multiplex arthrogryposis
		Congenital muscle absence
		Congenital musculoskeletal anomaly
		Congenital myopathy
		Congenital osteodystrophy
		Congenital pseudarthrosis
		Congenital scoliosis
		Congenital spinal fusion
		Congenital spinal stenosis
		Congenital spondylolisthesis
		Congenital spondylolysis
		Congenital syphilitic osteochondritis
		Congenital torticollis
		Cornelia de Lange syndrome
		Costello syndrome
		Craniofacial deformity
		Craniofacial dysostosis
		Craniolacunia
		Craniorachischisis
		Craniosynostosis
		Craniotabes
		Cryopyrin associated periodic syndrome
		Cyclopia

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Adverse event class	System organ class	Preferred term
Rare	Musculoskeletal and connective tissue disorders	Cystic angiomatosis
		Deficiency of the interleukin-1 receptor antagonist
		Dentofacial anomaly
		Dermatofibrosis lenticularis disseminata
		Developmental hip dysplasia
		Dubowitz syndrome
		Duchenne muscular dystrophy
		Dyschondrosteosis
		Dysgnathia
		Dysmorphism
		Ehlers-Danlos syndrome
		Ellis-van Creveld syndrome
		Epidermal naevus syndrome
		Faciodigitogenital dysplasia
		Facioscapulohumeral muscular dystrophy
		Familial cold autoinflammatory syndrome
		Familial scaphocephaly syndrome
		Familial tremor
		Femoral anteversion
		Femoral retroversion
		Femur-fibula-ulna complex
		Fibrodysplasia ossificans progressiva
		Fibrous dysplasia of bone
		Fibrous dysplasia of jaw
		Fibula agenesis
		Foramen magnum stenosis
		Freeman-Sheldon syndrome
		GNE myopathy
		Glycogen storage disease type II
		Glycogen storage disease type III
		Glycogen storage disease type V
		Glycogen storage disease type VII
		Gnathoschisis
		Gorham's disease
		Greig's syndrome
		Hand-foot-genital syndrome
		Hemivertebra
		Hereditary hypophosphataemic rickets
		Hereditary motor neurone disease
		Hereditary multiple osteochondromas
		Hyper IgD syndrome
		Hypertelorism of orbit
		Hypocalvaria
		Hypochondroplasia
		Hypoplastic nasal cartilage
		Hypotelorism of orbit
		Infantile cortical hyperostosis
		Iniencephaly
		Juvenile Paget's disease
		Kabuki make-up syndrome

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Adverse event class	System organ class	Preferred term
Rare	Musculoskeletal and connective tissue disorders	Kearns-Sayre syndrome
		Kenny-Caffey syndrome
		Kimmerle's anomaly
		Kinematic imbalances due to suboccipital strain
		Kleefstra syndrome
		Klippel-Feil syndrome
		Klippel-Trenaunay syndrome
		Kyphosis congenital
		Laron syndrome
		Larsen syndrome
		Limb hypoplasia congenital
		Limb malformation
		Limb reduction defect
		Long-chain acyl-coenzyme A dehydrogenase deficiency
		Lowry-Wood syndrome
		Lumbarisation
		Lupoid hepatic cirrhosis
		Lupus hepatitis
		Lupus nephritis
		Lupus pancreatitis
		MELAS syndrome
		MLASA syndrome
		Macrocephaly
		Macrocheilia
		Macrodactyly
		Macrogenia
		Macrognathia
		Macrostomia
		Majeed's syndrome
		Mandibulofacial dysostosis
		Marfan's syndrome
		Maxillonasal dysplasia
		Medium-chain acyl-coenzyme A dehydrogenase deficiency
		Meier-Gorlin syndrome
		Metabolic myopathy
		Metaphyseal dysplasia
		Metatarsus primus varus
		Microcephaly
		Microcheilia
		Microgenia
		Micrognathia
		Microstomia
		Mitochondrial encephalomyopathy
		Mitochondrial myopathy
		Monopodia
		Morton's syndrome
		Muckle-Wells syndrome
		Multiple epiphyseal dysplasia

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Adverse event class	System organ class	Preferred term
Rare	Musculoskeletal and connective tissue disorders	Muscular dystrophy
		Myoclonic epilepsy and ragged-red fibres
		Myotonia congenita
		Myotonic dystrophy
		Nail-patella syndrome
		Neonatal lupus erythematosus
		Neuroleptic malignant syndrome
		Nijmegen breakage syndrome
		Noonan syndrome
		Oculoauriculovertebral dysplasia
		Oculodentodigital dysplasia
		Opitz-G/BBB syndrome
		Oral-facial-digital syndrome type II
		Os trigonum
		Osteogenesis imperfecta
		Osteopathia striata
		Osteopetrosis
		Osteopoikilosis
		Osteoporosis-pseudoglioma syndrome
		Otocephaly
		PHACES syndrome
		Pachydermoperiostosis
		Parkes-Weber syndrome
		Pectus carinatum
		Pectus excavatum
		Phalangeal agenesis
		Phalangeal hypoplasia
		Pierre Robin syndrome
		Plagiocephaly
		Platybasia
		Platyspondylia
		Poland's syndrome
		Polydactyly
		Potter's syndrome
		Preauricular cyst
		Proteus syndrome
		Proximal focal femoral deficiency
		Pseudoxanthoma elasticum
		Pterygium colli
		Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome
		Radioulnar synostosis
		Reynold's syndrome
		Rib hypoplasia
		Rib synostosis
		Rippling muscle disease
		Rubinstein-Taybi syndrome
		Sacral hypoplasia
		Sacralisation
		Scaphocephaly
		Schimke immunoosseous dysplasia

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Adverse event class	System organ class	Preferred term
Rare	Musculoskeletal and connective tissue disorders	Schinzel-Giedion syndrome
		Serotonin syndrome
		Short-chain acyl-coenzyme A dehydrogenase deficiency
		Silver-Russell syndrome
		Sirenomelia
		Skeletal dysplasia
		Skull malformation
		Smith-Lemli-Opitz syndrome
		Sotos' syndrome
		Spinal muscular atrophy
		Spine malformation
		Spondyloepiphyseal dysplasia
		Stickler's syndrome
		Supernumerary vertebra
		Syndactyly
		Synostosis
		Talipes
		Thalidomide embryopathy
		Thanatophoric dwarfism
		Thrombocytopenia-absent radius syndrome
		Tibial torsion
		Transitional vertebrae
		Trichorhinophalangeal syndrome
		VACTERL syndrome
		Velo-cardio-facial syndrome
		Vertical talus
		Very long-chain acyl-coenzyme A dehydrogenase deficiency
		Weill-Marchesani syndrome
		Welander distal myopathy
		Werner's syndrome
		Wildervanck syndrome
		Winchester syndrome
		Wolf-Hirschhorn syndrome
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenomatous polyposis coli
		Basal cell naevus syndrome
		Biliary hamartoma
		Birt-Hogg-Dube syndrome
		Branchial cyst
		Carcinogenic effect in offspring
		Cardiac lymphangioma
		Carney complex
		Central nervous system dermoid tumour
		Choledochal cyst
		Congenital acrochordon
		Congenital benign neoplasm
		Congenital cerebral cyst

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Adverse event class	System organ class	Preferred term
Rare	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Congenital cerebral haemangioma
		Congenital choroid plexus cyst
		Congenital cyst
		Congenital cystic disease of liver
		Congenital cystic kidney disease
		Congenital eye naevus
		Congenital fibrosarcoma
		Congenital malignant neoplasm
		Congenital melanocytic naevus
		Congenital naevus
		Congenital neoplasm
		Congenital renal cyst
		Congenital retinoblastoma
		Congenital teratoma
		Congenital vaginal cyst
		Cowden's disease
		Cystic angiomatosis
		Cystic eyeball, congenital
		Cystic lymphangioma
		Denys-Drash syndrome
		Dermoid cyst
		Dysplastic naevus syndrome
		Epidermal naevus syndrome
		Familial haemophagocytic lymphohistiocytosis
		Familial medullary thyroid cancer
		Foetal cystic hygroma
		Gorham's disease
		Haemangioma congenital
		Haemangioma of retina
		Hamartoma
		Hamartoma vascular
		Hereditary leiomyomatosis renal cell carcinoma
		Hereditary multiple osteochondromas
		Hereditary non-polyposis colorectal cancer syndrome
		Hereditary papillary renal carcinoma
		Hypothalamic hamartoma
		Infantile septic granulomatosis
		Inferior vena cava syndrome
		Lipodermoid tumour
		Mesoblastic nephroma
		Mesonephric duct cyst
		Mismatch repair cancer syndrome
		Muir-Torre syndrome
		Multiple cutaneous and uterine leiomyomatosis
		Multiple endocrine neoplasia
		Multiple endocrine neoplasia Type 1

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Adverse event class	System organ class	Preferred term
Rare	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Multiple endocrine neoplasia Type 2
		Multiple endocrine neoplasia Type 2A
		Multiple endocrine neoplasia Type 2B
		Myelodysplastic syndrome
		Myelodysplastic syndrome transformation
		Myelofibrosis
		Myeloid metaplasia
		Neonatal leukaemia
		Neurofibromatosis
		Odontogenic cyst
		Oesophageal cyst
		Omenn syndrome
		Ota's naevus
		PHACES syndrome
		Paraneoplastic glomerulonephritis
		Paraneoplastic nephrotic syndrome
		Peutz-Jeghers syndrome
		Phakomatosis
		Primary myelofibrosis
		Splenic hamartoma
		Steatocystoma multiplex
		Thyroglossal cyst
		Tornwaldt cyst
		Trisomy 12
		Venous angioma of brain
		X-linked lymphoproliferative syndrome
	Nervous system disorders	18q minus syndrome
		2-Hydroxyglutaric aciduria
		Acute motor axonal neuropathy
		Acute motor-sensory axonal neuropathy
		Adams-Stokes syndrome
		Adrenoleukodystrophy
		Adult polyglucosan body disease
		Aicardi's syndrome
		Allan-Herndon-Dudley syndrome
		Alpers' disease
		Alternating hemiplegia of childhood
		Anencephaly
		Angelman's syndrome
		Arnold-Chiari malformation
		Asterixis
		Ataxia telangiectasia
		Auditory neuropathy spectrum disorder
		Baltic myoclonic epilepsy
		Basal cell naevus syndrome
		Becker's muscular dystrophy
		Benign congenital hypotonia
		Benign familial neonatal convulsions
		Bezold-Jarisch reflex
		Bickerstaff's encephalitis

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Adverse event class	System organ class	Preferred term
Rare	Nervous system disorders	Biotinidase deficiency
		Bloch-Sulzberger syndrome
		Brain malformation
		Bulbospinal muscular atrophy congenital
		CHARGE syndrome
		Canavan disease
		Caudal regression syndrome
		Central bradycardia
		Central nervous system dermoid tumour
		Cerebellar dysplasia
		Cerebellar hypoplasia
		Cerebral arteriovenous malformation haemorrhagic
		Cerebral atrophy congenital
		Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
		Cerebral dysgenesis
		Cerebral palsy
		Cerebrohepatorenal syndrome
		Cerebrovascular arteriovenous malformation
		Chronic infantile neurological cutaneous and articular syndrome
		Chronic inflammatory demyelinating polyradiculoneuropathy
		Citrate transporter deficiency
		Cobb syndrome
		Cockayne's syndrome
		Cohen syndrome
		Coma hepatic
		Congenital aqueductal stenosis
		Congenital brain damage
		Congenital central hypoventilation syndrome
		Congenital central nervous system anomaly
		Congenital cerebellar agenesis
		Congenital cerebral cyst
		Congenital cerebral haemangioma
		Congenital cerebrovascular anomaly
		Congenital choroid plexus cyst
		Congenital cranial nerve paralysis
		Congenital facial nerve hypoplasia
		Congenital flaccid paralysis
		Congenital floppy infant
		Congenital hemiparesis
		Congenital hydrocephalus
		Congenital neurological degeneration
		Congenital neurological disorder
		Congenital neuropathy
		Congenital nystagmus
		Congenital oculomotor apraxia

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Adverse event class	System organ class	Preferred term
Rare	Nervous system disorders	Congenital optic nerve anomaly
		Congenital spinal cord anomaly
		Congenital spinal stenosis
		Congenital syphilitic encephalitis
		Congenital syphilitic meningitis
		Congenital torticollis
		Congenital visual acuity reduced
		Cornelia de Lange syndrome
		Cortical dysplasia
		Craniolacunia
		Craniorachischisis
		Cri du Chat syndrome
		Dandy-Walker syndrome
		Deaf mutism
		Demyelinating polyneuropathy
		Dentatorubral-pallidoluysian atrophy
		Diastematomyelia
		Diencephalic syndrome of infancy
		Double cortex syndrome
		Duane's syndrome
		Dubowitz syndrome
		Duchenne muscular dystrophy
		Dysmyelination
		Early onset familial Alzheimer's disease
		Early onset primary dystonia
		Emanuel syndrome
		Encephalocele
		Epidermal naevus syndrome
		Epilepsy congenital
		Eyelid ptosis congenital
		Fabry's disease
		Facioscapulohumeral muscular dystrophy
		Familial amyloidosis
		Familial amyotrophic lateral sclerosis
		Familial hemiplegic migraine
		Familial infantile bilateral striatal necrosis
		Familial periodic paralysis
		Familial scaphocephaly syndrome
		Familial tremor
		Fatal familial insomnia
		Foetal alcohol syndrome
		Fragile X syndrome
		Friedreich's ataxia
		Galactosaemia
		Gaucher's disease
		Gaucher's disease type II
		Gaucher's disease type III
		Glucose transporter type 1 deficiency syndrome
		Glycogen storage disease type II
		Glycogen storage disease type III
		Glycogen storage disease type V

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Adverse event class	System organ class	Preferred term
Rare	Nervous system disorders	Glycogen storage disease type VII
		Greig's syndrome
		Guillain-Barre syndrome
		Hemimegalencephaly
		Hepatic encephalopathy
		Hepato-lenticular degeneration
		Hereditary areflexic dystasia
		Hereditary cerebral degeneration
		Hereditary motor and sensory neuropathy
		Hereditary motor neurone disease
		Hereditary neuropathic amyloidosis
		Hereditary neuropathy with liability to pressure palsies
		Hereditary spastic paraplegia
		Holoprosencephaly
		Huntington's disease
		Hydranencephaly
		Hyperexplexia
		Hypothalamic hamartoma
		Iniencephaly
		Intracranial arterial fenestration
		Intracranial lipoma
		Johanson-Blizzard syndrome
		Joubert syndrome
		Kabuki make-up syndrome
		Kearns-Sayre syndrome
		Kleefstra syndrome
		Krabbe's disease
		Lafora's myoclonic epilepsy
		Langer-Giedion syndrome
		Laurence-Moon-Bardet-Biedl syndrome
		Leukodystrophy
		Lipomeningocele
		Lissencephaly
		Loss of consciousness
		Lowry-Wood syndrome
		MELAS syndrome
		Marcus Gunn syndrome
		Melkersson-Rosenthal syndrome
		Membranous lipodystrophy
		Meningocele
		Meningomyelocele
		Menkes' syndrome
		Metabolic myopathy
		Metachromatic leukodystrophy
		Methylenetetrahydrofolate reductase deficiency
		Mevalonic aciduria
		Microencephaly
		Miller Fisher syndrome
		Minimal hepatic encephalopathy
		Mitochondrial encephalomyopathy

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Adverse event class	System organ class	Preferred term
Rare	Nervous system disorders	Mitochondrial neurogastrointestinal encephalopathy
		Moebius II syndrome
		Molybdenum cofactor deficiency
		Morning glory syndrome
		Mount-Reback syndrome
		Muscular dystrophy
		Myoclonic epilepsy and ragged-red fibres
		Myotonia congenita
		Myotonic dystrophy
		Neural tube defect
		Neurofibromatosis
		Neuroleptic malignant syndrome
		Neuronal ceroid lipofuscinosis
		Neuronal migration disorder
		Neuropathy, ataxia, retinitis pigmentosa syndrome
		Niemann-Pick disease
		Nonketotic hyperglycinaemia
		Norrie's disease
		Oculocerebrorenal syndrome
		Olfacto genital dysplasia
		Olfactory nerve agenesis
		Optic nerve hypoplasia
		Oral-facial-digital syndrome type II
		Osteoporosis-pseudoglioma syndrome
		PHACES syndrome
		Pachygyria
		Pelizaeus-Merzbacher disease
		Periventricular nodular heterotopia
		Perry syndrome
		Phakomatosis
		Phenylketonuria
		Polymicrogyria
		Porencephaly
		Porphyria acute
		Prader-Willi syndrome
		Primary cerebellar degeneration
		Primary familial brain calcification
		Progressive cerebellar degeneration
		Progressive external ophthalmoplegia
		Rathke's cleft cyst
		Refsum's disease
		Rett syndrome
		Reye's syndrome
		Riley-Day syndrome
		Rippling muscle disease
		Rubinstein-Taybi syndrome
		Schinzel-Giedion syndrome
		Schizencephaly
		Sensory neuropathy hereditary
		Septo-optic dysplasia
		Septum pellucidum agenesis

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Adverse event class	System organ class	Preferred term
Rare	Nervous system disorders	Serotonin syndrome
		Severe myoclonic epilepsy of infancy
		Sjogren-Larsson syndrome
		Smith-Lemli-Opitz syndrome
		Spina bifida
		Spina bifida cystica
		Spina bifida occulta
		Spinal muscular atrophy
		Spinal vessel congenital anomaly
		Spinocerebellar ataxia
		Strabismus congenital
		Sturge-Weber syndrome
		Subependymal nodular heterotopia
		Syncope
		Syringomyelia
		Tay-Sachs disease
		Tetrahydrobiopterin deficiency
		Timothy syndrome
		Tourette's disorder
		Trisomy 13
		Trisomy 14
		Trisomy 17
		Trisomy 18
		Trisomy 21
		Trisomy 22
		Tuberous sclerosis
		Vein of Galen aneurysmal malformation
		Velo-cardio-facial syndrome
		Venous angioma of brain
		Vertebral artery hypoplasia
		Von Hippel-Lindau disease
		Welander distal myopathy
		Williams syndrome
		Wolf-Hirschhorn syndrome
		Wyburn Mason's syndrome
	Pregnancy, puerperium and perinatal conditions	ABO haemolytic disease of newborn
		Acardia
		Adrenal insufficiency neonatal
		Alveolar capillary dysplasia
		Amniotic band syndrome
		Angiotensin converting enzyme inhibitor foetopathy
		Arrhythmia neonatal
		Atrioventricular node dispersion
		Baseline foetal heart rate variability disorder
		Benign familial neonatal convulsions
		Blood incompatibility haemolytic anaemia of newborn
		Bradycardia foetal
		Bradycardia neonatal
		Cardiac arrest neonatal

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Adverse event class	System organ class	Preferred term
Rare	Pregnancy, puerperium and perinatal conditions	Cardio-respiratory arrest neonatal
		Cerebral palsy
		Collodion baby
		Congenital HIV infection
		Congenital chylothorax
		Congenital condyloma
		Congenital cytomegalovirus infection
		Congenital floppy infant
		Congenital hepatitis B infection
		Congenital herpes simplex infection
		Congenital infection
		Congenital malaria
		Congenital pneumonia
		Congenital pulmonary hypertension
		Congenital rubella infection
		Congenital syphilis
		Congenital syphilitic encephalitis
		Congenital syphilitic meningitis
		Congenital toxoplasmosis
		Congenital tuberculosis
		Congenital varicella infection
		Conjoined twins
		Conjunctivitis gonococcal neonatal
		Craniotabes
		Diabetic foetopathy
		Diethylstilboestrol syndrome
		Ductus arteriosus premature closure
		Ductus venosus agenesis
		Erythroblastosis foetalis
		Foetal alcohol syndrome
		Foetal anticonvulsant syndrome
		Foetal arrhythmia
		Foetal chromosome abnormality
		Foetal heart rate acceleration abnormality
		Foetal heart rate deceleration abnormality
		Foetal heart rate disorder
		Foetal malformation
		Foetal methotrexate syndrome
		Foetal renal impairment
		Foetal retinoid syndrome
		Foetal tachyarrhythmia
		Foetal warfarin syndrome
		Granulocytopenia neonatal
		Harlequin foetus
		Hypopituitarism foetal
		Inferior vena cava syndrome
		Junctional ectopic tachycardia
		Leukopenia neonatal
		Lymphocytopenia neonatal
		Neonatal alloimmune thrombocytopenia

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Adverse event class	System organ class	Preferred term
Rare	Pregnancy, puerperium and perinatal conditions	Neonatal anuria
		Neonatal haemochromatosis
		Neonatal leukaemia
		Neonatal lupus erythematosus
		Neonatal tachycardia
		Netherton's syndrome
		Neutropenia neonatal
		Nonketotic hyperglycinaemia
		Nonreassuring foetal heart rate pattern
		Persistent foetal circulation
		Primary familial hypomagnesaemia
		Pulmonary lymphangiectasia
		Renal failure neonatal
		Renal impairment neonatal
		Rhesus haemolytic disease of newborn
		Single umbilical artery
		Tachycardia foetal
		Thalidomide embryopathy
		Twin reversed arterial perfusion sequence malformation
		Umbilical artery hypoplasia
		Umbilical malformation
		Virilism foetal
	Psychiatric disorders	2-Hydroxyglutaric aciduria
		Allan-Herndon-Dudley syndrome
		Baltic myoclonic epilepsy
		CHARGE syndrome
		Cohen syndrome
		Congenital brain damage
		Cornelia de Lange syndrome
		Cri du Chat syndrome
		Deaf mutism
		Diencephalic syndrome of infancy
		Dubowitz syndrome
		Early onset familial Alzheimer's disease
		Emanuel syndrome
		Familial scaphocephaly syndrome
		Fragile X syndrome
		Galactosaemia
		Greig's syndrome
		Johanson-Blizzard syndrome
		Kabuki make-up syndrome
		Kleefstra syndrome
		Langer-Giedion syndrome
		Laurence-Moon-Bardet-Biedl syndrome
		Membranous lipodystrophy
		Mevalonic aciduria
		Norrie's disease
		Oculocerebrorenal syndrome
		Osteoporosis-pseudoglioma syndrome
		Perry syndrome
		Phenylketonuria

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Adverse event class	System organ class	Preferred term
Rare	Psychiatric disorders	Porphyria acute
		Prader-Willi syndrome
		Primary familial brain calcification
		Rett syndrome
		Rubinstein-Taybi syndrome
		Schinzel-Giedion syndrome
		Sjogren-Larsson syndrome
		Smith-Lemli-Opitz syndrome
		Tetrahydrobiopterin deficiency
		Timothy syndrome
		Tourette's disorder
		Trisomy 14
		Trisomy 17
		Trisomy 18
		Trisomy 21
		Trisomy 22
		Velo-cardio-facial syndrome
		Williams syndrome
		Wolf-Hirschhorn syndrome
	Renal and urinary disorders	2-Hydroxyglutaric aciduria
		Accessory kidney
		Acute focal bacterial nephritis
		Acute kidney injury
		Acute phosphate nephropathy
		Acute prerenal failure
		Adult polyglucosan body disease
		Alkaptonuria
		Alport's syndrome
		Aminoaciduria
		Anuria
		Aspartylglucosaminuria
		Autoimmune nephritis
		Azotaemia
		Barakat syndrome
		Bartter's syndrome
		Benign familial haematuria
		Berdon's syndrome
		Bladder agenesis
		Branchio-oto-renal syndrome
		C3 glomerulopathy
		CHARGE syndrome
		Chronic autoimmune glomerulonephritis
		Cloacal exstrophy
		Congenital bladder anomaly
		Congenital bladder diverticulum
		Congenital bladder neck obstruction
		Congenital calyceal diverticulum
		Congenital cystic kidney disease
		Congenital ectopic bladder
		Congenital genitourinary abnormality
		Congenital hydrocele renalis
		Congenital hydronephrosis

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Adverse event class	System organ class	Preferred term
Rare	Renal and urinary disorders	Congenital megaureter
		Congenital nephrogenic diabetes insipidus
		Congenital nephrotic syndrome
		Congenital oxalosis
		Congenital pyelocaliectasis
		Congenital renal cyst
		Congenital renal disorder
		Congenital ureteric anomaly
		Congenital ureterocele
		Congenital ureterovesical junction anomaly
		Congenital urethral anomaly
		Congenital urinary tract obstruction
		Congenital vesicoureteric reflux
		Cystinosis
		Cystinuria
		Cytomegalovirus nephritis
		Dent's disease
		Denys-Drash syndrome
		Double ureter
		Eagle Barrett syndrome
		Ectopic kidney
		Ectopic ureter
		Epispadias
		Essential fructosuria
		Extrarenal pelvis
		Familial hypocalciuric hypercalcaemia
		Familial renal glycosuria
		Fanconi syndrome
		Fibrillary glomerulonephritis
		Focal segmental glomerulosclerosis
		Foetal megacystis
		Foetal renal impairment
		Gitelman's syndrome
		Glomerulonephritis
		Glomerulonephritis acute
		Glomerulonephritis chronic
		Glomerulonephritis membranoproliferative
		Glomerulonephritis membranous
		Glomerulonephritis minimal lesion
		Glomerulonephritis proliferative
		Glomerulonephritis rapidly progressive
		Goodpasture's syndrome
		Granulomatosis with polyangiitis
		HIV associated nephropathy
		Hand-foot-genital syndrome
		Henoch-Schonlein purpura nephritis
		Hepatitis virus-associated nephropathy
		Hepatorenal failure
		Hepatorenal syndrome

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Rare	Renal and urinary disorders	Hereditary leiomyomatosis renal cell carcinoma
		Hereditary papillary renal carcinoma
		Hollow visceral myopathy
		Homocystinuria
		Hydronephrosis
		Hydroureter
		Hypermethioniuria
		Hyponatriuria
		Hypospadias
		IgA nephropathy
		IgM nephropathy
		Immunotactoid glomerulonephritis
		Kaufman-McKusick syndrome
		Kidney duplex
		Kidney malformation
		Kidney malrotation
		Liddle's syndrome
		Lupus nephritis
		MYH9-related disease
		Mesangioproliferative glomerulonephritis
		Methylmalonic aciduria
		Microscopic polyangiitis
		Nail-patella syndrome
		Neonatal anuria
		Nephritic syndrome
		Nephritis
		Nephritis allergic
		Nephritis haemorrhagic
		Nephritis radiation
		Nephropathy toxic
		Nephrotic syndrome
		Obstructive uropathy
		Oculocerebrorenal syndrome
		Oliguria
		Opitz-G/BBB syndrome
		Oroticaciduria congenital
		Pancreatorenal syndrome
		Paraneoplastic glomerulonephritis
		Paraneoplastic nephrotic syndrome
		Pelvi-ureteric obstruction
		Pelvic kidney
		Perinephritis
		Persistent cloaca
		Persistent urogenital sinus
		Phenylketonuria
		Porphyrinuria
		Post infection glomerulonephritis
		Post streptococcal glomerulonephritis
		Potter's syndrome
		Prerenal failure
		Primary familial hypomagnesaemia
		Pulmonary renal syndrome

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Rare	Renal and urinary disorders	Renal aplasia
		Renal arteriovenous malformation
		Renal dysplasia
		Renal failure
		Renal failure neonatal
		Renal fusion anomaly
		Renal hypoplasia
		Renal impairment
		Renal impairment neonatal
		Renal malposition
		Retroperitoneal fibrosis
		Schinzel-Giedion syndrome
		Sirenomelia
		Tubulointerstitial nephritis
		Tubulointerstitial nephritis and uveitis syndrome
		Urachal abnormality
		Ureteric atresia
		Ureteric compression
		Ureteric dilatation
		Ureteric obstruction
		Ureteric stenosis
		Urethral atresia
		Urethral valves
		Urinary tract malformation
	Reproductive system and breast disorders	Accessory breast
		Adrenogenital syndrome
		Albright's disease
		Androgen insensitivity syndrome
		Anorchism
		Breast malformation
		Buried penis syndrome
		Chordee
		Cloacal exstrophy
		Congenital androgen deficiency
		Congenital fallopian tube anomaly
		Congenital genital malformation
		Congenital genital malformation female
		Congenital genital malformation male
		Congenital genitourinary abnormality
		Congenital labia pudendi adhesions
		Congenital monorchidism
		Congenital ovarian anomaly
		Congenital scrotal hypertrophy
		Congenital teratoma
		Congenital uterine anomaly
		Congenital vaginal cyst
		Congenital varicocele
		Congenital vas deferens absence
		Cryptorchism
		Denys-Drash syndrome

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Rare	Reproductive system and breast disorders	Diethylstilboestrol syndrome
		Disorder of sex development
		Ectopic ovary
		Epispadias
		Faciodigitogenital dysplasia
		Frenulum breve
		Fryns syndrome
		Genitalia external ambiguous
		Hermaphroditism
		Hooded prepuce
		Hydrocele
		Hypospadias
		Imperforate hymen
		Mayer-Rokitansky-Kuster-Hauser syndrome
		Mesonephric duct cyst
		Micropenis
		Multiple cutaneous and uterine leiomyomatosis
		Olfacto genital dysplasia
		Ovarian agenesis
		Ovarian hypoplasia
		Penile torsion
		Penoscrotal fusion
		Penoscrotal transposition
		Persistent cloaca
		Persistent urogenital sinus
		Phimosis
		Primary ciliary dyskinesia
		Pseudohermaphroditism
		Pseudohermaphroditism female
		Pseudohermaphroditism male
		Reproductive tract hypoplasia, male
		Septate hymen
		Sertoli-cell-only syndrome
		Testicular dysplasia
		Testotoxicosis
		Uterine aplasia
		Uterine cervix hypoplasia
		Uterine hypoplasia
		Vaginal atresia
		Vaginal hypoplasia
		Vaginal septum
		Virilism foetal
		Young's syndrome
	Respiratory, thoracic and mediastinal disorders	Alveolar capillary dysplasia
		Angioedema
		Azygos lobe
		Bronchogenic cyst
		CHARGE syndrome
		Cardio-respiratory arrest
		Cardio-respiratory arrest neonatal

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Rare	Respiratory, thoracic and mediastinal disorders	Choanal atresia
		Choanal stenosis
		Congenital bronchiectasis
		Congenital bronchomalacia
		Congenital central hypoventilation syndrome
		Congenital chylothorax
		Congenital cystic lung
		Congenital diaphragmatic anomaly
		Congenital diaphragmatic eventration
		Congenital diaphragmatic hernia
		Congenital emphysema
		Congenital epiglottal anomaly
		Congenital hiatus hernia
		Congenital high airway obstruction syndrome
		Congenital laryngeal stridor
		Congenital nose malformation
		Congenital perforated nasal septum
		Congenital pharyngeal anomaly
		Congenital pneumonia
		Congenital pulmonary hypertension
		Congenital tracheomalacia
		Cystic fibrosis
		Cystic fibrosis lung
		Diaphragmatic aplasia
		Diverticulum of pharynx, congenital
		Fryns syndrome
		Goodpasture's syndrome
		Granulomatosis with polyangiitis
		Hepatic hydrothorax
		Hepatopulmonary syndrome
		Laryngeal cleft
		Laryngeal oedema
		Laryngeal web
		Laryngo-onycho-cutaneous syndrome
		Laryngocele
		Laryngomalacia
		Laryngotracheal oedema
		Nasopharyngeal atresia
		Oculopharyngeal dystrophy
		Oculorespiratory syndrome
		Oropharyngeal oedema
		Oropharyngeal swelling
		Paranasal sinus aplasia
		Pectus carinatum
		Pectus excavatum
		Perry syndrome
		Pharyngeal oedema
		Portopulmonary hypertension
		Primary ciliary dyskinesia
		Pulmonary aplasia

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Rare	Respiratory, thoracic and mediastinal disorders	Pulmonary arteriovenous fistula
		Pulmonary artery stenosis congenital
		Pulmonary hypoplasia
		Pulmonary lymphangiectasia
		Pulmonary malformation
		Pulmonary renal syndrome
		Pulmonary sequestration
		Respiratory tract malformation
		Right-to-left cardiac shunt
		Tornwaldt cyst
		Tracheal atresia
		Tracheal web
		Tracheo-oesophageal fistula
		VACTERL syndrome
		Young's syndrome
	Skin and subcutaneous tissue disorders	Abnormal palmar/plantar creases
		Achromotrichia congenital
		Acral peeling skin syndrome
		Acrodermatitis enteropathica
		Acrokeratosis verruciformis
		Acute generalised exanthematous pustulosis
		Adams-Oliver syndrome
		Albinism
		Albright's disease
		Angioedema
		Aplasia cutis congenita
		Ash leaf macule
		Ataxia telangiectasia
		Basal cell naevus syndrome
		Benign familial pemphigus
		Birt-Hogg-Dube syndrome
		Birth mark
		Blau syndrome
		Bloch-Sulzberger syndrome
		Bloom syndrome
		CANDLE syndrome
		Carney complex
		Cholestatic pruritus
		Chronic infantile neurological cutaneous and articular syndrome
		Circumoral oedema
		Cobb syndrome
		Collodion baby
		Congenital acrochordon
		Congenital cutis laxa
		Congenital dermal sinus
		Congenital dyskeratosis
		Congenital ectodermal dysplasia
		Congenital eyelid malformation
		Congenital generalised lipodystrophy

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Rare	Skin and subcutaneous tissue disorders	Congenital hair disorder
		Congenital hypertrichosis
		Congenital melanocytic naevus
		Congenital melanosis
		Congenital naevus
		Congenital nail disorder
		Congenital pigmentation disorder
		Congenital poikiloderma
		Congenital skin dimples
		Congenital skin disorder
		Congenital trichomegaly
		Cullen's sign
		Cutaneous vasculitis
		Cutaneovisceral angiomatosis with thrombocytopenia
		Deficiency of the interleukin-36 receptor antagonist
		Dermatitis bullous
		Dermatitis exfoliative
		Dermatitis exfoliative generalised
		Dermatofibrosis lenticularis disseminata
		Dermatoglyphic anomaly
		Dowling-Degos disease
		Drug reaction with eosinophilia and systemic symptoms
		Dysplastic naevus syndrome
		Ehlers-Danlos syndrome
		Epidermal naevus
		Epidermal naevus syndrome
		Epidermal necrosis
		Epidermolysis
		Epidermolysis bullosa
		Erythema multiforme
		Erythrokeratodermia variabilis
		Exfoliative rash
		Eyelid oedema
		Fabry's disease
		Face oedema
		Familial cold autoinflammatory syndrome
		Gleich's syndrome
		Grey Turner's sign
		Harlequin foetus
		Hartnup disease
		Henoch-Schonlein purpura nephritis
		Hereditary angioedema
		Hereditary haemorrhagic telangiectasia
		Hereditary palmoplantar keratoderma
		Hermansky-Pudlak syndrome
		Hyper IgD syndrome
		Hypomelanosis of Ito
		Ichthyosis
		Idiopathic angioedema

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Rare	Skin and subcutaneous tissue disorders	Intestinal angioedema
		Jaundice
		Keratitis-ichthyosis-deafness syndrome
		Keratolysis exfoliativa congenital
		Keratosis follicular
		Laryngeal oedema
		Laryngo-onycho-cutaneous syndrome
		Laryngotracheal oedema
		Lichen spinulosus
		Lip oedema
		Lip swelling
		Melkersson-Rosenthal syndrome
		Menkes' syndrome
		Mouth swelling
		Muir-Torre syndrome
		Multiple cutaneous and uterine leiomyomatosis
		Multiple lentigines syndrome
		Naevus anaemicus
		Naevus flammeus
		Naevus spider congenital
		Nail-patella syndrome
		Neonatal lupus erythematosus
		Netherton's syndrome
		Oculomucocutaneous syndrome
		Oculorespiratory syndrome
		Oedema mouth
		Olmsted syndrome
		Oropharyngeal oedema
		Oropharyngeal swelling
		Ota's naevus
		Periorbital oedema
		Peutz-Jeghers syndrome
		Phakomatosis
		Pharyngeal oedema
		Pilonidal cyst congenital
		Platonychia
		Porokeratosis
		Porphyria non-acute
		Postauricular fistula
		Progeria
		Proteus syndrome
		Pseudoxanthoma elasticum
		Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome
		Reynold's syndrome
		Sclerotylosis
		Sebaceous naevus
		Sjogren-Larsson syndrome
		Skin hypoplasia
		Skin malformation
		Skin necrosis

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Rare	Skin and subcutaneous tissue disorders	Steatocystoma multiplex
		Stevens-Johnson syndrome
		Sturge-Weber syndrome
		Supernumerary nipple
		Swelling face
		Swollen tongue
		Telangiectasia congenital
		Tongue oedema
		Toxic epidermal necrolysis
		Toxic skin eruption
		Tuberous sclerosis
		Tumour necrosis factor receptor-associated periodic syndrome
		Umbilical malformation
		Waardenburg syndrome
		Wiskott-Aldrich syndrome
		Xeroderma pigmentosum
		Yellow skin
	Surgical and medical procedures	Continuous haemodiafiltration
		Dialysis
		Gastric variceal injection
		Gastric variceal ligation
		Haemodialysis
		Haemofiltration
		Hepatectomy
		Hepatic encephalopathy prophylaxis
		Liver and small intestine transplant
		Liver dialysis
		Liver operation
		Liver transplant
		Pancreatic pseudocyst drainage
		Peritoneal dialysis
		Renal and liver transplant
	Vascular disorders	Acute prerenal failure
		Alveolar capillary dysplasia
		Anaphylactic reaction
		Anaphylactic shock
		Anaphylactoid reaction
		Anaphylactoid shock
		Anomalous pulmonary venous connection
		Aorta hypoplasia
		Aorticopulmonary septal defect
		Arteriovenous malformation
		Benign familial haematuria
		Bezold-Jarisch reflex
		Bone marrow necrosis
		Cerebral arteriovenous malformation haemorrhagic
		Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Rare	Vascular disorders	Cerebrovascular arteriovenous malformation
		Circulatory collapse
		Coarctation of the aorta
		Cobb syndrome
		Congenital aortic anomaly
		Congenital aortic atresia
		Congenital aortic dilatation
		Congenital aortic stenosis
		Congenital arterial malformation
		Congenital arteriovenous fistula
		Congenital cardiovascular anomaly
		Congenital cerebral haemangioma
		Congenital cerebrovascular anomaly
		Congenital coronary artery malformation
		Congenital gastrointestinal vessel anomaly
		Congenital great vessel anomaly
		Congenital lymphoedema
		Congenital pulmonary artery anomaly
		Congenital varicocele
		Corrected transposition of great vessels
		Cullen's sign
		Cutaneous vasculitis
		Diencephalic syndrome of infancy
		Disseminated intravascular coagulation
		Ductus arteriosus premature closure
		Ductus arteriosus stenosis foetal
		Ductus venosus agenesis
		Duodenal varices
		Encephalocutaneous angiomatosis
		Familial hemiplegic migraine
		Gallbladder varices
		Gastric varices
		Gastric varices haemorrhage
		Gastrointestinal arteriovenous malformation
		Gorham's disease
		Granulomatosis with polyangiitis
		Grey Turner's sign
		Haemangioma congenital
		Haemangioma of retina
		Haemorrhagic arteriovenous malformation
		Haemorrhagic necrotic pancreatitis
		Hamartoma vascular
		Henoch-Schonlein purpura nephritis
		Hepatic arteriovenous malformation
		Hepatic fibrosis
		Hepatic steato-fibrosis
		Hereditary haemorrhagic telangiectasia
		Inferior vena cava syndrome
		Interruption of aortic arch
		Intestinal varices

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Rare	Vascular disorders	Intestinal varices haemorrhage
		Intracranial arterial fenestration
		Ischaemic hepatitis
		Ischaemic pancreatitis
		Klippel-Trenaunay syndrome
		Kounis syndrome
		Left ventricle outflow tract obstruction
		Liddle's syndrome
		Malformation venous
		Marfan's syndrome
		Microscopic polyangiitis
		Naevus anaemicus
		Naevus flammeus
		Naevus spider congenital
		Nephritis haemorrhagic
		Non-cirrhotic portal hypertension
		Oesophageal varices haemorrhage
		PHACES syndrome
		Pancreatic haemorrhage
		Parkes-Weber syndrome
		Patent ductus arteriosus
		Peripancreatic varices
		Persistent foetal circulation
		Persistent left superior vena cava
		Portal fibrosis
		Portal hypertension
		Portal hypertensive colopathy
		Portal hypertensive enteropathy
		Portal hypertensive gastropathy
		Portal vein cavernous transformation
		Portal vein dilatation
		Portal venous system anomaly
		Portopulmonary hypertension
		Preduodenal portal vein
		Prerenal failure
		Proximal focal femoral deficiency
		Pseudotruncus arteriosus
		Pseudoxanthoma elasticum
		Pulmonary arteriovenous fistula
		Pulmonary artery stenosis congenital
		Pulmonary lymphangiectasia
		Renal arteriovenous malformation
		Renal vessel congenital anomaly
		Retinal arteriovenous malformation
		Retinopathy congenital
		Retrograde portal vein flow
		Right aortic arch
		Right ventricle outflow tract obstruction
		Right-to-left cardiac shunt
		Scimitar syndrome
		Shock
		Shock symptom

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Rare	Vascular disorders	Single umbilical artery
		Spinal vessel congenital anomaly
		Splenic hamartoma
		Splenic varices
		Splenic varices haemorrhage
		Sturge-Weber syndrome
		Syncope
		Telangiectasia congenital
		Transposition of the great vessels
		Truncus arteriosus persistent
		Umbilical artery hypoplasia
		VACTERL syndrome
		Varices oesophageal
		Varicose veins of abdominal wall
		Vascular malformation
		Vein of Galen aneurysmal malformation
		Venous angioma of brain
		Vertebral artery hypoplasia
		Von Hippel-Lindau disease
		White nipple sign
		Wyburn Mason's syndrome
Refraction disorders	Eye disorders	Accommodation disorder
		Acute myopia
		Altered visual depth perception
		Aniseikonia
		Anisometropia
		Antimetropia
		Astigmatism
		Hypermetropia
		Myopia
		Pathologic myopia
		Presbyopia
		Pseudomyopia
		Refraction disorder
Suspected transmission of infectious agent	Infections and infestations	Air-borne transmission
		Bacterial disease carrier
		Community acquired infection
		Diphtheria carrier
		Direct infection transmission
		Faecal-oral transmission of infection
		HIV carrier
		HTLV-1 carrier
		Human immunodeficiency virus transmission
		Iatrogenic infection
		Indirect infection transmission
		Infection transmission via personal contact
		Infection via vaccinee

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Preferred terms used for search for adverse events - cardiovascular, diabetic retinopathy, refraction disorders, peripheral neuropathy, rare events and suspected transmission of infectious agent via trial product adverse events - listing

Adverse event class	System organ class	Preferred term
Suspected transmission of infectious agent	Infections and infestations	Infectious disease carrier
		Mycobacterial disease carrier
		Nosocomial infection
		Primary transmission
		Secondary transmission
		Sexual transmission of infection
		Sexually transmitted disease carrier
		Suspected transmission of an infectious agent via product
		Transmission of an infectious agent via product
		Typhoid carrier
		Vaccine virus shedding
		Vector-borne transmission of infection
		Vertical infection transmission
		Viral hepatitis carrier

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2.7.4.7.8.2. 器官別大分類別及び基本語別の解析に含めた有害事象の検索方法

Title for search	**Search – all in MedDRA version 20.0**
Cardiovascular disorders	SMQ_Ischaemic heart disease (narrow terms) + SMQ_Central nervous vascular disorders (narrow terms)
Medication errors	SMQ_medication errors (broad and narrow terms)
Immunogenicity-related events (allergic reactions)	SMQ_Anaphylactic reaction (narrow terms) SMQ_Angioedema (narrow terms) SMQ_Severe cutaneous reactions (narrow terms) SMQ_Anaphylactic/anaphylactoid shock conditions (narrow terms) SMQ_Hypersensiticity (narrow terms)
Injection/infusion site and lipodystrophy	HLT_Application and installation site reactions HLT_Administration site reactions NEC HLT_Infusion site reactions HLT_Injection site reactions HLT_lipodystrophies

	Including both primary and secondary PTs
Peripheral oedema	PT_generalised oedema PT_oedema PT_oedema peripheral PT_gravitational oedema
Eye disorder – diabetic retinopathy	List of PTs: 'Amaurosis' 'Diabetic blindness' 'Diabetic eye disease' 'Diabetic glaucoma' 'Diabetic retinal oedema' 'Diabetic retinopathy' 'Diabetic uveitis' 'Exudative retinopathy' 'Macular oedema' 'Macular opacity' 'Maculopathy' 'Night blindness' 'Papilloedema' 'Retinal deposits' 'Retinal detachment' 'Retinal exudates' 'Retinal haemorrhage' 'Retinal ischaemia' 'Retinal oedema' 'Retinal pallor' 'Retinal vascular occlusion' 'Retinopathy' 'Retinopathy proliferative' 'Sudden visual loss' 'Visual acuity reduced' 'Visual acuity reduced transiently' 'Vitreous detachment' 'Vitreous haemorrhage' 'Vitreous opacities' 'Retinal neovascularisation' 'Cystoid macular oedema' 'Macular pseudohole' 'Papillophlebitis' 'Macular ischaemia' 'Vitreal cells'
Eye disorder – refraction disorders	HLT_Refractive and accomodative disorders Excluding secondary terms
Peripheral neuropathy	SMQ_peripheral neuropathy (broad and narrow terms) PT_Diabetic neuropathy PT_Diabetic mononeuropathy PT_Diabetic autonomin neuropathy
Hyperglycaemia	In NN1218-4101: Identified by the hyperglycaemic event form
Unexplained hyperglycaemia	In NN1218-3854: Identified via the unexplained hyperglycaemic event form
Rare events	SMQ_Acute renal failure (narrow terms) SMQ_Agranulocytosis (narrow terms) SMQ_Anaphylactic reaction (narrow terms) SMQ_Cardiac arrhythmias (broad and narrow terms) SMQ_Cholestasis and jaundice of hepatic origin (broad and narrow terms)

	SMQ_Guillain-Barre syndrome (narrow terms) SMQ_Haematopoietic cytopenias affecting more than one type of blood cell (broad and narrow) SMQ_Haematopoietic leukopenia (broad and narrow terms) SMQ_Haematopoietic thrombocytopenia (narrow terms) SMQ_Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow terms) SMQ_Hepatitis, non-infectious (broad and narrow terms) SMQ_Severe cutaneous adverse reactions (narrow terms) SMQ_Interstitial lung disease (narrow terms) SMQ_Neuroleptic malignant syndrome (narrow terms) SMQ_Pseudomembranous colitis (narrow terms) SMQ_Retroperitoneal fibrosis (narrow terms) SMQ_Acute Pancreatitis (narrow (A) terms) SOC_Congenital, familial and genetic disorders (primary and secondary routed PTs) HLT_Acute and chronic pancreatitis (primary and secondary routed PTs) HLT_Angioedemas (primary and secondary routed PTs) HLT_Glomerulonephritis and nephrotic syndrome (primary and secondary routed PTs) HLT_Nephritis NEC (primary and secondary routed PTs) PT_disseminated intravascular coagulation PT_Multi-organ failure
Suspected transmission of infectious agent via trial product	HLT_Infectious dirsorders carrier (only primary terms) HLT_Infectious transmission (only primary terms)

2.7.4.7.8.3. 自動車運転及び機械操作の能力又は精神機能の障害に関連する有害事象の検索に用いた基本語の一覧

Adverse event class	System organ class	Preferred term
Ability to drive	Cardiac disorders	Dizziness
		Dizziness postural
		Presyncope
		Syncope
	Ear and labyrinth disorders	Vertigo
		Vestibular disorder
	Eye disorders	Metamorphopsia
		Vision blurred
		Visual impairment
	General disorders and administration site conditions	Asthenia
		Fatigue
		Lethargy
	Injury, poisoning and procedural complications	Fall
		Road traffic accident
	Nervous system disorders	Balance disorder
		Cerebrovascular accident
		Clonic convulsion
		Confusional state
		Disorientation
		Dizziness
		Dizziness postural
		Generalised tonic-clonic seizure
		Lethargy
		Loss of consciousness
		Metamorphopsia
		Presyncope
		Seizure
		Sensory disturbance
		Sensory loss
		Somnolence
		Syncope
		Tonic convulsion
		Transient ischaemic attack
		Vertigo
		Vestibular disorder
		Vision blurred
	Psychiatric disorders	Confusional state
		Disorientation
		Lethargy
		Somnolence
	Vascular disorders	Cerebrovascular accident
		Dizziness
		Dizziness postural
		Presyncope
		Syncope
		Transient ischaemic attack

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2.7.4.7.8.4. 過量投与に関連する有害事象の検索に用いた基本語の一覧

Adverse event class	System organ class	Preferred term
Overdose	General disorders and administration site conditions	Completed suicide
	Injury, poisoning and procedural complications	Accidental overdose
		Intentional overdose
		Overdose
		Prescribed overdose
	Psychiatric disorders	Completed suicide
		Suicide attempt

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