ゾルトファイ配合注フレックスタッチ

2.7.4 臨床的安全性

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目次

ページ

目次 2
図目次 7
表目次 8
略語一覧 10
2.7.4.1 医薬品への曝露 12
2.7.4.1.1 総括的安全性評価計画及び安全性試験の記述 12
2.7.4.1.1.1 総括的安全性評価計画 12
2.7.4.1.1.1.1 インスリン デグルデク／リラグルチド 12
2.7.4.1.1.1.2 臨床開発プログラム 13
2.7.4.1.1.1.3 非臨床プログラム 14
2.7.4.1.1.1.4 安全性評価方法 15
2.7.4.1.1.2 安全性試験の記述 17
2.7.4.1.2 全般的な曝露状況 18
2.7.4.1.2.1 曝露 18
2.7.4.1.2.2 投与量 19
2.7.4.1.2.3 被験者の内訳 19
2.7.4.1.3 試験対象集団の人口統計学的特性及びその他の特性 19
2.7.4.2 有害事象 20
2.7.4.2.1 有害事象の解析 20
2.7.4.2.1.1 評価方法 20
2.7.4.2.1.1.1 定義 20
2.7.4.2.1.1.2 有害事象の記録 23
2.7.4.2.1.1.3 有害事象のコーディング 23
2.7.4.2.1.1.4 有害事象の分類 23
2.7.4.2.1.2 比較的よくみられる有害事象 26
2.7.4.2.1.3 死亡 32
2.7.4.2.1.4 その他の重篤な有害事象 33
2.7.4.2.1.5 その他の重要な有害事象 35
2.7.4.2.1.5.1 試験の中止に至った有害事象 36
2.7.4.2.1.5.2 投与の中止に至った有害事象 36
2.7.4.2.1.5.3 治験薬の一時的な投与の中断に至った有害事象 37
2.7.4.2.1.5.4 投与量の減量に至った有害事象 37

2.7.4.2.1.6 器官別又は症候群別有害事象の解析 38
2.7.4.2.1.7 心血管系事象 39
2.7.4.2.1.7.1 評価方法 39
2.7.4.2.1.7.2 イベント判定委員会により確定された心血管系事象 39
2.7.4.2.1.7.3 MedDRA 検索により特定された心血管系事象 43
2.7.4.2.1.7.4 MedDRA 検索により特定された不整脈に関連する有害事象 44
2.7.4.2.1.7.5 心血管系疾患に関連するその他の安全性所見の要約 44
2.7.4.2.1.7.6 要約 45
2.7.4.2.1.8 膵炎又は膵炎が疑われる事象 46
2.7.4.2.1.8.1 評価方法 46
2.7.4.2.1.8.2 イベント判定委員会により判定された膵炎又は膵炎が疑われる事象 47
2.7.4.2.1.8.3 MedDRA 検索により特定された膵炎又は膵炎が疑われる有害事象 47
2.7.4.2.1.8.4 MedDRA 検索により特定されたリパーゼ及びアミラーゼ増加に関連する有害事象 47
2.7.4.2.1.8.5 要約 48
2.7.4.2.1.9 新生物 48
2.7.4.2.1.9.1 評価方法 48
2.7.4.2.1.9.2 イベント判定委員会により確定された新生物 48
2.7.4.2.1.9.3 MedDRA 検索により特定された新生物に関連する有害事象 50
2.7.4.2.1.9.4 要約 51
2.7.4.2.1.10 甲状腺疾患 51
2.7.4.2.1.10.1 評価方法 51
2.7.4.2.1.10.2 イベント判定委員会により確定された甲状腺疾患 51
2.7.4.2.1.10.3 MedDRA 検索により特定された甲状腺疾患に関連する有害事象 52
2.7.4.2.1.10.4 MedDRA 検索により特定されたカルシトニン増加に関連する有害事象 52
2.7.4.2.1.10.5 要約 52
2.7.4.2.1.11 腎機能の悪化 53
2.7.4.2.1.11.1 評価方法 53
2.7.4.2.1.11.2 MedDRA 検索により特定された腎機能の悪化に関連する事象 53
2.7.4.2.1.11.3 要約 53
2.7.4.2.1.12 免疫原性 53
2.7.4.2.1.12.1 評価方法 53
2.7.4.2.1.12.2 MedDRA 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 53
2.7.4.2.1.12.3 MedDRA 検索により特定された注射部位反応に関連する有害事象 54

2.7.4.2.1.12.4 要約 54
2.7.4.2.1.13 投薬過誤 54
2.7.4.2.1.13.1 評価方法 54
2.7.4.2.1.13.2 MedDRA 検索により特定された投薬過誤に関連する有害事象 55
2.7.4.2.1.13.3 要約 55
2.7.4.2.1.14 治験薬による病原体感染の疑い 55
2.7.4.2.1.15 胃腸障害の有害事象 56
2.7.4.2.1.15.1 評価方法 56
2.7.4.2.1.15.2 MedDRA 検索により特定された胃腸障害の有害事象 56
2.7.4.2.1.15.3 要約 61
2.7.4.2.1.16 高血糖 62
2.7.4.2.1.16.1 評価方法 62
2.7.4.2.1.16.2 MedDRA 検索により特定された高血糖に関連する有害事象 62
2.7.4.2.1.16.3 要約 62
2.7.4.2.1.17 稀な事象 62
2.7.4.2.1.18 低血糖 62
2.7.4.2.1.18.1 評価方法 62
2.7.4.2.1.18.2 すべての低血糖（分類別） 64
2.7.4.2.1.18.3 重大な又は血糖値確定低血糖 66
2.7.4.2.1.18.4 重大な又は血糖値確定症候性低血糖 69
2.7.4.2.1.18.5 夜間低血糖 72
2.7.4.2.1.18.6 要約 74
2.7.4.2.1.19 急性胆石症 75
2.7.4.2.1.19.1 評価方法 75
2.7.4.2.1.19.2 MedDRA 検索により特定された急性胆石症に関連する有害事象 75
2.7.4.2.1.19.3 要約 75
2.7.4.2.2 個別有害事象の文章による説明 76
2.7.4.3 臨床検査値の評価 77
2.7.4.3.1 血液学的検査 77
2.7.4.3.2 血液生化学的検査 78
2.7.4.3.3 空腹時脂質プロファイル 79
2.7.4.3.4 カルシトニン 83
2.7.4.3.5 アミラーゼ及びリパーゼ 84
2.7.4.3.6 抗 IDeg 抗体及び抗リラグルチド抗体 89

2.7.4.3.7 妊娠検査 91
2.7.4.3.8 要約 91
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 92
2.7.4.4.1 身体所見 92
2.7.4.4.2 眼底検査／眼底写真 92
2.7.4.4.3 心電図 93
2.7.4.4.4 脈拍数 93
2.7.4.4.5 血圧 95
2.7.4.4.6 苦情 98
2.7.4.4.7 要約 98
2.7.4.5 特別な患者集団及び状況下における安全性 99
2.7.4.5.1 内因性要因 99
2.7.4.5.1.1 年齢 99
2.7.4.5.1.2 腎機能 104
2.7.4.5.1.3 肝機能 108
2.7.4.5.1.4 要約 112
2.7.4.5.2 外因性要因 113
2.7.4.5.2.1 前治療の糖尿病治療 113
2.7.4.5.2.2 抗体産生 119
2.7.4.5.2.3 要約 119
2.7.4.5.3 薬物相互作用 120
2.7.4.5.4 妊娠及び授乳時の使用 120
2.7.4.5.5 過量投与 120
2.7.4.5.6 薬物乱用 121
2.7.4.5.7 離脱症状及び反跳現象 121
2.7.4.5.8 自動車運転及び機械操作に対する影響又は精神機能の障害 121
2.7.4.5.9 海外試験における安全性情報 121
2.7.4.5.9.1 GLP-1 受容体作動薬から IDegLira への切り替え時の安全性の評価 121
2.7.4.5.9.2 グローバル併合データの安全性情報 123
2.7.4.6 市販後データ 126
2.7.4.7 付録 127
参考文献 128

2.7.4.7　付録

2.7.3.7.1　内因性及び外因性民族的要因の影響の検討に関する安全性データ

2.7.3.7.2　4183 試験の安全性データ

2.7.3.7.3　4184 試験の安全性データ

2.7.3.7.4　併合データ及び市販後データ

2.7.3.7.5　4183 試験及び 4184 試験における過量投与及び急性胆石症に関連する有害事象

図目次

ページ

図 2.7.4.1-1 IDegLira の臨床開発プログラム....14
図 2.7.4.2-1 各時点に胃腸障害の有害事象を発現していた被験者の割合 - SAS（4183 試験）....58
図 2.7.4.2-2 各時点に胃腸障害の有害事象を発現していた被験者の割合 - SAS（4184 試験）....61
図 2.7.4.2-3 重大な又は血糖値確定低血糖 - 平均累積関数 - SAS（4183 試験）....67
図 2.7.4.2-4 重大な又は血糖値確定低血糖 - 平均累積関数 - SAS（4184 試験）....69
図 2.7.4.2-5 重大な又は血糖値確定症候性低血糖 - 平均累積関数 - SAS（4183 試験）....70
図 2.7.4.2-6 重大な又は血糖値確定症候性低血糖 - 平均累積関数 - SAS（4184 試験）....72
図 2.7.4.3-1 空腹時脂質–統計解析（IDegLira vs. IDeg） - FAS（4183 試験）....81
図 2.7.4.3-2 空腹時脂質–統計解析（IDegLira vs.リラグルチド） - FAS（4183 試験）....81
図 2.7.4.3-3 空腹時脂質 - 統計解析（IDegLira vs.IDeg） - FAS（4184 試験）....82
図 2.7.4.3-4 リパーゼ（U/L） - 箱ひげ図 - SAS（4183 試験）....85
図 2.7.4.3-5 リパーゼ（U/L） - 箱ひげ図 - SAS（4184 試験）....88
図 2.7.4.4-1 脈拍数（拍／分）のベースラインからの変化量の経時推移 - SAS（4183 試験及び 4184 試験）....94
図 2.7.4.4-2 血圧のベースラインからの変化量の経時推移 - FAS（4183 試験及び 4184 試験）....96

表目次

ページ

表 2.7.4.1-1 曝露状況 - SAS（4183 試験）.....18
表 2.7.4.1-2 曝露状況 - SAS（4184 試験）.....19
表 2.7.4.2-1 特に注目すべき医学的事象、追加データ収集が必要な有害事象（4183 試験及び 4184 試験）.....22
表 2.7.4.2-2 有害事象 - SAS（4183 試験）.....26
表 2.7.4.2-3 5%以上の被験者で報告された有害事象–器官別大分類及び基本語別 - SAS（4183 試験）.....28
表 2.7.4.2-4 有害事象 - SAS（4184 試験）.....30
表 2.7.4.2-5 5%以上の被験者で報告された有害事象–器官別大分類及び基本語別 - SAS（4184 試験）.....31
表 2.7.4.2-6 重篤な有害事象 - SAS（4183 試験）.....34
表 2.7.4.2-7 重篤な有害事象 - SAS（4184 試験）.....35
表 2.7.4.2-8 特に注目すべき安全性領域.....38
表 2.7.4.2-9 イベント判定委員会により確定された心血管系事象（イベント判定委員会の分類別） - SAS（4183 試験）.....40
表 2.7.4.2-10 イベント判定委員会により確定された心血管系事象（イベント判定委員会の分類別） - SAS（4184 試験）.....43
表 2.7.4.2-11 イベント判定委員会により確定された新生物（イベント判定委員会の分類別） - SAS（4183 試験）.....49
表 2.7.4.2-12 イベント判定委員会により確定された新生物（イベント判定委員会の分類別） - SAS（4184 試験）.....50
表 2.7.4.2-13 高頻度（5%以上の被験者）で報告された胃腸障害の有害事象 - SAS（4183 試験）.....56
表 2.7.4.2-14 胃腸障害の有害事象の持続時間 - SAS（4183 試験）.....57
表 2.7.4.2-15 高頻度（5%以上の被験者）で報告された胃腸障害の有害事象 - SAS（4184 試験）.....59
表 2.7.4.2-16 胃腸障害の有害事象の持続時間 - SAS（4184 試験）.....60
表 2.7.4.2-17 すべての低血糖（分類別） - SAS（4183 試験）.....65
表 2.7.4.2-18 すべての低血糖（分類別） - SAS（4184 試験）.....66
表 2.7.4.2-19 重大な又は血糖値確定低血糖 - 統計解析 - FAS（4183 試験）.....67
表 2.7.4.2-20 重大な又は血糖値確定低血糖 - 統計解析 - FAS（4184 試験）.....68
表 2.7.4.2-21 重大な又は血糖値確定症候性低血糖 - 統計解析 - FAS（4183 試験）.....70
表 2.7.4.2-22 重大な又は血糖値確定症候性低血糖 - 統計解析 - FAS（4184 試験）.....71
表 2.7.4.2-23 夜間低血糖（分類別） - SAS（4183 試験）.....73

表 2.7.4.2-24　夜間低血糖（分類別）‐SAS（4184 試験）.....74
表 2.7.4.3-1　ベースライン及び投与後 52 週の空腹時脂質‐ 幾何平均‐FAS（4183 試験）.....80
表 2.7.4.3-2　ベースライン及び投与後 26 週の空腹時脂質‐幾何平均‐FAS（4184 試験）.....82
表 2.7.4.3-3　リパーゼ（U/L）の要約‐SAS（4183 試験）.....84
表 2.7.4.3-4　アミラーゼ（U/L）の要約‐SAS（4183 試験）.....86
表 2.7.4.3-5　リパーゼ（U/L）の要約‐SAS（4184 試験）.....87
表 2.7.4.3-6　アミラーゼ（U/L）の要約‐SAS（4184 試験）.....89
表 2.7.4.5-1　年齢グループ別の有害事象‐SAS（4183 試験）.....100
表 2.7.4.5-2　年齢グループ別の低血糖‐SAS（4183 試験）.....101
表 2.7.4.5-3　年齢グループ別の有害事象‐SAS（4184 試験）.....102
表 2.7.4.5-4　年齢グループ別の低血糖‐SAS（4184 試験）.....103
表 2.7.4.5-5　ベースラインの腎機能別の有害事象‐SAS（4183 試験）.....105
表 2.7.4.5-6　ベースラインの腎機能別の低血糖‐SAS（4183 試験）.....106
表 2.7.4.5-7　ベースラインの腎機能別の有害事象‐SAS（4184 試験）.....107
表 2.7.4.5-8　ベースラインの腎機能別の低血糖‐SAS（4184 試験）.....108
表 2.7.4.5-9　ベースラインの肝機能別の有害事象‐SAS（4183 試験）.....109
表 2.7.4.5-10　ベースラインの肝機能別の低血糖‐SAS（4183 試験）.....110
表 2.7.4.5-11　ベースラインの肝機能別の有害事象‐SAS（4184 試験）.....111
表 2.7.4.5-12　ベースラインの肝機能別の低血糖‐SAS（4184 試験）.....112
表 2.7.4.5-13　前治療の経口糖尿病薬別の有害事象‐SAS（4183 試験）.....114
表 2.7.4.5-14　前治療の経口糖尿病薬別の低血糖‐SAS（4183 試験）.....115
表 2.7.4.5-15　前治療の糖尿病治療別の有害事象‐SAS（4184 試験）.....117
表 2.7.4.5-16　前治療の糖尿病治療別の低血糖‐SAS（4184 試験）.....118
表 2.7.4.5-17　2018 年 3 月 31 日までに完了した IDegLira（被験薬として使用）の臨床試験における累積曝露.....124
表 2.7.4.5-18　IDegLira（被験薬として使用）の臨床試験において最も高頻度に報告された重篤な有害事象（器官別大分類）.....125
表 2.7.4.6-1　市販後の曝露（地域別）.....126

略語一覧

α-GI	:	α-glucocidase inhibitor （α-グルコシダーゼ阻害薬）
ADA	:	American Diabetes Association（米国糖尿病学会）
AE	:	adverse event（有害事象）
ALT	:	alanine aminotransferase（アラニンアミノトランスフェラーゼ）
ANCOVA	:	analysis of covariance（共分散分析）
AST	:	aspartate aminotransferase（アスパラギン酸アミノトランスフェラーゼ）
BG	:	blood glucose（血糖値）
BMI	:	body mass index〔体容量指数：体重(kg)／身長$(m)^2$〕
CI	:	confidence interval（信頼区間）
eCRF	:	electronic case report form（電子症例報告書）
CV	:	cardiovascular（心血管系）
EAC	:	event adjudication committee（イベント判定委員会）
eGFR	:	estimated glomerular filtration rate
EOT	:	end of text
EU	:	European Union
FAS	:	full analysis set（最大の解析対象集団）
FDA	:	US Food and Drug Administration（米国食品医薬品局）
GLP-1	:	glucagon-like peptide-1（グルカゴン様ペプチド-1）
GLP-1 RA	:	GLP-1 受容体作動薬
HDL	:	high density lipoprotein（高比重リポタンパク）
ICH	:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use（日米 EU 医薬品規制調和国際会議）
IDeg	:	insulin degludec（インスリン デグルデク）
IDegLira	:	insulin degludec/liraglutide（インスリン デグルデク／リラグルチド）
LDL	:	low density lipoprotein（低比重リポタンパク）
ITT	:	intention-to-treat
LLOQ	:	lower limit of quantification（定量下限値）
LOCF	:	last observation carried forward
MACE	:	major adverse cardiovascular event （主要な心血管イベント）
MedDRA	:	Medical Dictionary for Regulatory Activities（ICH 国際医薬用語集）
NSTEMI	:	Non ST-segment elevation myocardial infarction（非 ST 上昇型心筋梗塞）
OAD	:	oral anti-diabetic drug（経口糖尿病薬）
PK	:	pharmacokinetic（薬物動態）
PYE	:	patient years of exposure
QOL	:	quality of life（生活の質）
SAE	:	serious adverse event（重篤な有害事象）
SAS	:	safety analysis set（安全性対象集団）
SD	:	standard deviation（標準偏差）
SGLT-2	:	sodium-glucose cotransporter-2（ナトリウム-グルコース共輸送体 2）
SU	:	sulphonylureas（スルホニルウレア薬）
T2DM	:	type 2 diabetes mellitus（2 型糖尿病）
TZD	:	thiazolidinediones（チアゾリジン薬）

US	:	United States（米国）
VLDL	:	very low density lipoprotein（超低比重リポタンパク）

2.7.4.1 医薬品への曝露

2.7.4.1.1 総括的安全性評価計画及び安全性試験の記述

2.7.4.1.1.1 総括的安全性評価計画

2.7.4.1.1.1.1 インスリン デグルデク／リラグルチド

インスリン デグルデク／リラグルチド（IDegLira）は、持効型インスリン製剤であるインスリン デグルデク（IDeg）と、グルカゴン様ペプチド-1（GLP-1）受容体作動薬であるリラグルチドの配合剤である。IDegLira は、食事・運動療法と合わせて 1 日 1 回皮下投与することにより、2 型糖尿病患者の血糖コントロールの改善を目的としている。

Basal インスリンアナログである IDeg は、1 型及び 2 型糖尿病の治療薬（1 日 1 回皮下投与）として、2012 年の最初の承認（日本）以降、これまでに多くの国々で承認を取得している（販売名：トレシーバ®）。IDeg は、臨床用量での作用持続時間が 42 時間を超えており、平坦かつ安定した薬力学的作用プロファイルを示し、血糖降下作用の日間変動が小さいという特徴を有している。本臨床概要では、トレシーバ®はその有効成分である IDeg の名称で記載する。

内因性のヒト GLP-1 アナログであるリラグルチドは、2009 年の最初の承認以降（日本は 2010 年）、2 型糖尿病患者の治療薬として多くの国々で承認を取得している（販売名：ビクトーザ®）。2 型糖尿病患者の治療におけるリラグルチド（1 日 1 回皮下投与）の承認最高用量は、日本では 0.9 mg、海外は 1.8 mg である。現在、日本ではリラグルチドの最高用量を 1.8 mg とする承認事項一部変更承認申請を行い、審査中である。リラグルチドはグルコース濃度依存的にインスリン分泌を促進し、血糖値が高い場合にグルカゴン分泌を抑制する。また、リラグルチドは空腹感を低減し、エネルギー摂取量の低下に関連する作用機序により、体重及び体脂肪を減少させる。本臨床概要では、全般的にビクトーザ®はその有効成分であるリラグルチドの名称で記載する。

IDegLira は、諸外国（欧州及び米国を含む）で 2 型糖尿病の治療薬として承認を取得し、販売されている。IDegLira は、Basal インスリンと GLP-1 受容体作動薬の持つそれぞれのベネフィットを 1 日 1 回の注射で提供可能な製剤として開発された。2 つの有効成分の作用を併せ持つ IDegLira による治療により、2 型糖尿病患者において、Basal インスリン単剤に比べ低血糖及び体重増加のリスクを抑えながら、空腹時及び食後の血糖コントロールを改善すると期待される。また、リラグルチド単剤での治療と比較して、IDegLira では用量漸増が緩徐であるため、胃腸障害（一過性）の副作用の発現頻度が低くなると考えられる。これらのことは、IDegLira の臨床試験プログラムで確認されている。

IDegLira はペン型注入器と一体化したプレフィルド製剤として提供される（1 mL あたり IDeg 100 単位とリラグルチド 3.6 mg）。この IDeg とリラグルチドの配合比率は固定であり、IDegLira の用量を増減しても両有効成分の比率は一定となる。IDegLira は、最適な血糖コントロールと低血糖リスクのバランスを考慮しながら、患者個々の必要性に応じて投与する製剤である。Basal インスリン製剤による治療と同様に、患者の空腹時血糖値に基づく投与量調節を用いて血糖コントロールを最適化する。

IDegLira は IDeg 1 単位／リラグルチド 0.036 mg ずつの投与量調節が可能であり、プレフィルド製剤のペンで、1 回の投与において 1 から 50 の範囲（IDeg：1～50 単位、リラグルチド：0.036～1.8 mg に相当）で設定できる。なお、IDegLira の臨床開発プログラムでは、投与量の単位に「用量ステップ」を用いており、本臨床概要でも IDegLira の投与量の単位は「用量ステップ」と表記する。

IDegLira の臨床試験は、プロジェクト番号（NN9068）と固有の 4 桁の番号にて特定する。本臨床概要では、臨床試験は 4 桁の固有の番号「XXXX」を用いて「XXXX 試験」と表記する。

2.7.4.1.1.1.2　臨床開発プログラム

本臨床概要には、IDegLira のすべての試験より得られた 2 型糖尿病患者における IDegLira の忍容性及び安全性に関するデータを含めた。日本人 2 型糖尿病患者を対象とした以下の 2 つの第 3 相試験は完了（試験の完了は治験総括報告書の完成と定義した）しており、これらの試験のデータを本臨床概要に含めた。

4183 試験：

本試験は、経口糖尿病薬単剤〔メトホルミン、α-グルコシダーゼ阻害薬（α-GI）、チアゾリジン薬（TZD）、スルホニルウレア薬（SU）、ナトリウム-グルコース共輸送体 2 阻害薬（SGLT-2 阻害薬）又はグリニドのいずれか〕による治療で十分な血糖コントロールが得られていない日本人 2 型糖尿病患者を対象とした、52 週間、多施設共同、無作為割り付け、3 群並行、非盲検試験であった。

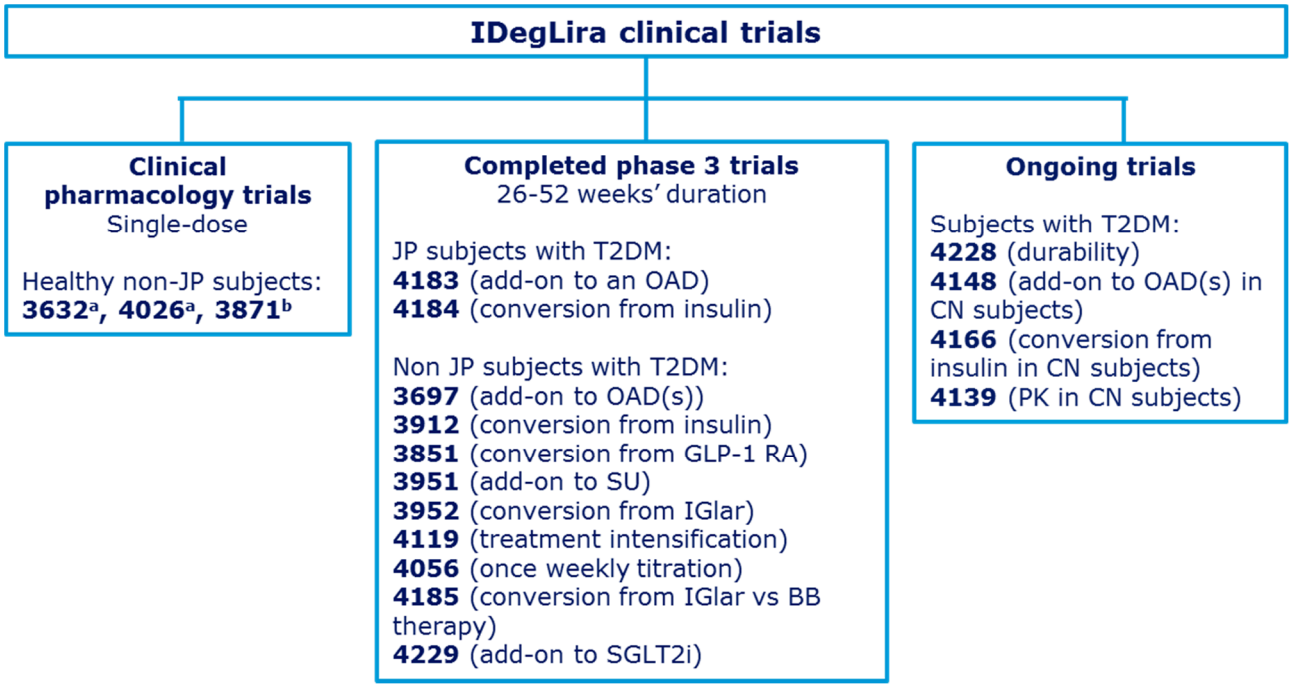
4184 試験

本試験は、メトホルミン単剤、又はメトホルミン及び経口糖尿病薬を併用した Basal インスリン又は混合／配合インスリンによる治療で十分な血糖コントロールが得られていない日本人 2 型糖尿病患者を対象とした、26 週間、多施設共同、無作為割り付け、2 群並行、二重盲検、treat-to-target 試験であった。

4183 試験の治験総括報告書の完成時点では、以下の海外試験が完了していた。

- 非日本人 2 型糖尿病患者を対象とした 26 週間又は 52 週間の 9 つの第 3 相試験（3697 試験、3912 試験、3851 試験、3951 試験、3952 試験、4119 試験、4056 試験、4185 試験及び 4229 試験）
- 非日本人健康被験者を対象とした 3 つの単回投与の臨床薬理試験（3632 試験、4026 試験及び 3871 試験）

IDegLira のグローバル開発プログラムの概要を図 2.7.4.1-1 に示す。



a: Trials 3632 and 4026 tested the IDeg/liraglutide ratio of 100 units/3.6 mg per mL used in phase 3 trials and intended for the market.

b: Trial 3871 tested an alternative IDeg/liraglutide ratio of 100 units/6.0 mg per mL, which did not undergo further clinical development.

JP: Japan, CN: China

BB: basal bolus, GLP-1 RA: glucagon-like-peptide 1 receptor agonist, IGlar: insulin glargine, OAD: oral antidiabetic drug, PK: pharmacokinetic, SGLT2i: sodium-glucose cotransporter-2 inhibitors, SU: sulphonylurea,

Trial 4228; durability = 104 week, long term trial. Phase 3 trials 4228, 4148 and 4166 are ongoing.

The trials are defined as 'completed' if the clinical trial report was final.

図 2.7.4.1-1　　IDegLira の臨床開発プログラム

各試験のデザインの詳細は Module 2.7.6 及び治験総括報告書（Module 5）を参照のこと。

2.7.4.1.1.1.3　　非臨床プログラム

日米 EU 医薬品規制調和国際会議（ICH）-M3（R2）ガイドラインに従い、IDegLira に関して最長 13 週間の反復投与毒性試験ならびにウサギ及びブタを用いた局所刺激性試験を実施した。非臨床プログラムから、インスリン及び GLP-1 アナログによる既知の薬理作用及び過剰な薬理作用に起因する予期された所見が明らかになった。IDegLira の非臨床試験プログラムから、ヒトへの長期間の皮下投与に関して安全性上の懸念がないことが明らかになった。

2.7.4.1.1.1.4　安全性評価方法

安全性情報の提示

本臨床概要では、主に国内第 3 相臨床試験（4183 試験及び 4184 試験）の安全性データを試験別に提示する。

グローバル併合データを補足的な情報として提示する。グローバル併合データのデータロック時点は 2018 年 3 月 31 日である。本臨床概要（2.7.4.5.9.2）では、2018 年 3 月 31 日時点で完了した又は進行中の臨床試験のグローバル併合データにおける重篤な有害事象を提示する。また、GLP-1 受容体作動薬から IDegLira への切り替えに関する補足情報として、GLP-1 受容体作動薬による治療で十分な血糖コントロールが得られない 2 型糖尿病患者を対象とした海外第 3 相臨床試験（3851 試験）の安全性の結果を 2.7.4.5.9.1 に提示する。

IDegLira は、諸外国（欧州及び米国を含む）で 2 型糖尿病の治療薬として承認を取得し、販売されているため、市販後の安全性の累積データ〔データロック時点（2018 年 3 月 31 日）までの副作用情報〕も本臨床概要に含める（2.7.4.6）。

健康被験者を対象とした第 1 相単回投与試験は、プログラム全体に対して治験薬への曝露が限られており、また、これらの試験の設定も想定する IDegLira の使用環境と異なるため、本臨床概要には含めない。臨床薬理試験の安全性の結果については、Module 2.7.6 及び治験総括報告書（Module 5）を参照のこと。

構成及び項目

本臨床概要において、安全性情報は以下の安全性パラメータについて、主に 4183 試験及び 4184 試験結果に基づき提示する。

- 曝露
- 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（試験又は投与の中止に至った有害事象、減量又は一時的な投与の中断に至った有害事象）
  - 特に注目すべき安全性領域における有害事象（心血管系事象、膵炎又は膵炎の疑い、新生物、甲状腺疾患、腎機能の悪化、免疫原性、投薬過誤、治験薬による病原体感染の疑い、胃腸障害の有害事象、高血糖に関する有害事象、稀な事象、低血糖及び急性胆石症）
- 臨床検査項目の評価
  - 血液学的検査
  - 血液生化学的検査

- 空腹時脂質プロファイル
- カルシトニン
- リパーゼ及びアミラーゼ
- 抗薬物抗体
- 妊娠検査

- バイタルサイン、身体所見及び他の安全性に関連する観察項目
  - 身体所見
  - 眼底検査／眼底写真
  - 心電図
  - 脈拍数
  - 血圧
- 苦情
- 特別な患者集団及び状況下における安全性
  - 内因性民族的要因（年齢、ベースラインの腎機能、ベースラインの肝機能）別の有害事象及び低血糖
  - 外因性民族的要因（前治療の糖尿病治療、抗体の産生）
  - 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
- 海外試験における安全性情報
  - GLP-1 アナログからの切り替えにおける安全性
  - グローバル併合データの安全性情報
- 市販後データ

空腹時脂質、血圧及び脈拍数のデータは本臨床概要に記載する。体重及び投与量のデータは Module 2.7.3 に示す。

統計手法

解析対象集団

安全性の評価に使用した解析対象集団の定義は以下のとおり。

- 安全性対象集団〔safety analysis set（SAS）〕：治験薬又は対照薬を少なくとも 1 回投与された被験者を含める。SAS に含まれる被験者は as treated の評価に寄与する。
- 最大の解析対象集団〔full analysis set（FAS）〕：無作為割り付けされたすべての被験者を含めた。例外的な場合には症例を除外することがある。その場合、除外する正当な理由を示し文書化する。FAS における統計的な評価は ITT（intention-to-treat）の原則に従い、被験者は as randomised の評価に寄与する。

安全性情報の記述統計量及び被験者の内訳は SAS に基づく。統計解析（脂質、脈拍数、血圧及び低血糖）は FAS に基づく。

記述統計量

概して、安全性データの提示及び解釈には記述統計量を用いた。各変数は、規定の期間における平均値、範囲（最小値～最大値）、又は人数／件数（被験者数等）で要約する。カテゴリカル変数のデータについては、各カテゴリー内の被験者の割合を提示する。来院別の要約には予定来院を用いる。

有害事象及び低血糖は、これらの事象を発現した被験者数（N）、被験者の割合（%）、発現した事象の件数（E）及び単位時間あたりの発現件数（R）を提示する。投与群間で比較する場合は、IDegLira 群及び対照群の被験者の割合及び単位時間あたりの発現件数を考慮した。

統計解析

4183 試験及び 4184 試験の統計解析（脂質、脈拍数、血圧及び低血糖）は FAS に基づく。連続変数のエンドポイント（脂質、脈拍数及び血圧）は治療及び前治療の糖尿病治療を固定効果、対応するベースライン値を共変量として含めた、標準的な共分散分析（ANCOVA）モデルを用いて解析した。脂質のエンドポイントの統計解析においては、エンドポイント及びベースライン共変量は対数変換した。解析結果はもとのスケールに逆変換し提示した。

低血糖の発現件数は、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析回帰モデルを用いて解析した。本モデルには治療及び前治療の糖尿病治療を固定効果として含めた。

欠測値（間欠的なものを含む）は、last observation carried forward（LOCF）法を用いて補完した。定量下限値（LLOQ）を下回る臨床検査値は、LLOQ の 1/2 の値として取り扱った。

2.7.4.1.1.2　安全性試験の記述

4183 試験及び 4184 試験のデザインは Module 2.7.3.2 を参照のこと。IDegLira の臨床開発プログラムのすべての臨床試験の要約表は Module 2.7.6 を参照のこと。

2.7.4.1.2　全般的な曝露状況

2.7.4.1.2.1　曝露

評価方法

4183 試験及び 4184 試験における IDegLira 又は対照薬の曝露状況は、各治験薬への実際の曝露期間に基づいて評価した。

4183 試験

本試験では、計 819 例が治験薬の投与を受けた〔IDegLira 群：275 例、IDeg 群：271 例、リラグルチド群：273 例〕（表 2.7.4.1-1）。

表 2.7.4.1-1　曝露状況 - SAS（4183 試験）

	IDegLira	IDeg	Lira	Total
Number of subjects	275	271	273	819
PYE (years)				
N	275	271	273	819
Sum	268.00	261.81	271.84	801.65
Mean (SD)	0.97 (0.16)	0.97 (0.17)	1.00 (0.11)	0.98 (0.15)
Median	1.02	1.02	1.02	1.02
Min; Max	0.14; 1.03	0.10; 1.03	0.06; 1.04	0.06; 1.04

PYE: Patient years of exposure (1 PYE = 365.25 days), N: Number of subjects,
SD: Standard deviation

いずれの投与群においても、被験者の 90%以上で投与期間は 51 週間超であった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT table 14.2.2〕。

性別及び年齢サブグループ別でも、投与群間で曝露状況に明らかな違いは認められなかった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.2.3 及び 14.2.4〕。

4184 試験

本試験では、計 210 例が治験薬の投与を受けた（IDegLira 群 105 例、IDeg 群 105 例）（表 2.7.4.1-2）。

表 2.7.4.1-2　　曝露状況 - SAS（4184 試験）

	IDegLira	IDeg	Total
Number of subjects	105	105	210
PYE (years)			
N	105	105	210
Sum	54.28	52.27	106.54
Mean (SD)	0.52 (0.01)	0.50 (0.08)	0.51 (0.06)
Median	0.52	0.52	0.52
Min; Max	0.51; 0.56	0.06; 0.56	0.06; 0.56

PYE: Patient years of exposure (1 PYE = 365.25 days), N: Number of subjects,
SD: Standard deviation

いずれの投与群においても、被験者の大部分の投与期間は 25 週超であった〔4184 試験の治験総括報告書（Module 5.3.5.1）参照〕。

性別及び年齢サブグループ別でも、投与群間で曝露状況に明らかな違いは認められなかった〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.2.3 及び 14.2.4〕。

2.7.4.1.2.2　　投与量

4183 試験及び 4184 試験における投与開始時及び終了時の投与量、投与量調節及び投与量の推移については Module 2.7.3.3.2.1.4 及び Module 2.7.3.3.2.2.3 を参照のこと。

2.7.4.1.2.3　　被験者の内訳

4183 試験及び 4184 試験の被験者の内訳は、Module 2.7.3.3.1.2 を参照のこと。

選択基準、除外基準及び中止・脱落基準の詳細は各試験の治験総括報告書（Module 5）を参照のこと。4183 試験及び 4184 試験の試験を中止した被験者の一覧は、各試験の治験総括報告書（Module 5.3.5.1）、listing 16.2.1 を参照のこと。

2.7.4.1.3　　試験対象集団の人口統計学的特性及びその他の特性

4183 試験及び 4184 試験の試験対象集団の人口統計学的特性及びその他の特性は、Module 2.7.3.3.1.2 を参照のこと。

2.7.4.2 有害事象

2.7.4.2.1 有害事象の解析

2.7.4.2.1.1 評価方法

2.7.4.2.1.1.1 定義

有害事象は以下の定義に従って分類した。

有害事象

有害事象（adverse event：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、必ずしも投与との因果関係があるとは限らないこととした。

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こととした。被験者が同意書に署名をした後、最初の「治験に関連する手順」開始以降、事後調査が終了するまでに観察された有害事象を報告することとした。

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：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こととした。

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：

- スクリーニング手順により発見された、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。

重篤な有害事象（SAE）

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）」として取り扱った：

- 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。
- 治験薬による病原体感染の疑いがある場合、必ず重篤な有害事象として扱うこと。

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、患者又は被験者の身体機能、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。

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は、重篤でない有害事象として取り扱った。

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は、投与開始日から、投与終了 7 日後までに発現した有害事象として定義した。

特記しない限り、本臨床概要に記載する有害事象は治験投与下で発現した有害事象である。

苦情

苦情とは、治験薬等（薬剤及び医療機器）の不具合を主張する書面又は電子的及び口頭による連絡とした。苦情は有害事象を伴うことがあるが、有害事象自体にかかわるものではないとした。

苦情の例：

- 治験薬の物理的及び化学的な外観（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、ペンと針の連結部の不具合等）

特に注目すべき医学的事象及び追加データ収集が必要な有害事象

事象の包括的な叙述の補足及び安全性領域の詳細な評価のための追加情報を収集する手法として、「特に注目すべき医学的事象」及び「追加情報の収集が必要な有害事象」を治験実施計画書で規定した。これらの事象を表 2.7.4.2-1 に示す。

表 2.7.4.2-1　　特に注目すべき医学的事象、追加データ収集が必要な有害事象（4183 試験及び 4184 試験）

Area	**Adjudicated (Y/N)**
Fatal events	Y
Cardiovascular disorders:	
- Acute coronary syndrome: myocardial infarction or unstable angina pectoris	Y
- Cerebrovascular event: stroke or transient ischemic attack	Y
- Heart failure requiring hospital admission	Y
Pancreatitis	Y
Neoplasms	Y
Thyroid disease	Y
Renal failure	N
Medication errors concerning trial products	N

Y: yes; N: no

表 2.7.4.2-1 に示した事象のうち特定のもの（「Adjudication」欄に「Y」で示される事象）について、試験実施中に判定を行うため、外部のイベント判定委員会を設定した。イベント判定委員会は、独立の立場で、盲検下でこれらの事象を判定及び評価した。

イベント判定委員会は、必須の医学的専門性を有する常任委員により構成された。イベント判定委員は利益相反に関する情報を開示し、ノボ ノルディスク社との独立性を保持することとした。イベント判定委員会は、構成、業務、責任及び委員会の手順が詳細に記載されているイベント判定委員会チャーター（憲章）を含むガイドラインに従って業務を行った。詳細については 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1、Sections 9.5.5.3 及び Appendix 16.1.13）を参照のこと。

2.7.4.2.1.1.2　有害事象の記録

治験責任医師はすべての有害事象を電子症例報告書（eCRF）の「AE form」に記録することとした。治験責任医師は診断名を記録することとし、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記録することとした。

重篤な有害事象を報告する際には、「AE form」に加えて「safety information form」を作成することとした。特に注目すべき医学的事象や追加データ収集が必要な有害事象については、専用フォームを作成することとした。

糖尿病患者を組み入れる試験では低血糖が高頻度に報告されることが予測されるため、低血糖は専用の「hypoglycaemic episode form」に記録し、当該フォームには事前に規定した定義（2.7.4.2.1.18）に基づく低血糖の分類ができるように追加情報も含めることとした。

治験薬又は医療機器に関する苦情が有害事象と関連する場合には、治験責任医師がその苦情と有害事象の関連性を評価し、「AE form」に加えて「technical complaint form」も用いて eCRF で報告することとした。関連する有害事象が重篤である場合は、「AE form」、「technical complaint form」に加えて「safety information form」も用いてノボ ノルディスク社に報告することとした。

IDegLira の臨床試験において、妊娠又は妊娠を希望する被験者は除外基準に含まれており、女性被験者が妊娠した場合には直ちに治験薬の投与を中止し、治験への参加を中止することとした。試験期間中の妊娠は治験責任医師が報告することとし、妊娠の転帰が異常（例：先天性異常、胎児死亡、自然流産又は新生児の重篤な有害事象）の場合、「AE form」及び「safety information form」を作成することとした。

2.7.4.2.1.1.3　有害事象のコーディング

すべての重篤な有害事象及び重篤でない有害事象は、ICH 国際医療用語集（MedDRA）を用いてコード化された。4183 試験及び 4184 試験では MedDRA version 20.0 を使用した。有害事象データの原著は英語であり、日本語翻訳にあたっては MedDRA/J Version 20.0 を使用した。臨床データベースのすべての有害事象は、ノボ ノルディスク社データマネジメント部門の医師免許を有するスタッフによりコード化された。安全性データベースの重篤な有害事象は、ノボ ノルディスク社 Global Safety 部門の医師免許を有するスタッフによりコード化された。臨床データベースと安全性データベースの間の差異は、個々の試験のデータベースロックの前に調整された。

2.7.4.2.1.1.4　有害事象の分類

治験責任医師はすべての有害事象を、事象ごとに重症度、治験薬との因果関係、転帰及び治験薬の投与への対応について分類した。

重症度

- 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等度に妨げる程度
- 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

- 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

- 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）：有害事象の結果、永続的かつ顕著な障害・機能不全（失明・聴力喪失・麻痺等）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報告される。
- 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（Recovered/resolved）」、「軽快（Recovering/resolving）」、「回復したが後遺症あり（Recovered/resolved with sequelae）」又は「未回復（Not recovered/not resolved）」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。

治験薬の投与への対応

有害事象における治験薬の投与への対応（action taken）は以下のとおり：

- 治験薬の一時的な投与の中断（Product withdrawn temporarily）
- 治験薬の投与中止（Product withdrawn permanently）

- 投与量の減量（Dose reduced）
- 投与量の増量（Dose increased）
- 投与量の変更なし（Dose not changed）
- 不明（Unknown）
- 該当無し（N/A）

2.7.4.2.1.2　比較的よくみられる有害事象

4183 試験

有害事象の要約を表 2.7.4.2-2 に示す。

表 2.7.4.2-2　有害事象 - SAS（4183 試験）

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	275				271				273			
PYE (years)	268.00				261.81				271.84			
Events	229	(83.3)	873	325.75	216	(79.7)	829	316.65	229	(83.9)	885	325.56
Serious												
Yes	17	(6.2)	18	6.72	13	(4.8)	16	6.11	14	(5.1)	14	5.15
No	227	(82.5)	855	319.03	215	(79.3)	813	310.53	229	(83.9)	871	320.41
Severity												
Severe	6	(2.2)	6	2.24	6	(2.2)	8	3.06	4	(1.5)	4	1.47
Moderate	31	(11.3)	40	14.93	29	(10.7)	40	15.28	23	(8.4)	29	10.67
Mild	223	(81.1)	827	308.58	209	(77.1)	781	298.31	225	(82.4)	852	313.42
Related to IDegLira/IDeg/Lira												
Probable	23	(8.4)	29	10.82	28	(10.3)	29	11.08	36	(13.2)	60	22.07
Possible	71	(25.8)	123	45.90	35	(12.9)	55	21.01	83	(30.4)	150	55.18
Unlikely	214	(77.8)	715	266.79	205	(75.6)	742	283.41	217	(79.5)	674	247.94
Missing	5	(1.8)	6	2.24	3	(1.1)	3	1.15	1	(0.4)	1	0.37
Related to technical complaints												
Yes	7	(2.5)	7	2.61	4	(1.5)	4	1.53	6	(2.2)	6	2.21
No	227	(82.5)	860	320.90	215	(79.3)	822	313.97	228	(83.5)	878	322.99
Missing	5	(1.8)	6	2.24	3	(1.1)	3	1.15	1	(0.4)	1	0.37
Outcome												
Fatal	1	(0.4)	1	0.37	0				0			
Not recovered/ not resolved	118	(42.9)	224	83.58	127	(46.9)	250	95.49	97	(35.5)	166	61.07
Recovered/resolved with sequelae	1	(0.4)	1	0.37	1	(0.4)	1	0.38	0			
Recovering/ resolving	28	(10.2)	33	12.31	31	(11.4)	39	14.90	30	(11.0)	45	16.55
Recovered/ resolved	207	(75.3)	614	229.10	184	(67.9)	539	205.88	212	(77.7)	674	247.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days).

有害事象を発現した被験者の割合は、IDegLira 群で 83.3%、IDeg 群で 79.7%、リラグルチド群で 83.9%であった。すべての有害事象の単位時間あたりの発現件数は、IDegLira 群で 325.7 件/100 人・年、

IDeg 群で 316.6 件/100 人・年、リラグルチド群で 325.6 件/100 人・年であった。大部分の有害事象は非重篤、軽度であり、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。また、大部分の有害事象の試験終了時の転帰は「回復」又は「軽快」であった（表 2.7.4.2-2）。

最も高頻度で報告された有害事象の器官別大分類は「感染症および寄生虫症」であり、単位時間あたりの発現件数は、IDegLira 群で 108.6 件/100 人・年、IDeg 群で 104.7 件/100 人・年、リラグルチド群で 99.7 件/100 人・年であった。器官別大分類の「胃腸障害」に分類される有害事象の単位時間あたりの発現件数は、IDegLira 群で 69.8 件/100 人・年であり、IDeg 群（42.0 件/100 人・年）と比較して多く、リラグルチド群（80.2 件/100 人・年）と比較して少なかった（Module 2.7.6.4、表 2.7.6.4.2-1）。

最も高頻度で報告された有害事象は、いずれの投与群においても「ウイルス性上気道感染」であった。IDegLira 群における「便秘」、「下痢」及び「悪心」の発現件数は、IDeg 群と比較して多かったが、リラグルチド群と比較して少なかった（表 2.7.4.2-3）。

表 2.7.4.2-3　5%以上の被験者で報告された有害事象−器官別大分類及び基本語別 - SAS（4183 試験）

	IDegLira			IDeg			Lira		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	275			271			273		
PYE (years)	268.00			261.81			271.84		
感染症および寄生虫症									
ウイルス性上気道感染	106 (38.5)	166	61.94	91 (33.6)	161	61.50	94 (34.4)	155	57.02
咽頭炎	11 (4.0)	13	4.85	15 (5.5)	18	6.88	9 (3.3)	9	3.31
インフルエンザ	15 (5.5)	15	5.60	9 (3.3)	9	3.44	9 (3.3)	9	3.31
胃腸障害									
便秘	27 (9.8)	28	10.45	12 (4.4)	12	4.58	38 (13.9)	42	15.45
下痢	15 (5.5)	20	7.46	12 (4.4)	14	5.35	24 (8.8)	31	11.40
悪心	9 (3.3)	13	4.85	5 (1.8)	7	2.67	23 (8.4)	30	11.04
臨床検査									
体重増加	4 (1.5)	4	1.49	19 (7.0)	19	7.26	1 (0.4)	1	0.37
リパーゼ増加	6 (2.2)	8	2.99	0			15 (5.5)	15	5.52
眼障害									
糖尿病網膜症	17 (6.2)	17	6.34	12 (4.4)	14	5.35	11 (4.0)	11	4.05
皮膚および皮下組織障害									
湿疹	16 (5.8)	18	6.72	6 (2.2)	6	2.29	9 (3.3)	10	3.68
神経系障害									
頭痛	7 (2.5)	11	4.10	7 (2.6)	12	4.58	15 (5.5)	17	6.25

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events R: Rate (number of adverse events divided by patient years of exposure multiplied by 100) PYE: Patient years of exposure (1 PYE = 365.25 days) ≥ 5% is defined as any treatment column having percentage of subjects with one or more events larger than or equal to 5%. MedDRA version 20.0.

重症度別の有害事象

いずれの投与群でも、有害事象の大部分は治験責任医師により軽度又は中等度と判定された（表 2.7.4.2-2、Module 2.7.6.4、表 2.7.6.4.2-5 及び表 2.7.6.4.2-6）。重度の有害事象は少なく、IDegLira 群で 6 例 6 件、IDeg 群で 6 例 8 件、リラグルチド群で 4 例 4 件であった（表 2.7.4.2-2 及び Module 2.7.6.4、表 2.7.6.4.2-4）。このうち、治験薬との因果関係が「あり」又は「可能性あり」と判定された重度の有害事象は、IDegLira 群で 1 件、IDeg 群で 2 例 2 件、リラグルチド群で 1 件であった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT table 14.3.1.57〕。

治験薬との因果関係別の有害事象

いずれの投与群においても、有害事象の大部分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（表 2.7.4.2-2）。治験薬との因果関係が「あり」又は「可能性あり」と判定された有害事象の単位時間あたりの発現件数は、IDegLira 群で 56.7 件/100 人・年であり、IDeg 群（32.1 件/100 人・年）と比較して多く、リラグルチド群（77.3 件/100 人・年）と比較して少なかった（Module 2.7.6.4、表 2.7.6.4.2-2）。

治験薬との因果関係が「あり」又は「可能性あり」と判定された有害事象のうち、最も高頻度で報告されたものは、器官別大分類の「胃腸障害」と「臨床検査」に含まれる事象であった。器官別大分類の「胃腸障害」に含まれるこれらの有害事象の単位時間あたりの発現件数は、IDegLira 群で 25.4 件/100 人・年であり、IDeg 群（5.0 件/100 人・年）と比較して多く、リラグルチド群（47.1 件/100 人・年）と比較して少なかった。器官別大分類「臨床検査」に含まれるこれらの有害事象の単位時間あたりの発現件数は、IDegLira 群で 10.8 件/100 人・年、IDeg 群で 13.8 件/100 人・年、リラグルチド群で 8.1 件/100 人・年であった（Module 2.7.6.4、表 2.7.6.4.2-2）。

器官別大分類の「臨床検査」に含まれる有害事象のうち、いくつかの基本語で投与群間の違いが認められた。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「リパーゼ増加」は、IDegLira 群で 8 件及びリラグルチド群で 10 件報告されたが、IDeg 群では報告されなかった。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「体重増加」は、IDegLira 群で 4 件及び IDeg 群で 19 件報告されたが、リラグルチド群では報告されなかった（Module 2.7.6.4、表 2.7.6.4.2-2）。

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について、その他の器官別大分類及び基本語別で投与群間に明らかな違いは認められなかった（Module 2.7.6.4、表 2.7.6.4.2-2）。

4184 試験

有害事象の要約を表 2.7.4.2-4 に示す。

表 2.7.4.2-4　　有害事象 - SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	105				105			
PYE (Years)	54.28				52.27			
Events	82	(78.1)	280	515.86	80	(76.2)	210	401.79
Serious								
Yes	3	(2.9)	4	7.37	4	(3.8)	6	11.48
No	82	(78.1)	276	508.49	79	(75.2)	204	390.31
Severity								
Severe	3	(2.9)	4	7.37	1	(1.0)	2	3.83
Moderate	10	(9.5)	14	25.79	9	(8.6)	11	21.05
Mild	82	(78.1)	262	482.70	80	(76.2)	197	376.92
Related to IDegLira/IDeg								
Probable	12	(11.4)	19	35.01	6	(5.7)	9	17.22
Possible	29	(27.6)	53	97.65	22	(21.0)	32	61.23
Unlikely	73	(69.5)	206	379.53	72	(68.6)	166	317.61
Missing	2	(1.9)	2	3.68	3	(2.9)	3	5.74
Related to technical complaints								
Yes	0				2	(1.9)	2	3.83
No	82	(78.1)	278	512.18	78	(74.3)	205	392.23
Missing	2	(1.9)	2	3.68	3	(2.9)	3	5.74
Outcome								
Fatal	0				0			
Not recovered/not resolved	52	(49.5)	88	162.13	45	(42.9)	71	135.84
Recovered/resolved with sequela	0				0			
Recovering/resolving	10	(9.5)	15	27.64	10	(9.5)	12	22.96
Recovered/resolved	68	(64.8)	177	326.10	59	(56.2)	127	242.99
Missing	0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days).

有害事象を発現した被験者の割合は、IDegLira 群で 78.1%、IDeg 群で 76.2%であった。有害事象の単位時間あたりの発現件数は、IDegLira 群で 515.9 件/100 人・年、IDeg 群で 401.8 件/100 人・年であった。有害事象の大部分は非重篤、軽度であり、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。また、大部分の有害事象の試験終了時の転帰は「回復」又は「軽快」であった（表 2.7.4.2-4）。

器官別大分類の「胃腸障害」に分類され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、IDeg 群（22.9%及び 76.5 件/100 人・年）と比較して IDegLira 群（42.9%及び 162.1 件/100

人・年）で高かった。「食欲減退」は IDegLira 群では被験者の 7.6%で報告されたが、IDeg 群では報告されなかった〔表 2.7.4.2-5 及び Module 2.7.6.5、表 2.7.6.5.2-1〕。

いずれの投与群でも、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。当該事象を発現した被験者の割合は、IDegLira 群で 20.0%（49.7 件/100 人・年）、IDeg 群で 22.9%（57.4 件/100 人・年）であった（表 2.7.4.2-5）。

表 2.7.4.2-5　5%以上の被験者で報告された有害事象−器官別大分類及び基本語別 - SAS（4184 試験）

	IDegLira			IDeg		
	N (%)	E	R	N (%)	E	R
Number of subjects	105			105		
PYE (years)	54.28			52.27		
胃腸障害						
下痢	15 (14.3)	20	36.85	5 (4.8)	6	11.48
悪心	10 (9.5)	12	22.11	4 (3.8)	5	9.57
便秘	9 (8.6)	10	18.42	4 (3.8)	4	7.65
嘔吐	9 (8.6)	11	20.27	2 (1.9)	2	3.83
腹部不快感	8 (7.6)	8	14.74	5 (4.8)	5	9.57
感染症および寄生虫症						
ウイルス性上気道感染	21 (20.0)	27	49.74	24 (22.9)	30	57.40
眼障害						
糖尿病網膜症	17 (16.2)	18	33.16	17 (16.2)	18	34.44
代謝および栄養障害						
食欲減退	8 (7.6)	8	14.74	0		

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days). ≥ 5% is defined as any treatment column having percentage of subjects with one or more events larger than or equal to 5%. MedDRA version 20.0.

重症度別の有害事象

有害事象の大部分は軽度（IDegLira 群で 482.7 件/100 人・年、IDeg 群で 376.9 件/100 人・年）又は中等度（IDegLira 群で 25.8 件/100 人・年、IDeg 群で 21.0 件/100 人・年）と判定された（表 2.7.4.2-4 ならびに Module 2.7.6.5、表 2.7.6.5.2-5 及び表 2.7.6.5.2-6）。

重度の有害事象を発現した被験者の割合は、IDegLira 群で 2.9%、IDeg 群で 1.0%であり（表 2.7.4.2-4）、単位時間あたりの発現件数は IDegLira 群で 7.4 件/100 人・年、IDeg 群で 3.8 件/100 人・年であった。2 例以上で発現した重度の有害事象（基本語）はみられなかった（Module 2.7.6.5、表 2.7.6.5.2-4）。

2 件の重度の有害事象が、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〔IDeg 群の 1 例（被験者番号：214003）2 件の「意識消失」〕。いずれの事象も重篤な有害事象であった〔4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.2〕。

治験薬との因果関係別の有害事象

いずれの投与群においても、有害事象の大部分は治験責任医師により治験薬との因果関係が「なし」と判定された（表 2.7.4.2-4）。治験薬との因果関係が「あり」又は「可能性あり」と判定された有害事象の単位時間あたりの発現件数は、IDegLira 群（132.7 件/100 人・年）及び IDeg 群（78.5 件/100 人・年）であった（Module 2.7.6.5、表 2.7.6.5.2-2）。

IDegLira 群において、治験薬との因果関係が「あり」又は「可能性あり」と判定された有害事象のうち、最も高頻度で報告されたものは、器官別大分類の「胃腸障害」に含まれる事象であった。これらの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、「下痢」は 10.5%及び 22.1 件/100 人・年であり、「悪心」、「便秘」、「嘔吐」及び「腹部不快感」は 4.8～7.6%及び 11.1～14.7 件/100 人・年であった。IDeg 群では、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「嘔吐」はなかった。「嘔吐」を除くこれらの事象の単位時間あたりの発現件数は 5.7～9.6 件/100 人・年であった（Module 2.7.6.5、表 2.7.6.5.2-2）。

上記以外の、IDegLira 群で高頻度に報告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、「食欲減退」及び「糖尿病網膜症」（いずれの事象も単位時間あたりの発現件数は 12.9 件/100 人・年）であった。IDeg 群では「糖尿病網膜症」の単位時間あたりの発現件数は 7.7 件/100 人・年であったが、「食欲減退」は認められなかった。なお、IDeg 群で最も高頻度で報告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、「腹部不快感」、「下痢」、「悪心」及び「糖尿病網膜症」であった（Module 2.7.6.5、表 2.7.6.5.2-2）。

2.7.4.2.1.3　死亡

4183 試験

試験期間中に IDegLira 群で 1 件の死亡が報告された（表 2.7.4.2-2）。本事象は器官別大分類の「心臓障害」に分類され、イベント判定委員会により心血管死と確定された〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Listing14.3.2.3 及び Table 14.3.1.148〕。

本被験者は IDegLira 群の 75 歳女性で、投与開始後 291 日目に「心臓障害」により死亡した。治験責任医師により本事象の治験薬との因果関係は「なし」と判定された。試験期間中にその他の有害事象や重大な又は血糖値確定低血糖の報告はなかった。詳細は、4183 試験の治験総括報告書（Module 5.3.5.1）、Section 14.3.3 を参照のこと。

4184 試験

本試験では死亡は報告されなかった（表 2.7.4.2-4）。

2.7.4.2.1.4　その他の重篤な有害事象

4183 試験

試験期間中、重篤な有害事象が 44 例 48 件報告された。重篤な有害事象を 1 件以上発現した被験者の割合は、IDegLira 群で 6.2%、IDeg 群で 4.8%、リラグルチド群で 5.1%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、IDegLira 群で 6.7 件/100 人・年、IDeg 群で 6.1 件/100 人・年、リラグルチド群で 5.2 件/100 人・年であった（表 2.7.4.2-6）。重篤な有害事象の叙述は 4183 試験の治験総括報告書（Module 5.3.5.1）、Section 14.3.3、重篤な有害事象の一覧表は 4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Listing 14.3.2.1 及び Appendix 16.2.7, Listing 16.2.7.2 を参照のこと。

最も高頻度で報告された重篤な有害事象は、器官別大分類の「心臓障害」に含まれる事象であり、IDegLira 群で被験者の 1.1%（3 例 3 件）、IDeg 群で被験者の 1.1%（3 例 3 件）、リラグルチド群で被験者の 0.4%（1 件）に発現した。その他の重篤な有害事象（基本語）はいずれも 1 件の報告であり、その発現状況に 3 群間で明らかな違いはみられなかった（Module 2.7.6.4、表 2.7.6.4.2-3）。

治験薬との因果関係が「あり」又は「可能性あり」と判定された重篤な有害事象は、4 例に 4 件報告された。その内訳は、IDegLira 群で 2 件（「胆嚢炎」及び「低血糖」）、IDeg 群で 1 件（「低血糖性意識消失」）、リラグルチド群で 1 件（「自己免疫性膵炎」）であった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.36〕。

表 2.7.4.2-6　　重篤な有害事象 - SAS（4183 試験）

	IDegLira			IDeg			Lira		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	275			271			273		
PYE (years)	268.00			261.81			271.84		
Events	17 (6.2)	18	6.72	13 (4.8)	16	6.11	14 (5.1)	14	5.15
Severity									
Severe	5 (1.8)	5	1.87	5 (1.8)	7	2.67	3 (1.1)	3	1.10
Moderate	8 (2.9)	8	2.99	7 (2.6)	8	3.06	5 (1.8)	5	1.84
Mild	4 (1.5)	5	1.87	1 (0.4)	1	0.38	6 (2.2)	6	2.21
Related to IDegLira/IDeg/Lira									
Probable	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0		
Possible	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37
Unlikely	15 (5.5)	16	5.97	12 (4.4)	15	5.73	13 (4.8)	13	4.78
Related to technical complaints									
Yes	0			0			0		
No	17 (6.2)	18	6.72	13 (4.8)	16	6.11	14 (5.1)	14	5.15
Outcome									
Fatal	1 (0.4)	1	0.37	0			0		
Not recovered/ not resolved	2 (0.7)	2	0.75	4 (1.5)	6	2.29	1 (0.4)	1	0.37
Recovered/resolved with sequelae	1 (0.4)	1	0.37	0			0		
Recovering/ resolving	3 (1.1)	3	1.12	4 (1.5)	5	1.91	3 (1.1)	3	1.10
Recovered/ resolved	10 (3.6)	11	4.10	5 (1.8)	5	1.91	10 (3.7)	10	3.68
Unknown	0			0			0		

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days). MedDRA version 20.0.

4184 試験

試験期間中、重篤な有害事象が 7 例 10 件（IDegLira 群で 3 例 4 件、IDeg 群で 4 例 6 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、IDegLira 群で 7.4 件/100 人・年、IDeg 群で 11.5 件/100 人・年であった（表 2.7.4.2-7）。重篤な有害事象の叙述及び重篤な有害事象の一覧はそれぞれ 4184 試験の治験総括報告書（Module 5.3.5.1）、Section 14.3.3 及び EOT Listing 14.3.2.1 を参照のこと。

表 2.7.4.2-7　　重篤な有害事象 - SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	105				105			
PYE (Years)	54.28				52.27			
Events	3	(2.9)	4	7.37	4	(3.8)	6	11.48
Severity								
Severe	3	(2.9)	4	7.37	1	(1.0)	2	3.83
Moderate	0				2	(1.9)	2	3.83
Mild	0				2	(1.9)	2	3.83
Related to IDegLira/IDeg								
Probable	0				0			
Possible	0				2	(1.9)	3	5.74
Unlikely	3	(2.9)	4	7.37	3	(2.9)	3	5.74
Related to technical complaints								
Yes	0				0			
No	3	(2.9)	4	7.37	4	(3.8)	6	11.48
Outcome								
Fatal	0				0			
Not recovered/not resolved	0				2	(1.9)	2	3.83
Recovered/resolved with sequelae	0				0			
Recovering/resolving	1	(1.0)	2	3.68	0			
Recovered/resolved	2	(1.9)	2	3.68	2	(1.9)	4	7.65
Unknown	0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days). MedDRA version 20.0.

IDegLira 群で報告された 4 件及び IDeg 群で報告された 6 件中 3 件の重篤な有害事象は、治験責任医師により治験薬との因果関係が「なし」と判定された（表 2.7.4.2-7）。IDeg 群で報告された「意識消失」2 件（同一被験者で発現）及び「急性胆嚢炎」1 件が、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〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.12〕。

「意識消失」の 2 件を除き、2 件以上で報告された重篤な有害事象（基本語）はなかった（Module 2.7.6.5、表 2.7.6.5.2-3）。

2.7.4.2.1.5　　その他の重要な有害事象

本項では、その他の重要な有害事象として、試験の中止に至った有害事象、投与の中止に至った有害事象、投与量の減量に至った有害事象及び一時的な投与の中断に至った有害事象について検討する。試験の中止に至った有害事象は、eCRF の end of trial form に主な中止理由として有害事象が記録されて

いるものと定義される。それ以外の上述の有害事象については、有害事象の投与への対応（治験薬の投与中止、 治験薬の一時的な投与の中断、投与量の減量）に基づき要約、及び一覧に提示した。

2.7.4.2.1.5.1　　試験の中止に至った有害事象

4183 試験

試験の中止に至った有害事象は 20 例 21 件（重篤な有害事象 7 件）報告された。その内訳は、IDegLira 群で 8 例 9 件（重篤な有害事象 3 件）、IDeg 群で 6 例 6 件（重篤な有害事象 1 件）、リラグルチド群で 6 例 6 件（重篤な有害事象 3 件）であった（Module 2.7.6.4、表 2.7.6.4.2-7）。

これらの有害事象が最も多く報告された器官別大分類は「胃腸障害」であった〔6 例 6 件（IDegLira 群：2 例、IDeg 群：1 例、リラグルチド群：3 例）〕。上記以外の試験の中止に至った有害事象（基本語）は、いずれも 1～2 件の報告であり、その発現状況に 3 群間で明らかな違いはみられなかった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.43〕。

有害事象により試験を中止した被験者の叙述は 4183 試験の治験総括報告書（Module 5.3.5.1）、Section 14.3.3 を参照のこと。

4184 試験

試験の中止に至った有害事象は報告されなかった（Module 2.7.6.5、表 2.7.6.5.2-7）。

2.7.4.2.1.5.2　　投与の中止に至った有害事象

4183 試験

1 件の「心臓障害」（IDegLira 群で報告された死亡に至った有害事象、2.7.4.2.1.3 参照）を除き、上述の試験の中止に至った有害事象（2.7.4.2.1.5.1 参照）は、治験薬の投与中止に至った有害事象であった。これに加え、IDegLira 群で報告された 1 件の「裂傷」（非重篤）は、治験薬の投与中止に至った有害事象であった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Listing 14.3.2.5（「drug withdrawn」と表記）〕。当該被験者は、本事象発現後に被験者の希望で試験を中止した。

4184 試験

IDeg 群において、投与の中止に至った有害事象が 1 件（「膵癌」、重篤な有害事象）報告された〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Tables 14.3.1.25 及び 28、EOT Listing 14.3.2.5（「drug withdrawn」と表記）〕。当該重篤な有害事象は治験責任医師により治験薬（IDeg）との因果関係が「なし」と判定された。当該被験者は誤って無作為割り付けされたことを理由に試験を中止した（本件は治験実施計画書からの重要な逸脱として報告された）。

2.7.4.2.1.5.3　治験薬の一時的な投与の中断に至った有害事象

4183 試験

一時的な投与の中断に至った有害事象は 15 例 25 件報告された。その内訳は、IDegLira 群で 5 例 8 件、IDeg 群で 1 件、リラグルチド群で 9 例 16 件であった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.72〕。一時的な投与の中断に至った有害事象のうち、重篤な有害事象は IDegLira 群で 2 件、リラグルチド群で 2 件であり、IDeg 群では認められなかった。治験薬との因果関係が「あり」又は「可能性あり」と判定された一時的な投与の中断に至った有害事象は、IDegLira 群で 3 例 5 件、リラグルチド群で 5 例 10 件であり、IDeg 群では認められなかった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.72 及び EOT Listing14.3.2.5〕。一時的な投与の中断に至った有害事象（基本語）は、いずれも各投与群で 1～3 件の報告であった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.75〕。

4184 試験

一時的な投与の中断に至った有害事象が IDegLira 群の 2 例 2 件報告された（交通事故による「股関節部骨折」1 件及び「胃腸炎」1 件）。これらの事象はいずれも重篤であり、治験責任医師により治験薬（IDegLira）との因果関係は「なし」と判定された。いずれの事象も転帰は「回復」であった〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.27 及び EOT Listing 14.3.2.5（「drug interrupted」と表記）〕。IDeg 群では投与の中断に至った有害事象を発現した被験者は認められなかった。

2.7.4.2.1.5.4　投与量の減量に至った有害事象

4183 試験

試験期間中に投与量の減量に至った有害事象が 24 例 31 件報告された。その内訳は、IDegLira 群で 6 例 8 件、IDeg 群で 13 例 16 件、リラグルチド群で 5 例 7 件であった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.74〕。投与量の減量に至った有害事象のうち、重篤な有害事象は IDeg 群で 2 件であり、IDegLira 群及びリラグルチド群では認められなかった。治験薬との因果関係が「あり」又は「可能性あり」と判定された投与量の減量に至った有害事象は、IDegLira 群で 4 例 4 件、IDeg 群で 9 例 10 件、リラグルチド群で 3 例 5 件であった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.74 及び EOT Listing 14.3.2.4〕。投与量の減量に至った有害事象（基本語）は、いずれも各投与群で 1～2 件であった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.77〕。

4184 試験

投与量の減量に至った有害事象が 8 例 11 件（いずれも IDegLira 群）報告された（単位時間あたりの発現件数：20.3 件/100 人・年）〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.26〕。

これらの事象はいずれも非重篤であり、重度ではなかった。これらの事象の治験薬（IDegLira）との因果関係は、4 件は「あり」、3 件は「可能性あり」、4 件は「なし」と判定された。

2.7.4.2.1.6　　器官別又は症候群別有害事象の解析

特に注目すべき安全性領域

IDegLira の特に注目すべき安全性領域（表 2.7.4.2-8）の検討は 2.7.4.2.1.7～2.7.4.2.1.19 に示す。これらの安全性領域は、IDegLira の成分である IDeg 及びリラグルチドで既知の注目すべき安全性領域に従って規定した。

事前に規定された心血管系事象、膵炎又は膵炎の疑い、新生物、甲状腺摘出を必要とする甲状腺疾患及び死亡の事象は、イベント判定のために外部の独立したイベント判定委員会の判定に送られた（表 2.7.4.2-1）。イベント判定委員会はこれらの事象を盲検下で継続的に評価するために設立された。この評価には、診断の確定や事前に規定したサブカテゴリーへの追加的な分類も含まれた。イベント判定委員会が判定した事象の定義及び分類の詳細については、4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Section 9.5.5.3 及び Appendix 16.1.13 を参照のこと。

表 2.7.4.2-8　　特に注目すべき安全性領域

特に注目すべき安全性領域	参照先（項）
心血管系事象	2.7.4.2.1.7
膵炎又は膵炎の疑い（リパーゼ及びアミラーゼの増加を含む）	2.7.4.2.1.8
新生物	2.7.4.2.1.9
甲状腺疾患（カルシトニンの増加を含む）	2.7.4.2.1.10
腎機能の悪化	2.7.4.2.1.11
免疫原性（アレルギー反応及び注射部位反応）	2.7.4.2.1.12
投薬過誤	2.7.4.2.1.13
治験薬による病原体感染の疑い	2.7.4.2.1.14
胃腸障害	2.7.4.2.1.15
高血糖	2.7.4.2.1.16
稀な事象	2.7.4.2.1.17
低血糖	2.7.4.2.1.18
急性胆石症	2.7.4.2.1.19

イベント判定が行われた安全性領域（表 2.7.4.2-1 参照）については、イベント判定委員会の判定結果を主要な情報として取り扱い、事前に記載した MedDRA 検索に基づく結果は補足情報として含めた。

事前に規定された MedDRA 検索については、4183 試験と 4184 試験で同じ MedDRA 用語一覧を使用した。

2.7.4.2.1.7　心血管系事象

2.7.4.2.1.7.1　評価方法

心血管系事象の安全性は、有害事象（2.7.4.2.1.7.2～2.7.4.2.1.7.4）、安静時の脈拍数及び血圧（2.7.4.4.4 及び 2.7.4.4.5）及び脂質（2.7.4.3.3）に基づき評価した。

本項では、以下の事象について要約し、評価した。

- イベント判定委員会により確定された事象（分類別）：
  - 急性冠動脈症候群（心筋梗塞、入院を必要とする不安定狭心症）
  - 脳血管系事象（脳卒中、一過性脳虚血発作）
  - 入院を必要とする心不全
  - 冠動脈血行再建
  - 死亡（心血管死、非心血管死、不明）
  - 主要な心血管イベント（MACE）
- 事前規定した MedDRA 検索

MACE は米国食品医薬品局（FDA）のガイダンス（2008 年発行[1]）に従って定義され、非致死性心筋梗塞、非致死性脳卒中及び心血管死（イベント判定委員会により確定された事象に基づく）が含まれる。

2.7.4.2.1.7.2　イベント判定委員会により確定された心血管系事象

4183 試験

IDegLira 群の 4 例 4 件、IDeg 群の 4 例 5 件の心血管系事象がイベント判定委員会に送られた。リラグルチド群ではイベント判定委員会に送られた事象はなかった（表 2.7.4.2-9）。イベント判定委員会に送られた事象のうち、IDegLira 群の 3 件及び IDeg 群の 2 件がイベント判定委員会により心血管系事象と確定され、いずれも MACE に分類された〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.85〕。以下にイベント判定委員会が評価し、確定した事象を詳述する。

表 2.7.4.2-9　イベント判定委員会により確定された心血管系事象（イベント判定委員会の分類別）
- SAS（4183 試験）

	IDegLira			IDeg			Lira		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	275				271				273			
PYE (years)	268.00				261.81				271.84			
EAC evaluated events	4	(1.5)	4	1.5	4	(1.5)	4	1.5	0			
EAC confirmed events	3	(1.1)	3	1.1	2	(0.7)	2	0.8	0			
Acute coronary syndrome	0				1	(0.4)	1	0.4	0			
Acute myocardial infarction	0				1	(0.4)	1	0.4	0			
STEMI	0				0				0			
NSTEMI	0				1	(0.4)	1	0.4	0			
Silent myocardial infarction	0				0				0			
Unstable angina pectoris	0				0				0			
Cerebrovascular event	2	(0.7)	2	0.7	1	(0.4)	1	0.4	0			
Stroke	2	(0.7)	2	0.7	1	(0.4)	1	0.4	0			
Ischemic stroke	2	(0.7)	2	0.7	1	(0.4)	1	0.4	0			
Haemorrhagic stroke	0				0				0			
Transient ischaemic attack	0				0				0			
Ischemic stroke	0				0				0			
Haemorrhagic stroke	0				0				0			
Heart failure	0				0				0			
CV Death	1	(0.4)	1	0.4	0				0			

N: Number of subjects with one or more events,
%: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), EAC: Event adjudication committee
PYE: Patient years of exposure (1 PYE = 365.25 days),
STEMI: ST-segment elevation myocardial infarction
NSTEMI: Non ST-segment elevation myocardial infarction, CV: Cardiovascular,
Treatment emergent: 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.
Heart failure: All heart failures requiring hospitalisation defined as an admission that results in at least a 24 hour stay.

<u>イベント判定委員会により確定された心血管死</u>

IDegLira 群の 1 件の死亡に至った事象がイベント判定委員会により心血管死と確定された（2.7.4.2.1.3）。

<u>イベント判定委員会により確定された急性冠動脈症候群</u>

4 件の急性冠動脈症候群が疑われる事象がイベント判定委員会に送られ、そのうち 2 件がイベント判定委員会により確定された。この 2 件は同一の被験者に発現した事象であり、イベント判定委員会は

重複事象と判定した。その結果、IDeg 群で報告された当該事象は、イベント判定委員会により 1 件の急性心筋梗塞〔非 ST 上昇型心筋梗塞（NSTEMI）〕と確定され、要約表に含められた〔表 2.7.4.2-9 及び 4183 試験の治験総括報告書（Module 5.3.5.1）Appendix16.2.7, Listing 16.2.7.10〕。「急性心筋梗塞」は、重篤及び中等度の事象であり、IDeg の投与量の減量に至った。転帰は「回復」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〔4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.1〕。

イベント判定委員会により確定された脳血管系事象

3 件の脳血管系事象が疑われる事象がイベント判定委員会に送られた〔4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.9〕。いずれの事象もイベント判定委員会により脳血管系事象（虚血性脳卒中）と確定された〔4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.11〕。この内訳は、IDegLira 群で 2 件、IDeg 群で 1 件であった（表 2.7.4.2-9）。いずれの事象も重篤な有害事象、中等度で、治験薬との因果関係は「なし」と判定された。転帰は、IDeg 群の 1 件が「軽快」、IDegLira 群の 2 件が「未回復」又は「回復したが後遺症あり」であった。転帰が「回復したが後遺症あり」であった被験者は治験薬の投与を一時的に中断した〔4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.1〕。

イベント判定委員会により確定された入院を必要とする心不全

1 件の入院を必要とする心不全が疑われる事象がイベント判定委員会に送られた〔4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.9〕。当該事象は入院を必要とする心不全として確定されなかった〔4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.12〕。

イベント判定委員会により確定された MACE

イベント判定委員会に送られた 7 件の MACE のうち、IDegLira 群の 3 例 3 件及び IDeg 群の 2 例 2 件がイベント判定委員会により確定された〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.85〕（詳細は上述を参照のこと）。

4184 試験

IDegLira 群の 1 例 3 件、IDeg 群の 1 例 1 件の心血管系事象がイベント判定委員会に送られた（表 2.7.4.2-10）。イベント判定委員会に送られた事象のうち、IDegLira 群の 1 件がイベント判定委員会により心血管系事象と確定され、MACE に分類された〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.31〕。以下にイベント判定委員会が評価し、確定した事象を詳述する。

イベント判定委員会により確定された急性冠動脈症候群

IDegLira 群の 1 件の事象（「急性心筋梗塞」）がイベント判定委員会に送られ、イベント判定委員会により MACE として確定された〔表 2.7.4.2-10 及び 4184 試験の治験総括報告書（Module5.3.5.1）、Appendix 16.2.7, Listings 16.2.7.9〕。当該事象は重篤かつ重度で、転帰は「軽快」であった〔4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listings 16.2.7.1〕。治験責任医師により IDegLira との因果関係は「なし」と判定され、また当該事象による投与の変更はなかった（被験者番号：228001）。

イベント判定委員会により確定された脳血管系事象

2 件（各投与群に 1 件）の有害事象がイベント判定委員会に送られた〔4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.9〕が、いずれもイベント判定委員会により脳血管系事象として確定されなかった（表 2.7.4.2-10）。

イベント判定委員会により確定された入院を必要とする心不全

IDegLira 群の 1 件の心不全の事象がイベント判定委員会に送られた〔4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.9〕。当該事象はイベント判定委員会により入院を必要とする心不全として確定されなかった（表 2.7.4.2-10）。

表 2.7.4.2-10　イベント判定委員会により確定された心血管系事象（イベント判定委員会の分類別）
- SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	105				105			
PYE (years)	54.28				52.27			
EAC evaluated events	1	(1.0)	3	5.5	1	(1.0)	1	1.9
EAC confirmed events	1	(1.0)	1	1.8	0			
Acute coronary syndrome	1	(1.0)	1	1.8	0			
Acute myocardial infarction	1	(1.0)	1	1.8	0			
STEMI	0				0			
NSTEMI	1	(1.0)	1	1.8	0			
Silent myocardial infarction	0				0			
Unstable Angina pectoris	0				0			
Cerebrovascular event	0				0			
Stroke	0				0			
Ischaemic stroke	0				0			
Haemorrhagic stroke	0				0			
Transient ischaemic attack	0				0			
Ischaemic stroke	0				0			
Haemorrhagic stroke	0				0			
Heart failure	0				0			
CV Death	0				0			

N: Number of subjects with one or more events,
%: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days),
EAC: Event adjudication committee, STEMI: ST-segment elevation myocardial infarction, NSTEMI: Non ST-segment elevation myocardial infarction, CV: Cardiovascular,
Treatment emergent: 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.
Heart failure: All heart failures requiring hospitalisation defined as an admission that results in at least a 24 hour stay.

<u>イベント判定委員会により確定された MACE</u>

イベント判定委員会に送られた 3 件の MACE のうち、1 件の事象（上述した IDegLira 群の「急性心筋梗塞」）がイベント判定委員会により確定された〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.31〕（詳細は上述を参照のこと）。

2.7.4.2.1.7.3　MedDRA 検索により特定された心血管系事象

心血管系事象を抽出するため、事前規定した MedDRA 検索を実施した。検索に用いた基本語の一覧を 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.6 に示す。

4183 試験

MedDRA 検索で特定された心血管系事象を、器官別大分類及び基本語別に付録 2.7.4.7.2、表 2.7.4.7.2-1 に提示する。IDegLira 群において当該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（5.8%及び 6.0 件/100 人・年）は、IDeg 群（10.3%、11.8 件/100 人・年）と比較して少なく、リラグルチド群（6.2%、6.3 件/100 人・年）と同様であった。最も高頻度で報告された心血管系事象の器官別大分類は、「心臓障害」及び「一般・全身障害および投与部位の状態」であり、いずれの投与群でも特定の事象が多く発現することはなかった（付録 2.7.4.7.2、表 2.7.4.7.2-1）。

4184 試験

MedDRA 検索で特定された心血管系事象を、器官別大分類及び基本語別に付録 2.7.4.7.3、表 2.7.4.7.3-1 に提示する。当該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、IDeg 群（2.9%、7.7 件/100 人・年）と比較して、IDegLira 群（6.7%、16.6 件/100 人・年）で多かった。最も高頻度で報告された心血管系事象の器官別大分類は、「心臓障害」であり、いずれの投与群でも特定の事象が多く発現することはなかった（付録 2.7.4.7.3、表 2.7.4.7.3-1）。

2.7.4.2.1.7.4　MedDRA 検索により特定された不整脈に関連する有害事象

不整脈に関する事象を抽出するため、事前規定した MedDRA 検索を実施した。検索に用いた基本語の一覧を 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.6 に示す。

MedDRA 検索により特定された不整脈に関連する有害事象は、上述した心血管系事象の検索で特定された事象のみであった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.99 及び 4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.33〕。

2.7.4.2.1.7.5　心血管系疾患に関連するその他の安全性所見の要約

4183 試験

<u>脈拍数</u>

投与後 52 週において、脈拍数は IDeg 群と比較して IDegLira 群で有意に増加した〔群差（IDegLira 群－IDeg 群）の推定値：2.87 拍／分（95%信頼区間：1.43; 4.30）〕。IDegLira 群とリラグルチド群との間に統計的な有意差は認められなかった（2.7.4.4.4）。

<u>血圧</u>

投与後 52 週において、収縮期血圧は IDeg 群と比較しての IDegLira 群で有意に低下した〔群差（IDegLira 群－IDeg 群）の推定値：-2.05 mmHg（95%信頼区間：-4.02; -0.08）。IDegLira 群とリラグルチド群との比較では、統計的な有意差が認められた〔リラグルチド群に好ましい結果。群差（IDegLira

群－リラグルチド群）の推定値：2.88 mmHg（95%信頼区間：0.91; 4.85）〕。拡張期血圧については、投与群間に統計的な有意差は認められなかった（2.7.4.4.5）。

空腹時脂質

投与後 52 週において、総コレステロール及び低比重リポタンパク（LDL）コレステロールについて、IDegLira 群と IDeg 群との間で統計的な有意差が認められ（比の推定値に基づく）、IDegLira 群に好ましい結果が得られた。IDegLira 群とリラグルチド群との比較では、総コレステロール（IDegLira 群に好ましい結果）、遊離脂肪酸（IDegLira 群に好ましい結果）及び高比重リポタンパク（HDL）コレステロール（リラグルチド群に好ましい結果）に統計的な有意差が認められた（比の推定値に基づく）（2.7.4.3.3）。

4184 試験

脈拍数

投与後 26 週において、脈拍数は IDeg 群と比較して IDegLira 群で有意に増加した〔群差（IDegLira 群－IDeg 群）の推定値：7.73 拍／分（95%信頼区間：5.45; 10.01）〕（2.7.4.4.4）。

血圧

投与後 26 週における収縮期血圧及び拡張期血圧の変化量に、投与群間で統計的な有意差は認められなかった（2.7.4.4.5）。

空腹時脂質

投与後 26 週において、以下の空腹時脂質パラメータに投与群間で統計的な有意差が認められた：総コレステロール（IDegLira 群に好ましい結果）、LDL コレステロール（IDegLira 群に好ましい結果）及び HDL コレステロール（IDeg 群に好ましい結果）（2.7.4.3.3）。

2.7.4.2.1.7.6　要約

4183 試験では、5 件の心血管系事象がイベント判定委員会により確定された（いずれの事象も MACE に分類された）。その内訳は、IDegLira 群で 3 例 3 件、IDeg 群が 2 例 2 件であった。4184 試験では、IDegLira 群の 1 件の心血管系事象（MACE に分類）がイベント判定委員会により確定された。事前規定した心血管系事象の MedDRA 検索に基づく検討では、投与群間に一貫した違いは認められなかった。4183 試験では、心血管系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、IDeg 群と比較して、IDegLira 群で少なかった（IDegLira 群とリラグルチド群は同様）。一方、4184 試

験では、心血管系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、IDeg 群と比較して IDegLira 群で多かった。両試験ともに、最も高頻度で報告された心血管系事象の器官別大分類は、「心臓障害」及び「一般・全身障害および投与部位の状態」であり、いずれかの投与群で多く発現する事象はみられなかった。

いずれの試験でも、IDeg 群と比較して IDegLira 群で脈拍数の平均（安静時）の増加がみられた。4183 試験では、この IDegLira 群の増加の程度はリラグルチド群と同様であった。

投与終了時の収縮期血圧は、4183 試験では IDeg 群と IDegLira 群との間に統計的な有意差がみられた（IDegLira 群に好ましい結果）が、4184 試験では IDegLira 群と IDeg 群との間に有意差はみられなかった。いずれの試験でも、拡張期血圧において投与群間に統計的な有意差はみられなかった。

空腹時脂質については、IDegLira 群と IDeg 群との比較では、総コレステロール及び LDL コレステロールにおいて、いずれの試験でも投与群間に統計的な有意差がみられた（IDegLira 群に好ましい結果）。また、HDL コレステロールにおいて、4184 試験では投与群間に統計的な有意差がみられた（IDeg 群に好ましい結果）が、4183 試験では群間に有意差は認められなかった。IDegLira 群とリラグルチド群との比較では、総コレステロール（IDegLira 群に好ましい結果）、遊離脂肪酸（IDegLira 群に好ましい結果）及び HDL コレステロール（リラグルチド群に好ましい結果）に統計的な有意差が認められた。

2.7.4.2.1.8　膵炎又は膵炎が疑われる事象

2.7.4.2.1.8.1　評価方法

4183 試験及び 4184 試験では、急性膵炎又は慢性膵炎の既往歴がある被験者は除外された。また、試験期間中に無作為割り付けされた被験者において急性膵炎の疑いがあると治験責任医師が判断した場合、膵炎の確認検査が終了するまで、関連が疑われる治験薬（IDegLira を含む）の投与を中断することとした。膵炎が確認された場合は、被験者は試験を中止することとした。

膵炎又は膵炎が疑われる事象は、報告された有害事象に基づいて評価する。

本項では以下の事象について要約し、評価した。

- イベント判定委員会により確定された事象（膵炎、ならびにリパーゼ及びアミラーゼの増加）
- 事前規定した MedDRA 検索：
  - 膵炎に関連する有害事象
  - リパーゼ及びアミラーゼの増加に関連する有害事象

2.7.4.2.1.8.2　イベント判定委員会により判定された膵炎又は膵炎が疑われる事象

4183 試験

2 件の膵炎が疑われる事象がイベント判定委員会に送られた〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.134 及び Appendix 16.2.7、Listing 16.2.7.9〕。IDegLira 群の 1 件が軽度の急性膵炎と確定された〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.134 及び Appendix 16.2.7、Listing 16.2.7.15〕。当該事象は重篤及び重度で、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。治験薬の投与は中止され、本被験者は当該事象から回復した〔4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.2〕。

4184 試験

イベント判定委員会に送られた膵炎に関連する事象はなかった〔4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.15〕。

2.7.4.2.1.8.3　MedDRA 検索により特定された膵炎又は膵炎が疑われる有害事象

膵炎又は膵炎が疑われる有害事象を抽出するため、事前規定した MedDRA 検索を実施した。検索に用いた基本語の一覧を 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.6 に示す。

4183 試験

MedDRA 検索により 2 件の膵炎に関連する有害事象〔IDegLira 群：1 件（「急性膵炎」、イベント判定委員会により確定された事象）、リラグルチド群：1 件（「自己免疫性膵炎」）〕が特定された（付録 2.7.4.7.2、表 2.7.4.7.2-2）。

4184 試験

MedDRA 検索で特定された膵炎に関連する有害事象はなかった（付録 2.7.4.7.3、表 2.7.4.7.3-2）。

2.7.4.2.1.8.4　MedDRA 検索により特定されたリパーゼ及びアミラーゼ増加に関連する有害事象

リパーゼ及びアミラーゼ増加に関連する有害事象を抽出するため、事前規定した MedDRA 検索を実施した。検索に用いた基本語の一覧を 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.6 に示す。リパーゼ及びアミラーゼの臨床検査値に関する結果の詳細は、2.7.4.3.5 を参照のこと。

4183 試験

IDeg 群では、MedDRA 検索によりリパーゼ及びアミラーゼ増加に関連する有害事象は特定されなかった。これらの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、リラグルチド群（6.6%、7.4 件/100 人・年）と比較して IDegLira 群（2.5%、4.1 件/100 人・年）で低かった（付録 2.7.4.7.2、表 2.7.4.7.2-3）。

4184 試験

MedDRA 検索により「アミラーゼ増加」は特定されなかったが、「リパーゼ増加」は IDegLira 群の 2 例で 2 件特定された（付録 2.7.4.7.3、表 2.7.4.7.3-3）。

2.7.4.2.1.8.5　要約

4183 試験において、イベント判定委員会により IDegLira 群で膵炎が 1 件確定された。4184 試験ではイベント判定委員会に送られた膵炎に関連する事象はなかった。

4183 試験では、事前規定した MedDRA 検索により膵炎に関連する有害事象が 2 件（IDegLira 群及びリラグルチド群で各 1 件）特定された。4184 試験では MedDRA 検索で特定された膵炎に関連する有害事象はなかった。

4183 試験において、MedDRA 検索で特定されたリパーゼ及びアミラーゼ増加に関連する有害事象を発現した被験者の割合は低く、また、この割合はリラグルチド群と比較して IDegLira 群で低かった（IDeg 群で特定された事象はなかった）。4184 試験では MedDRA 検索により「アミラーゼ増加」は特定されなかったが、「リパーゼ増加」が IDegLira 群の 2 例で 2 件特定された。

2.7.4.2.1.9　新生物

2.7.4.2.1.9.1　評価方法

新生物は、報告された有害事象に基づいて評価する。

本項では以下の事象について要約し、評価した。

- イベント判定委員会により確定された事象（良悪性、原発組織／臓器及びステージの分類）
- 事前規定した MedDRA 検索

2.7.4.2.1.9.2　イベント判定委員会により確定された新生物

4183 試験

68 例 86 件の新生物に関連する事象がイベント判定委員会に送られ、14 例 14 件がイベント判定委員会により確定された（表 2.7.4.2-11）。IDegLira 群では、悪性新生物 1 件（限局性、胃腸）を含む 4 件が確定された。IDeg 群では、悪性新生物 1 件（転移性、肺／気管支）を含む 3 件が確定された。リラ

グルチド群では、悪性新生物 2 件（限局性、乳房及び皮膚）を含む 7 件が確定された〔表 2.7.4.2-11 及び 4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.13〕。詳細は、4183 試験の治験総括報告書（Module 5.3.5.1）、Section 12.5.5.5 を参照のこと。

表 2.7.4.2-11　イベント判定委員会により確定された新生物（イベント判定委員会の分類別） - SAS（4183 試験）

	IDegLira			IDeg			Lira		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	275			271			273		
PYE (years)	268.00			261.81			271.84		
EAC evaluated events	22(8.0)	25	9.3	19(7.0)	27	10.3	27(9.9)	34	12.5
EAC confirmed events	4(1.5)	4	1.5	3(1.1)	3	1.1	7(2.6)	7	2.6
Benign	3(1.1)	3	1.1	2(0.7)	2	0.8	5(1.8)	5	1.8
Colorectal	3(1.1)	3	1.1	2(0.7)	2	0.8	5(1.8)	5	1.8
Malignant	1(0.4)	1	0.4	1(0.4)	1	0.4	2(0.7)	2	0.7
Stage Localized	1(0.4)	1	0.4	0			2(0.7)	2	0.7
Breast	0			0			1(0.4)	1	0.4
Gastric/Intestinal	1(0.4)	1	0.4	0			0		
Skin	0			0			1(0.4)	1	0.4
Stage Metastatic	0			1(0.4)	1	0.4	0		
Lung/Bronchus	0			1(0.4)	1	0.4	0		
Pre malignant/carcinoma in situ/borderline	0			0			0		

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), EAC: Event adjudication committee, Treatment emergent: 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.

4184 試験

14 件の新生物に関連する事象がイベント判定委員会に送られた〔4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.9〕。

14 件（治験薬投与下であったのは 12 件）のうち 3 件〔IDeg 群：1 件、IDegLira 群：2 件（1 例）〕がイベント判定委員会により確定された（表 2.7.4.2-12）。詳細については 4184 試験の治験総括報告書（Module 5.3.5.1）、Section 12.5.5.5 を参照のこと。

表 2.7.4.2-12　イベント判定委員会により確定された新生物（イベント判定委員会の分類別） - SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	105				105			
PYE (years)	54.28				52.27			
EAC evaluated events	4	(3.8)	6	11.1	4	(3.8)	6	11.5
EAC confirmed events	1	(1.0)	2	3.7	1	(1.0)	1	1.9
Benign	1	(1.0)	1	1.8	0			
Colorectal	1	(1.0)	1	1.8	0			
Malignant	0				1	(1.0)	1	1.9
Stage Undetermined	0				1	(1.0)	1	1.9
Pancreatic	0				1	(1.0)	1	1.9
Pre-Malignant/ Carcinoma In Situ/ Borderline	1	(1.0)	1	1.8	0			
Stage Situ	1	(1.0)	1	1.8	0			
Colorectal	1	(1.0)	1	1.8	0			

N: Number of subjects with one or more events,
%: Percentage of subjects with one or more events,
E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), EAC: Event adjudication committee
Treatment emergent: 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.

2.7.4.2.1.9.3　MedDRA 検索により特定された新生物に関連する有害事象

新生物を抽出するため、事前規定した MedDRA 検索を実施した。検索に用いた基本語の一覧を 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.6 に示す。

4183 試験

MedDRA 検索により特定された新生物に関連する有害事象について、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、IDegLira 群で 8.7%、10.4 件/100 人・年、IDeg 群で 8.5%、11.8 件/100 人・年、リラグルチド群で 9.5%、11.0 件/100 人・年であり、3 つの投与群で同様であった。大部分の事象は、器官別大分類の「胃腸障害」及び「良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）」に分類される事象であった（付録 2.7.4.7.2、表 2.7.4.7.2-4）。

4184 試験

MedDRA 検索により特定された新生物に関連する有害事象について、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、IDegLira 群（3.8%、11.1 件/100 人・年）及び IDeg 群（3.8%、9.6 件/100

人・年）で同様であった。大部分の事象は、器官別大分類の「良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）」に分類される事象であった（付録 2.7.4.7.3、表 2.7.4.7.3-4）。

2.7.4.2.1.9.4　　要約

いずれの試験でも、IDegLira 群におけるイベント判定委員会が確定した新生物の発現件数は少なく、対照群と同様であった。MedDRA 検索の結果は、イベント判定委員会の判定に基づく結果と同様の傾向を示した。

2.7.4.2.1.10　甲状腺疾患

2.7.4.2.1.10.1　評価方法

甲状腺疾患は、報告された有害事象及び臨床検査のカルシトニンに基づいて評価する。
本項では以下の事象について要約し、評価した。

- イベント判定委員会により確定された事象
- 事前規定した MedDRA 検索：
  - 甲状腺疾患に関連する有害事象
  - カルシトニン増加に関連する有害事象

甲状腺新生物及び甲状腺髄様癌は新生物の MedDRA 検索（2.7.4.2.1.9）で特定された。

2.7.4.2.1.10.2　イベント判定委員会により確定された甲状腺疾患

4183 試験

14 件の甲状腺疾患に関連する事象がイベント判定委員会に送られた〔4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.9〕。このうち、イベント判定委員会により確定された事象はなかった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.120〕。

4184 試験

IDegLira 群の 1 件の甲状腺疾患に関連する事象がイベント判定委員会に送られた〔4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.9〕。当該事象は、イベント判定委員会により甲状腺摘出を必要とする甲状腺疾患又は甲状腺新生物として確定されなかった〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.36 及び Appendix 16.2.7、Listing 16.2.7.14〕。

2.7.4.2.1.10.3　MedDRA 検索により特定された甲状腺疾患に関連する有害事象

甲状腺疾患に関連する有害事象を抽出するため、事前規定した MedDRA 検索を実施した。検索に用いた基本語の一覧を 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.6 に示す。

4183 試験

MedDRA 検索により、甲状腺疾患に関連する有害事象が 16 例 19 件（IDegLira 群：5 例 6 件、IDeg 群：7 例 9 件、リラグルチド群：4 例 4 件）特定された。大部分の事象の器官別大分類は「内分泌障害」であった（付録 2.7.4.7.2、表 2.7.4.7.2-5）。

4184 試験

MedDRA 検索により IDegLira 群に 1 件の「甲状腺腫瘤」が特定された（付録 2.7.4.7.3、表 2.7.4.7.3-5）。当該事象はイベント判定委員会に送られた事象であった（2.7.4.2.1.10.2 参照）。

2.7.4.2.1.10.4　MedDRA 検索により特定されたカルシトニン増加に関連する有害事象

カルシトニン増加に関連する有害事象を抽出するため、事前規定した MedDRA 検索を実施した。検索に用いた基本語の一覧を 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.6 に示す。

カルシトニン値の概要は、2.7.4.3.4 を参照のこと。

4183 試験

MedDRA 検索により、カルシトニン増加に関連する有害事象が IDegLira 群で 1 件、リラグルチド群で 2 例 2 件特定された（3 件の基本語はいずれも「血中カルシトニン増加」）。IDeg 群では、カルシトニン増加に関連する有害事象は特定されなかった（付録 2.7.4.7.2、表 2.7.4.7.2-6）。

4184 試験

本試験では MedDRA 検索により、カルシトニン増加に関連する有害事象は特定されなかった。また、本試験において 20 ng/L を超えるカルシトニン値は報告されなかった（付録 2.7.4.7.3、表 2.7.4.7.3-6）。

2.7.4.2.1.10.5　要約

4183 試験及び 4184 試験のいずれにおいても、イベント判定委員会が確定した甲状腺疾患に関連する事象はなかった。事前規定した MedDRA 検索の結果、いずれの試験においても甲状腺疾患に関連する有害事象及びカルシトニン増加に関連する有害事象について、投与群間で明らかな違いは認められなかった。いずれの試験においても、カルシトニンに臨床的に問題となる変化は認められなかった。

2.7.4.2.1.11　腎機能の悪化

2.7.4.2.1.11.1　評価方法

腎機能の悪化に関連する有害事象を抽出するため、事前規定した MedDRA 検索を実施した。検索に用いた基本語の一覧を 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.6 に示す。

2.7.4.2.1.11.2　MedDRA 検索により特定された腎機能の悪化に関連する事象

4183 試験

MedDRA 検索により、腎機能の悪化に関連する有害事象が IDegLira 群で 1 件（「糸球体濾過率減少」）、IDeg 群で 1 件（「腎機能障害」）特定された。リラグルチド群で特定された事象はなかった（付録 2.7.4.7.2、表 2.7.4.7.2-7）。

4184 試験

MedDRA 検索により、腎機能の悪化に関連する有害事象が 2 例 2 件（IDegLira 群：「急性腎障害」、IDeg 群：「糸球体濾過率減少」）特定された（付録 2.7.4.7.3、表 2.7.4.7.3-7）。

2.7.4.2.1.11.3　要約

事前規定した MedDRA 検索の結果、いずれの試験においても、腎機能の悪化に関連する有害事象の発現に投与群間で明らかな違いは認められなかった。また、いずれの事象も 1 例からの報告であった。

2.7.4.2.1.12　免疫原性

2.7.4.2.1.12.1　評価方法

免疫原性に関連する可能性がある有害事象は、以下の事前規定した MedDRA 検索で特定された有害事象に基づいて評価する。

- アレルギー反応
- 注射部位反応

検索に用いた基本語の一覧を 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.6 に示す。

2.7.4.2.1.12.2　MedDRA 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

4183 試験

アレルギー反応に関連す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、IDegLira 群で 11.6%、14.9 件/100 人・年、IDeg 群で 9.2%、11.5 件/100 人・年、リラグルチド群で 7.0%、

8.5 件/100 人・年であった。高頻度で報告されたアレルギー反応に関連する有害事象は、いずれの投与群においても器官別大分類の「皮膚および皮下組織障害」に分類される「湿疹」であった（付録 2.7.4.7.2、表 2.7.4.7.2-8）。

4184 試験

アレルギー反応に関連す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、IDegLira 群で 1.9%、3.7 件/100 人・年、IDeg 群で 5.7%、11.5 件/100 人・年であった。高頻度で報告されたアレルギー反応に関連する有害事象は、いずれの投与群においても器官別大分類の「皮膚および皮下組織障害」に分類される「湿疹」であった（付録 2.7.4.7.3、表 2.7.4.7.3-8）。

2.7.4.2.1.12.3　MedDRA 検索により特定された注射部位反応に関連する有害事象

4183 試験

注射部位反応に関連する有害事象は、IDegLira 群で 9 例 10 件、IDeg 群で 6 例 6 件、リラグルチド群で 12 例 13 件特定された（付録 2.7.4.7.2、表 2.7.4.7.2-9）。

4184 試験

MedDRA 検索により、注射部位反応に関連する有害事象が 4 例 4 件（IDegLira 群：1 例、IDeg 群：3 例）特定された（付録 2.7.4.7.3、表 2.7.4.7.3-9）。

2.7.4.2.1.12.4　要約

事前規定した MedDRA 検索の結果、いずれの試験においてもアレルギー反応に関連する有害事象及び注射部位反応に関連する有害事象の発現に、投与群間で明らかな違いは認められなかった。

2.7.4.2.1.13　投薬過誤

IDegLira の使用に関連する投薬過誤は、低血糖（又は高血糖）や胃腸障害の有害事象のリスク増加といった臨床的帰結につながる可能性がある。過量投与については 2.7.4.5.5 に提示する。

4183 試験及び 4184 試験とも、IDegLira の最大用量は 50 用量ステップ（IDeg 50 単位、リラグルチド 1.8 mg）であった。両試験で用いたペン型注入器は、IDegLira の最大用量である 50 用量ステップまで設定が可能であった。

市販を予定しているペン型注入器はプレフィルドペン（PDS290 ペン型注入器に基づく）で、最大用量の 50 用量ステップまで設定が可能である。ペン型注入器の詳細情報は、Module 3 の PDS290 注入器の記載を参照のこと。

2.7.4.2.1.13.1　評価方法

治験薬に関連する投薬過誤には以下が含まれる。

- 誤った薬剤の投与又は誤った機器の使用
- 誤った投与経路による投与（皮下注射を筋肉注射する等）
- 自身を傷つけることを意図した（自殺企図等）過量投与
- 予期しない低用量又は高用量の投与

投薬過誤に関連する有害事象は、事前規定した MedDRA 検索で特定された有害事象に基づいて評価する。

2.7.4.2.1.13.2　MedDRA 検索により特定された投薬過誤に関連する有害事象

投薬過誤に関連する有害事象を特定するため、事前に規定した MedDRA 検索を実施した。検索に用いた基本語の一覧を 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.6 に示す。

4183 試験

MedDRA 検索により、投薬過誤に関連する有害事象が 7 例 7 件（IDegLira 群：2 件、IDeg 群：2 件、リラグルチド群：3 件）特定された（付録 2.7.4.7.2、表 2.7.4.7.2-10）。各投与群とも 1 例に「偶発的過量投与」が認められた。IDegLira 群の 1 例で「過量投与」、IDeg 群の 1 例で「誤用量投与」が認められた。また、リラグルチド群の 1 例で「誤薬投与」、1 例で「自殺企図」が認められた。いずれの、投薬過誤に関連する有害事象も、これらの事象の発現時に低血糖や高血糖、胃腸障害の有害事象など他の有害事象の発現は認められなかった〔4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.1〕。

4184 試験

IDeg 群で 1 件の投薬過誤（「誤薬投与」）が報告された（付録 2.7.4.7.3、表 2.7.4.7.3-10）。当該事象は非重篤で、軽度であった〔4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.1〕。

2.7.4.2.1.13.3　要約

事前規定した MedDRA 検索の結果、いずれの試験でも、投薬過誤に関連する有害事象の発現に投与群間で明らかな違いは認められなかった。

2.7.4.2.1.14　治験薬による病原体感染の疑い

治験薬による病原体感染が疑われる有害事象を抽出するため、事前規定した MedDRA 検索を実施した。検索に用いた基本語の一覧を 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.6 に示す。

いずれの試験においても、治験薬による病原体感染が疑われる有害事象は認められなかった。

2.7.4.2.1.15　胃腸障害の有害事象

2.7.4.2.1.15.1　評価方法

胃腸障害の有害事象は、事前規定した MedDRA 検索で特定された有害事象に基づいて評価する。

2.7.4.2.1.15.2　MedDRA 検索により特定された胃腸障害の有害事象

器官別大分類の「胃腸障害」に含まれる事象を胃腸障害の有害事象とした。

4183 試験

器官別大分類の「胃腸障害」に含まれる事象のうち、高頻度で報告された事象（基本語）は、「便秘」、「下痢」、「悪心」であった。これらの事象はいずれも、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、IDegLira 群で IDeg 群と比較して高く、リラグルチド群と比較して低かった（表 2.7.4.2-13）。

表 2.7.4.2-13　高頻度（5%以上の被験者）で報告された胃腸障害の有害事象 - SAS（4183 試験）

	IDegLira			IDeg			Lira		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	275			271			273		
PYE (years)	268.00			261.81			271.84		
胃腸障害									
便秘	27 (9.8)	28	10.45	12 (4.4)	12	4.58	38 (13.9)	42	15.45
下痢	15 (5.5)	20	7.46	12 (4.4)	14	5.35	24 (8.8)	31	11.40
悪心	9 (3.3)	13	4.85	5 (1.8)	7	2.67	23 (8.4)	30	11.04

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days). Most frequent ≥ 5% is defined as any treatment column having percentage of subjects with one or more events larger than or equal to 5%. MedDRA version 20.0.

IDegLira 群において胃腸障害の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（34.9%、69.8 件/100 人・年）は、IDeg 群（22.9%、42.0 件/100 人・年）と比較して高く、リラグルチド群（41.8%、80.2 件/100 人・年）と比較して低かった（Module 2.7.6.4、表 2.7.6.4.2-1）。このうち、重篤な有害事象とされたものは、IDegLira 群で 3 件（「胃食道逆流性疾患」、「大腸ポリープ」、「急性膵炎」）、リラグルチド群で 1 件（「自己免疫性膵炎」）であり、IDeg 群では認められなかった（Module 2.7.6.4、表 2.7.6.4.2-3）。大部分の胃腸障害の有害事象は軽度であり（Module 2.7.6.4、表 2.7.6.4.2-5 及び表 2.7.6.4.2-6）、重度であったのは IDegLira 群の 2 件（「大腸炎」及び「急性膵炎」）のみで、IDeg 群及びリラグルチド群では認められなかった（Module 2.7.6.4、表 2.7.6.4.2-4）。治験薬との因果関係が「可能性あり」又は「あり」と判断された胃腸障害の有害事象は、IDegLira 群では 187 件

中 68 件、IDeg 群では 110 件中 13 件、リラグルチド群では 218 件中 128 件であった（Module 2.7.6.4、表 2.7.6.4.2-1 及び表 2.7.6.4.2-2）。

胃腸障害の有害事象の持続時間を表 2.7.4.2-14 に示す。

表 2.7.4.2-14　　胃腸障害の有害事象の持続時間 - SAS（4183 試験）

		IDegLira			IDeg			Lira		
Number of subjects		275			271			273		
便秘 (days)										
N (%)	E	27	(9.8)	28	12	(4.4)	12	38	(13.9)	42
	e			18			8			30
Mean		164.7			146.5			126.5		
Median		128.0			104.0			58.5		
Min ; Max		2 ; 364			17 ; 323			3 ; 370		
下痢 (days)										
N (%)	E	15	(5.5)	20	12	(4.4)	14	24	(8.8)	31
	e			15			13			30
Mean		34.3			51.5			16.2		
Median		5.0			3.0			5.5		
Min ; Max		1 ; 290			1 ; 247			1 ; 105		
悪心 (days)										
N (%)	E	9	(3.3)	13	5	(1.8)	7	23	(8.4)	30
	e			13			7			29
Mean		6.8			8.3			75.1		
Median		1.0			2.0			9.0		
Min ; Max		1 ; 54			1 ; 21			1 ; 355		

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events E: Number of adverse events, e: number of events that had recovered/resolved by end of trial. Duration is calculated based on events that had recovered/resolved by end of trial. MedDRA version 20.0.

各時点に「便秘」を発現していた被験者の割合は、IDegLira 群では試験開始後最初の 32 週間は増加したが、それ以降は 6.5%前後で安定した。IDeg 群では投与後 8 週まで増加したが、それ以降は試験終了まで 2%～4%の間を変動した。リラグルチド群では試験開始後最初の 10 週間は約 9%まで急速に増加したが、投与後 32 週以降は IDegLira 群と同様に 6.5%前後で安定した（図 2.7.4.2-1）。「便秘」の持続時間の中央値は、IDegLira 群で 128.0 日、IDeg 群で 104.0 日、リラグルチド群で 58.5 日であった（表 2.7.4.2-14）。

各時点に「悪心」を発現していた被験者の割合は、リラグルチド群では投与開始最初の 6 週後に約 5%に増加したが、それ以降は緩やかに減少し、試験終了時には約 1%であった。IDegLira 群及び IDeg 群では、この割合は試験期間を通して低かった（図 2.7.4.2-1）。「悪心」の持続時間の中央値は、IDegLira 群で 1 日、IDeg 群で 2 日、リラグルチド群で 9 日であった（表 2.7.4.2-14）。

各時点に「下痢」を発現していた被験者の割合は、3 つの投与群とも試験期間を通して 0%～2%の間を変動し、群間に明らかな違いは認められなかった（図 2.7.4.2-1）。

各時点に「嘔吐」を発現していた被験者の割合は、試験期間を通して 3 つの投与群とも低く、群間に違いは認められなかった（図 2.7.4.2-1）。

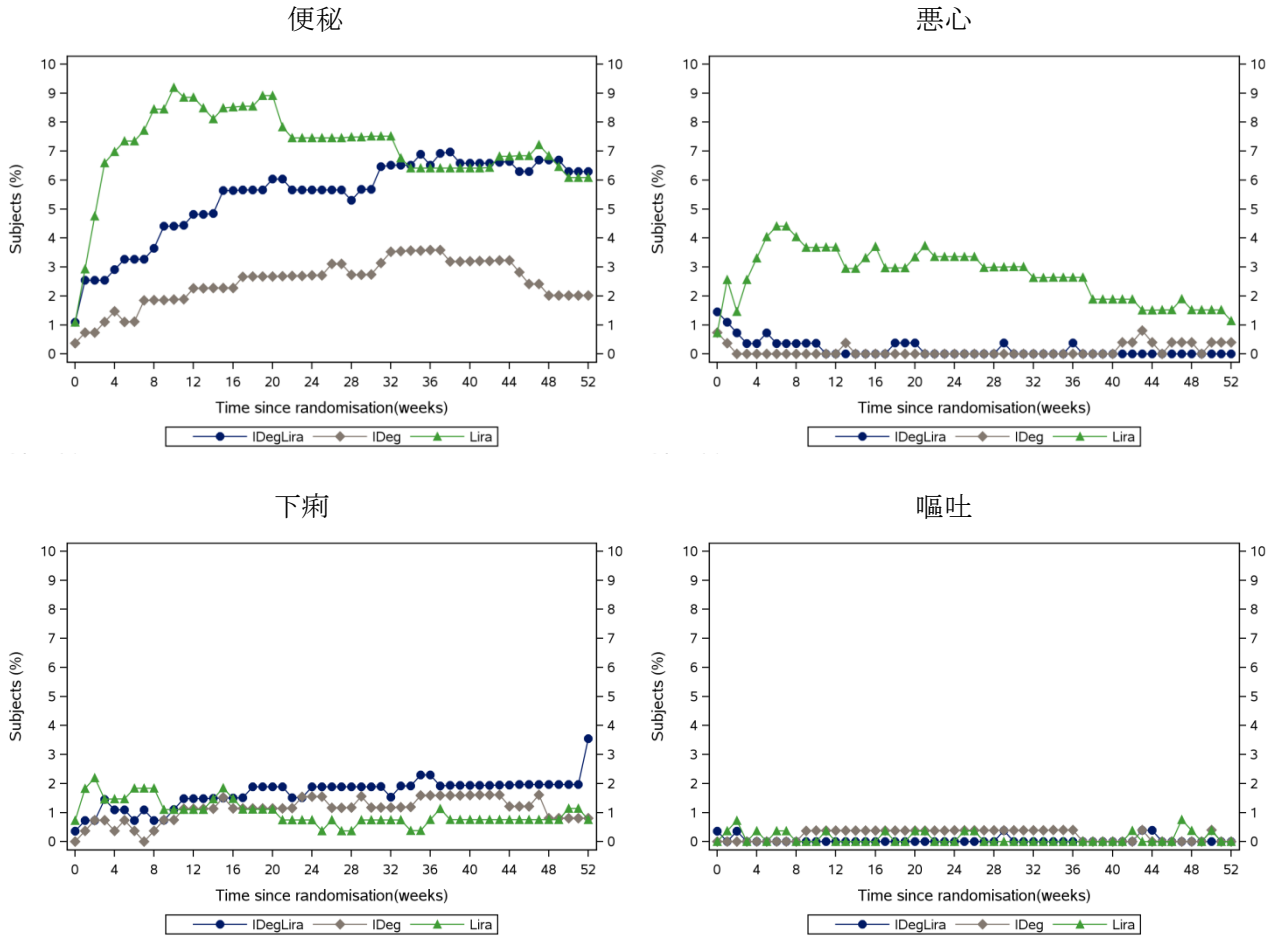


図 2.7.4.2-1　　各時点に胃腸障害の有害事象を発現していた被験者の割合 - SAS（4183 試験）

4184 試験

IDegLira 群において高頻度で報告された胃腸障害の有害事象は、「下痢」（36.8 件/100 人・年）、「悪心」（22.1 件/100 人・年）、「便秘」（18.4 件/100 人・年）、「嘔吐」（20.3 件/100 人・年）及び「腹部不快感」（14.7 件/100 人・年）であり、被験者の 7.6～14.3%で発現した（表 2.7.4.2-15）。同じ事象（基本語）は IDeg 群の被験者の 1.9～4.8%において報告され、その単位時間あたりの発現件数は 3.8～11.5 件/100 人・年であった。

表 2.7.4.2-15　高頻度（5%以上の被験者）で報告された胃腸障害の有害事象 - SAS（4184 試験）

	IDegLira			IDeg		
	N	(%)	E	R	N	(%)	E	R
Number of subjects	105				105			
胃腸障害								
下痢	15	(14.3)	20	36.85	5	(4.8)	6	11.48
悪心	10	(9.5)	12	22.11	4	(3.8)	5	9.57
便秘	9	(8.6)	10	18.42	4	(3.8)	4	7.65
嘔吐	9	(8.6)	11	20.27	2	(1.9)	2	3.83
腹部不快感	8	(7.6)	8	14.74	5	(4.8)	5	9.57

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days). Most frequent ≥ 5% is defined as any treatment column having percentage of subjects with one or more events larger than or equal to 5%. MedDRA version 20.0.

報告されたすべての胃腸障害の有害事象のうち（Module 2.7.6.5、表 2.7.6.5.2-1）、IDegLira 群の 88 件中 50 件及び IDeg 群の 40 件中 22 件は、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（Module 2.7.6.5、表 2.7.6.5.2-2）。報告された胃腸障害の有害事象はいずれも非重篤で、IDegLira 群の「悪心」1 件（中等度）を除き、軽度であった〔Module 2.7.6.5、表 2.7.6.5.2-3～表 2.7.6.5.2-6〕。この IDegLira 群の「悪心」1 件（中等度）は、非重篤であり、治験責任医師により治験薬（IDegLira）との因果関係が「あり」と判定された。

胃腸障害の有害事象の持続時間を表 2.7.4.2-16 に提示する。

表 2.7.4.2-16　　胃腸障害の有害事象の持続時間 - SAS（4184 試験）

		IDegLira		IDeg	
Number of subjects		105		105	
下痢 (days)					
N (%)	E	15 (14.3)	20	5 (4.8)	6
	e		17		6
Mean		23.4		41.3	
Median		15.0		9.0	
Min ; Max		1 ; 79		2 ; 164	
悪心 (days)					
N (%)	E	10 (9.5)	12	4 (3.8)	5
	e		12		4
Mean		22.9		42.0	
Median		6.0		12.5	
Min ; Max		1 ; 79		3 ; 140	
便秘 (days)					
N (%)	E	9 (8.6)	10	4 (3.8)	4
	e		5		2
Mean		42.8		10.0	
Median		21.0		10.0	
Min ; Max		6 ; 121		9 ; 11	

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, e: number of events that had recovered/resolved by end of trial, Duration is calculated based on events that had recovered/resolved by end of trial. MedDRA version 20.0.

各時点に「下痢」を発現していた被験者の割合は、IDeg 群と比較して IDegLira 群で高かった（図 2.7.4.2-2）。持続時間の中央値は IDegLira 群で 15.0 日間、IDeg 群で 9.0 日間であった（表 2.7.4.2-16）。

各時点に「悪心」を当該期間に発現していた被験者の割合は、IDegLira 群では試験後半の 12 週間と比較して前半の 12 週間で高かった（図 2.7.4.2-2）。IDeg 群では、「悪心」を発現していた被験者の割合は試験期間を通して安定していた。いずれの投与群においても「悪心」は一過性の事象であった。「悪心」の持続時間の中央値は、IDegLira 群で 6.0 日間、IDeg 群で 12.5 日間であった（表 2.7.4.2-16）。

各時点に「便秘」を発現していた被験者の割合は、IDegLira 群では投与開始最初の 6 週間と比較してその後の投与期間で高かった（図 2.7.4.2-2）。IDeg 群では「便秘」を発現していた被験者の割合は試験期間を通して安定していた。「便秘」の持続時間の中央値は、IDegLira 群で 21.0 日間、IDeg 群で 10.0 日間であった（表 2.7.4.2-16）。

「嘔吐」の発現は少なく、「嘔吐」を発現していた被験者の割合はいずれの投与群においても試験期間を通して安定していた（図 2.7.4.2-2）。

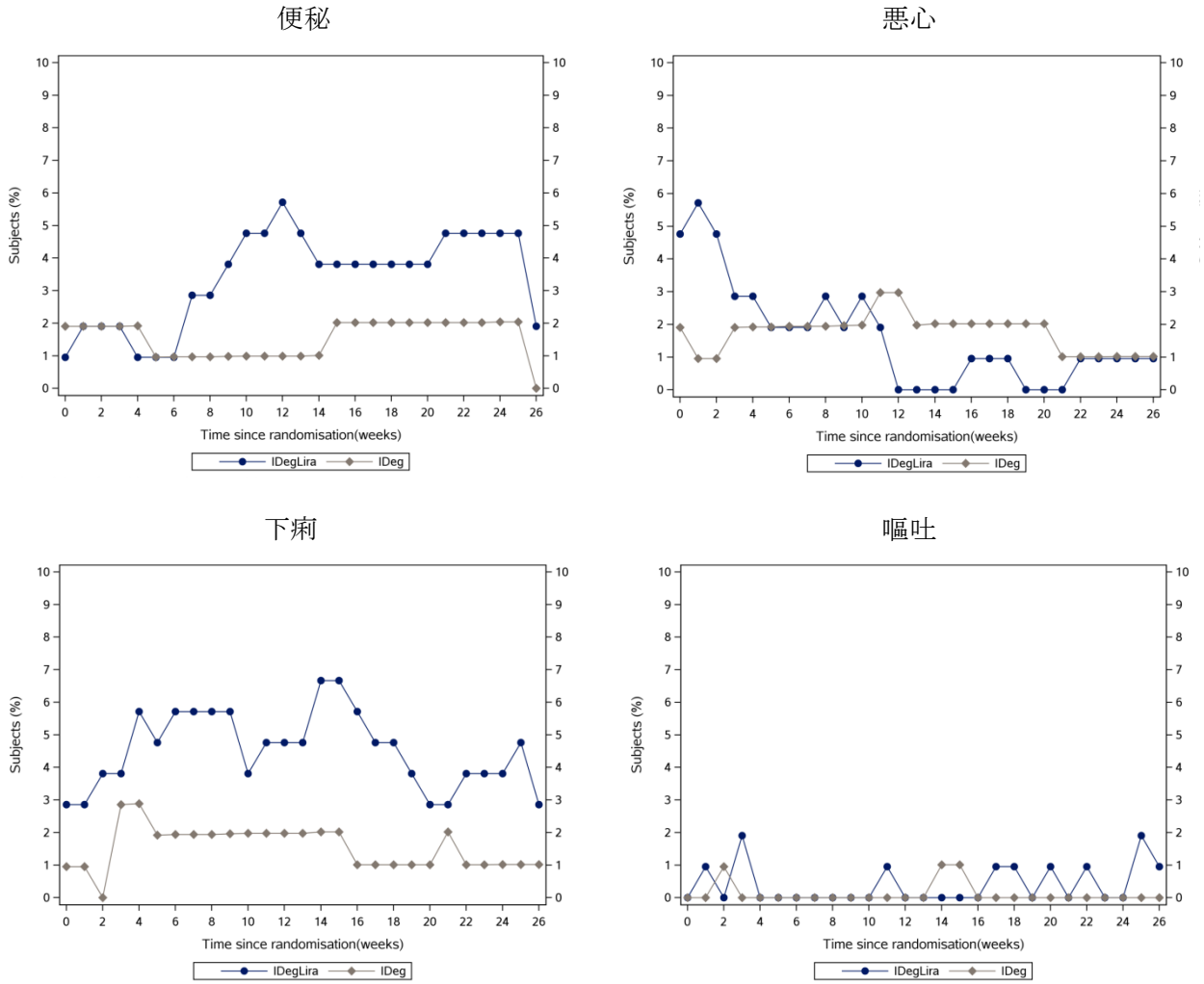


図 2.7.4.2-2　　各時点に胃腸障害の有害事象を発現していた被験者の割合 - SAS（4184 試験）

2.7.4.2.1.15.3　要約

IDegLira 群における胃腸障害の有害事象（器官別大分類「胃腸障害」に含まれる事象）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、IDeg 群と比較して高く、リラグルチド群（4183 試験）と比較して低かった。高頻度で報告された事象（基本語）は、「便秘」、「下痢」、「悪心」、「嘔吐」及び「腹部不快感」であった。いずれの投与群においても、これらの有害事象の大部分は非重篤で、軽度であり、一過性の事象であった。

2.7.4.2.1.16　高血糖

2.7.4.2.1.16.1　評価方法

高血糖に関連する有害事象は、事前規定した MedDRA 検索で特定された有害事象に基づいて評価する。

2.7.4.2.1.16.2　MedDRA 検索により特定された高血糖に関連する有害事象

これらの事象を抽出するため、すべての有害事象を対象に MedDRA 検索を実施した。検索に用いた基本語の一覧を 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.6 に示す。

4183 試験

本試験では、IDegLira 群で 1 件の高血糖に関連する有害事象（「尿中ケトン体陽性」）が特定された（付録 2.7.4.7.2、表 2.7.4.7.2-11）。

4184 試験

本試験で高血糖に関連する有害事象は特定されなかった（付録 2.7.4.7.3、表 2.7.4.7.3-11）。

2.7.4.2.1.16.3　要約

事前規定した MedDRA 検索により特定された高血糖に関連する有害事象は 1 件（4183 試験の IDegLira 群）のみであった。

2.7.4.2.1.17　稀な事象

稀な有害事象を抽出するため、事前規定した MedDRA 検索を実施した。検索に用いた基本語の一覧を 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.6 に示す。

両試験とも、抽出された事象は少なく（各投与群 7 件以下）、それぞれの器官別大分類及び基本語別の発現状況に、投与群間で明らかな違いは認められなかった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.204 及び 4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.48〕。

2.7.4.2.1.18　低血糖

2.7.4.2.1.18.1　評価方法

低血糖症状は血糖値が 3.1 mmol/L（56 mg/dL）未満のときに発現するため[2]、ノボ ノルディスク社は血糖値 3.1 mmol/L（56 mg/dL）未満を低血糖の cut-off 値として用いている。また、この cut-off 値〔3.1

mmol/L（56 mg/dL）未満〕は、IDegLira の臨床開発プログラムで使用した空腹時血糖値の目標値〔4～5 mmol/L（72～90 mg/dL）〕を十分に下回っており、この目標値をわずかに下回る程度の臨床的に問題とならないケースが低血糖として報告されることは避けられる。

本項では、低血糖（血糖自己測定による血糖値に基づく）を、ノボ ノルディスク社及び米国糖尿病学会（ADA）の低血糖の分類[3]に従って提示する（定義については後述を参照のこと）。

本項では、主に重大な又は血糖値確定低血糖について記載する（詳細は後述を参照のこと）。補足データ及び詳細情報については、4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1） Section 12.6 を参照のこと。

低血糖の定義

ノボ ノルディスク社の低血糖分類

- 重大な又は血糖値確定症候性低血糖：ADA の低血糖の分類[3]における重大な低血糖、又は低血糖の症状が認められ、血糖値が 3.1 mmol/L（56 mg/dL）未満と確認された低血糖。
- 重大な又は血糖値確定低血糖：ADA の低血糖の分類[3]における重大な低血糖、又は低血糖症状の有無に関わらず、血糖値が 3.1 mmol/L（56 mg/dL）未満と確認された低血糖。

ADA による低血糖の分類

- 重大な低血糖（severe hypoglycaemia）：第三者による処置（糖質の摂取、グルカゴンの投与又はその他の是正措置）が必要な低血糖。低血糖発現時に血糖値が測定されていない場合でも、血糖値が正常値に戻った後に神経学的回復がみられた場合、低血糖により症状が引き起こされたことの十分な根拠になると考えられる。
- 無症候性低血糖（asymptomatic hypoglycaemia）：発現時に典型的な低血糖の症状は認められないが、血糖値が 3.9 mmol/L（70 mg/dL）以下の低血糖。
- 確定症候性低血糖（documented symptomatic hypoglycaemia）：発現時に典型的な低血糖症状が認められ、血糖値が 3.9 mmol/L（70 mg/dL）以下の低血糖。
- 擬似低血糖（pseudo-hypoglycaemia）：糖尿病患者において典型的な低血糖の症状が認められ、血糖値が 3.9 mmol/L（70 mg/dL）を超えるが、それに近い値の低血糖。
- 推定症候性低血糖（probable symptomatic hypoglycaemia）：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 3.9 mmol/L（70 mg/dL）以下であると推測される低血糖。

夜間低血糖の定義

- 発現時刻が 00：01 から 05：59（両時刻を含む）の低血糖。

本臨床概要に記載する低血糖は、特段の記載がない限り、治験薬投与下で発現した低血糖である。治験薬投与下の低血糖は、無作為割り付けされた治療の投与開始日から最終投与 7 日後までに発現した低血糖と定義した。

低血糖の要約統計量は SAS を対象とし、低血糖の解析は FAS に基づき実施した。

低血糖の発現件数は、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析回帰モデルを用いて解析した。本モデルには治療及び前治療の糖尿病治療を固定効果として含めた。

2.7.4.2.1.18.2　すべての低血糖（分類別）

4183 試験

すべての低血糖の発現状況を表 2.7.4.2-17 に示す。低血糖を発現した被験者の一覧は 4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.7 を参照のこと。

重篤な有害事象として報告された低血糖が 2 件認められた。その内訳は、IDegLira 群の 1 件の「低血糖」及び IDeg 群の 1 件の「低血糖性意識消失」（Module 2.7.6.4、表 2.7.6.4.2-3）であった。いずれの事象も、1～2 日以内に回復した〔4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.2〕。

表 2.7.4.2-17　すべての低血糖（分類別） - SAS（4183 試験）

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	275				271				273			
PYE (years)	268.00				261.81				271.84			
Severe or BG confirmed symptomatic hypoglycaemia	53	(19.3)	135	50.37	80	(29.5)	362	138.27	3	(1.1)	4	1.47
Severe or BG confirmed hypoglycaemia	106	(38.5)	467	174.25	148	(54.6)	869	331.92	6	(2.2)	13	4.78
ADA	240	(87.3)	4830	1802.24	250	(92.3)	6340	2421.63	60	(22.0)	162	59.59
Severe hypoglycaemia	1	(0.4)	1	0.37	4	(1.5)	6	2.29	0			
Documented symptomatic hypoglycaemia	117	(42.5)	791	295.15	144	(53.1)	1375	525.20	16	(5.9)	26	9.56
Asymptomatic hypoglycaemia	229	(83.3)	3670	1369.40	224	(82.7)	4353	1662.68	43	(15.8)	113	41.57
Probably symptomatic hypoglycaemia	44	(16.0)	106	39.55	30	(11.1)	171	65.32	8	(2.9)	9	3.31
Pseudo-hypoglycaemia	37	(13.5)	262	97.76	51	(18.8)	435	166.15	8	(2.9)	14	5.15
ADA unclassifiable hypoglycaemia	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of events, R: Rate (number of events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association.
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode.
Confirmed symptomatic hypoglycaemia: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia.

4184 試験

すべての低血糖の発現状況を表 2.7.4.2-18 に示す。低血糖を発現した被験者の一覧は 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.7 を参照のこと。

重篤な有害事象として報告された低血糖はなかった（Module 2.7.6.5、表 2.7.6.5.2-3）。

表 2.7.4.2-18　　すべての低血糖（分類別） - SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	105				105			
PYE (years)	54.28				52.27			
Severe or BG confirmed symptomatic hypoglycaemia	15	(14.3)	52	95.80	18	(17.1)	43	82.27
Severe or BG confirmed hypoglycaemia	30	(28.6)	124	228.45	32	(30.5)	109	208.55
ADA	78	(74.3)	780	1437.05	69	(65.7)	717	1371.84
Severe hypoglycaemia	1	(1.0)	1	1.84	0			
Documented symptomatic hypoglycaemia	39	(37.1)	211	388.74	42	(40.0)	255	487.89
Asymptomatic hypoglycaemia	64	(61.0)	532	980.14	56	(53.3)	432	826.55
Probably symptomatic hypoglycaemia	12	(11.4)	19	35.01	5	(4.8)	7	13.39
Pseudo-hypoglycaemia	11	(10.5)	17	31.32	8	(7.6)	23	44.01
ADA unclassifiable hypoglycaemia	0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events,
E: Number of events,
R: Rate (number of events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association.
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode
Confirmed symptomatic hypoglycaemia: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia

2.7.4.2.1.18.3　重大な又は血糖値確定低血糖

4183 試験

4183 試験では、52 週間の投与期間における重大な又は血糖値確定低血糖の発現件数は、検証的セカンダリーエンドポイントであった。

52 週間の投与期間において重大な又は血糖値確定低血糖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、IDegLira 群で 38.5%及び 174.3 件/100 人・年、IDeg 群で 54.6%及び 331.9 件/100 人・年、リラグルチド群で 2.2%及び 4.8 件/100 人・年であった（表 2.7.4.2-17）。

統計解析結果：

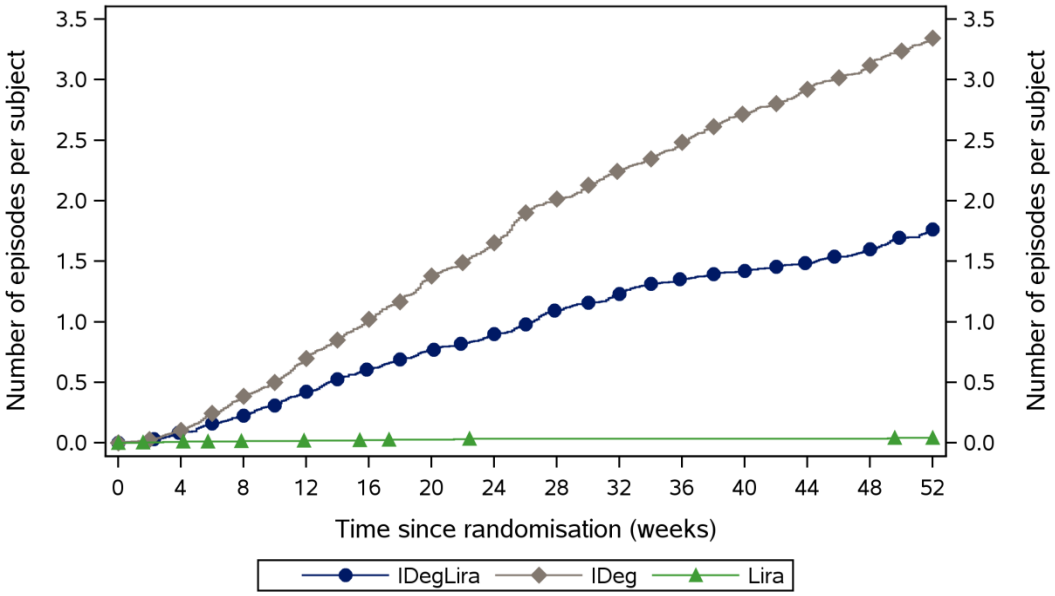
IDeg 群との比較では、比（IDegLira 群／IDeg 群）の推定値は 0.48〔95%信頼区間：0.35; 0.68、p<0.0001（優越性に対する p 値）〕であり、IDegLira の IDeg に対する優越性が検証された（表 2.7.4.2-19）。リラグルチド群との比較では、比（IDegLira 群／リラグルチド群）の推定値は 37.58（95%信頼区間：19.80; 71.31、p<0.0001）であり、52 週間の重大な又は血糖値確定低血糖の単位時間あたりの発現件数は、リラグルチド群と比較して IDegLira 群で統計的に有意に多かった。

表 2.7.4.2-19　　重大な又は血糖値確定低血糖 - 統計解析 - FAS（4183 試験）

	FAS	N	Estimate	95% CI	p-value
Severe or BG confirmed hypoglycaemia					
LSMeans, rate (events per 100 PYE)					
IDegLira	275	275	157.47		
IDeg	271	271	325.30		
Lira	273	273	4.19		
Treatment rate ratio					
IDegLira / IDeg			0.48	[0.35 ; 0.68]	<.0001
IDegLira / Lira			37.58	[19.80 ; 71.31]	<.0001

FAS: Full analysis set, N: Number of subjects contributing to the analysis, CI: Confidence interval, PYE: Patient years of exposure (1 PYE = 365.25 days), OAD: Oral antidiabetic drug. BG: Blood glucose. Negative binomial regression: The number of events is analysed using a negative binomial regression model (log link) with the logarithm of the treatment emergent exposure time (100 years) as offset. The model includes treatment and pre-trial OAD treatment as fixed factors. P-value: Two-sided p-value for test of superiority.

いずれの投与群でも、被験者あたりの重大な又は血糖値確定低血糖の発現件数は、試験期間を通して概ね一定に推移した（図 2.7.4.2-3）。



Safety analysis set, Observed data, Severe or BG confirmed: An episode that is severe according to the ADA classification or BG confirmed by a plasma glucose value <3.1 mmol/L (56mg/dL) with or without symptoms consistent with hypoglycaemia, ADA: American Diabetes Association, BG: Blood glucose

図 2.7.4.2-3　　重大な又は血糖値確定低血糖 - 平均累積関数 - SAS（4183 試験）

IDegLira 群及び IDeg 群の重大な又は血糖値確定低血糖の大部分は、午前 6:00～8:00 の間に発現した〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Figure 14.3.1.235～14.3.1.237〕。

4184 試験

重大な又は血糖値確定低血糖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、IDegLira 群で 28.6%及び 228.45 件/100 人・年、IDeg 群で 30.5%及び 208.55 件/100 人・年であった。

統計解析結果：

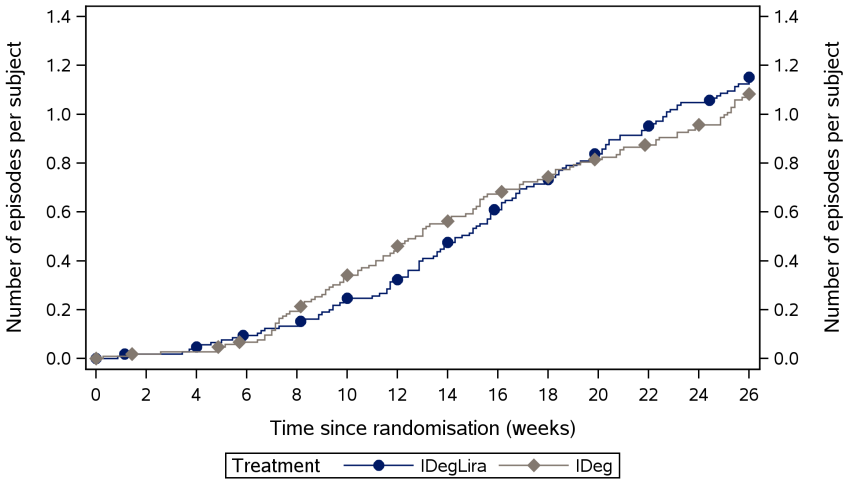
投与群間で統計的な有意差は認められなかった（表 2.7.4.2-20）。

表 2.7.4.2-20　　重大な又は血糖値確定低血糖 - 統計解析 - FAS（4184 試験）

	FAS	N	Estimate	95% CI	P-value
Severe or BG confirmed hypoglycaemia					
LSMeans, rate (events per 100 PYE)					
IDegLira	105	105	219.68		
IDeg	105	105	189.93		
Treatment rate ratio					
IDegLira / IDeg			1.16	[0.57;2.34]	0.6853

FAS: Number of subjects in full analysis set
N: Number of subjects contributing to the analysis, CI: Confidence interval
PYE: Patient years of exposure (1 PYE = 365.25 days)
BG: Blood glucose , ADA: American Diabetes Association
Severe or BG confirmed: An episode that is severe according to the ADA classification or BG confirmed by a plasma glucose value <3.1 mmol/L (56mg/dL) with or without symptoms consistent with hypoglycaemia
P-value: Two-sided p-value for test of no difference. No correction for multiplicity.
Number of hypoglycaemic episodes are analysed using a negative binomial regression model with a log link and the logarithm of the exposure time as offset.
The model includes treatment and pre-trial anti-diabetic treatment as fixed factors.

いずれの投与群でも、被験者あたりの重大な又は血糖値確定低血糖の発現件数は、試験期間を通して概ね一定に推移した（図 2.7.4.2-4）。



Safety analysis set, Observed data, BG: Blood glucose
Severe or BG confirmed: An episode that is severe according to the ADA classification or BG confirmed by a plasma glucose value <3.
1 mmol/L (56mg/dL) with or without symptoms consistent with hypoglycaemia
nn9068/nn9068-4184/ctr_20180417_er
18APR2018:10:45:49 - f_mcf_hypog.sas/f_mcf_sev_bg_conf_trtem_sas.png

図 2.7.4.2-4　　重大な又は血糖値確定低血糖 - 平均累積関数 - SAS（4184 試験）

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、午前 06:00 から 08:00 の間に発現した〔4184 試験の治験総括報告書（Module 5.3.5.1）, EOT Figure 14.3.1.64 及び 14.3.1.65〕。

2.7.4.2.1.18.4　重大な又は血糖値確定症候性低血糖

4183 試験

重大な又は血糖値確定症候性低血糖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、IDegLira 群で 19.3%及び 50.4 件/100 人・年、IDeg 群で 29.5%及び 138.3 件/100 人・年、リラグルチド群で 1.1%及び 1.5 件/100 人・年であった（表 2.7.4.2-17）。

統計解析結果：

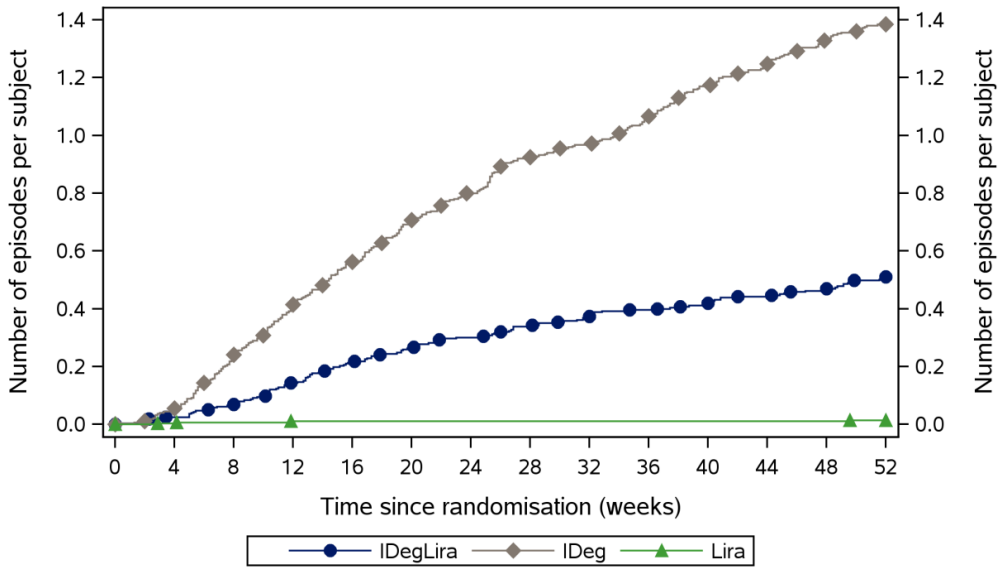
IDeg 群との比較では、比（IDegLira 群／IDeg 群）の推定値は 0.32（95%信頼区間：0.20; 0.51、p<0.0001）であり、重大な又は血糖値確定症候性低血糖の単位時間あたりの発現件数は、IDeg 群と比較して IDegLira 群で統計的に有意に少なかった（表 2.7.4.2-21）。リラグルチド群との比較では、比（IDegLira 群／リラグルチド群）の推定値は 34.49（95%信頼区間：11.51; 100.32、p<0.0001）であり、重大な又は血糖値確定症候性低血糖の単位時間あたりの発現件数は、リラグルチド群で統計的に有意に少なかった。

表 2.7.4.2-21　　重大な又は血糖値確定症候性低血糖 - 統計解析 - FAS（4183 試験）

	FAS	N	Estimate	95% CI	p-value
Severe or BG confirmed symptomatic hypoglycaemia					
LSMeans, rate (events per 100 PYE)					
IDegLira	275	275	42.42		
IDeg	271	271	134.39		
Lira	273	273	1.23		
Treatment rate ratio					
IDegLira / IDeg			0.32	[0.20 ; 0.51]	<.0001
IDegLira / Lira			34.49	[11.51 ;103.32]	<.0001

FAS: Full analysis set, N: Number of subjects contributing to the analysis, CI: Confidence interval, PYE: Patient years of exposure (1 PYE = 365.25 days), OAD: Oral antidiabetic drug. BG: Blood glucose. Negative binomial regression: The number of events is analysed using a negative binomial regression model (log link) with the logarithm of the treatment emergent exposure time (100 years) as offset. The model includes treatment and pre-trial OAD treatment as fixed factors. P-value: Two-sided p-value for test of no treatment difference. No correction for multiplicity.

いずれの投与群でも、被験者あたりの重大な又は血糖値確定症候性低血糖の発現件数は、試験期間を通して概ね一定に推移した（図 2.7.4.2-5）。



Safety analysis set, Observed data, Severe or BG confirmed symptomatic: An episode that is severe according to the ADA classification or BG confirmed by a plasma glucose value <3.1 mmol/L (56mg/dL) with symptoms consistent with hypoglycaemia, ADA: American Diabetes Association, BG: Blood glucose

図 2.7.4.2-5　　重大な又は血糖値確定症候性低血糖 - 平均累積関数 - SAS（4183 試験）

重大な又は血糖値確定症候性低血糖は一日を通してほぼ均等に発現した〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Figures 14.3.1.238～14.3.1.240〕。

4184 試験

重大な又は血糖値確定症候性低血糖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、IDegLira 群で 14.3%及び 95.80 件/100 人・年、IDeg 群で 17.1%及び 82.27 件/100 人・年であった（表 2.7.4.2-18）。

統計解析結果：

投与群間で統計的な有意差は認められなかった（表 2.7.4.2-22）。

表 2.7.4.2-22　　重大な又は血糖値確定症候性低血糖 - 統計解析 - FAS（4184 試験）

	FAS	N	Estimate	95% CI	P-value
Severe or BG confirmed symptomatic hypoglycaemia					
LSMeans, rate (events per 100 PYE)					
IDegLira	105	105	84.85		
IDeg	105	105	80.67		
Treatment rate ratio					
IDegLira / IDeg			1.05	[0.40;2.77]	0.9184

FAS: Number of subjects in full analysis set,
N: Number of subjects contributing to the analysis, CI: Confidence interval,
PYE: Patient years of exposure (1 PYE = 365.25 days),
BG: Blood glucose , ADA: American Diabetes Association,
Severe or BG confirmed symptomatic: An episode that is severe according to the ADA classification or BG confirmed by a plasma glucose value <3.1 mmol/L (56mg/dL) with symptoms consistent with hypoglycaemia,
P-value: Two-sided p-value for test of no difference. No correction for multiplicity. Number of hypoglycaemic episodes are analysed using a negative binomial regression model with a log link and the logarithm of the exposure time as offset. The model includes treatment and pre-trial anti-diabetic treatment as fixed factors.

いずれの投与群でも、被験者あたりの重大な又は血糖値確定症候性低血糖の発現件数は、試験期間を通して概ね一定に推移した（図 2.7.4.2-6）。

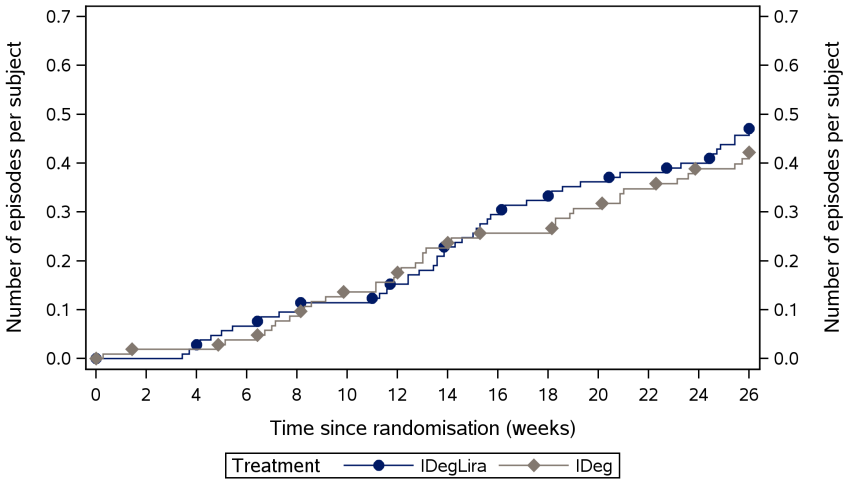


図 2.7.4.2-6　　重大な又は血糖値確定症候性低血糖 - 平均累積関数 - SAS（4184 試験）

いずれの投与群でも、重大な又は血糖値確定症候性低血糖の大部分は、午前 06:00 から 08:00 の間に発現した〔4184 試験の治験総括報告書（Module 5.3.5.1）, EOT Figure 14.3.1.66 及び 14.3.1.67〕。

2.7.4.2.1.18.5　夜間低血糖

4183 試験

夜間低血糖の発現状況を表 2.7.4.2-23 に示す。低血糖を発現した被験者の一覧は 4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.7 を参照のこと。

表 2.7.4.2-23　　夜間低血糖（分類別） - SAS（4183 試験）

	IDegLira			IDeg			Lira		
	N	(%)	E R	N	(%)	E R	N	(%)	E R
Number of subjects	275			271			273		
PYE (years)	268.00			261.81			271.84		
Nocturnal severe or BG confirmed symptomatic hypoglycaemia	13	(4.7)	16 5.97	21	(7.7)	42 16.04	0		
Nocturnal severe or BG confirmed hypoglycaemia	27	(9.8)	66 24.63	45	(16.6)	132 50.42	0		
ADA	103	(37.5)	529 197.39	136	(50.2)	1050 401.06	5	(1.8)	6 2.21
Severe hypoglycaemia	0			0			0		
Documented symptomatic hypoglycaemia	30	(10.9)	61 22.76	52	(19.2)	195 74.48	0		
Asymptomatic hypoglycaemia	83	(30.2)	439 163.81	103	(38.0)	724 276.54	5	(1.8)	6 2.21
Probably symptomatic hypoglycaemia	6	(2.2)	12 4.48	7	(2.6)	11 4.20	0		
Pseudo-hypoglycaemia	2	(0.7)	17 6.34	12	(4.4)	120 45.84	0		
Unclassifiable hypoglycaemia	0			0			0		

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E:Number of events, R: Rate (number of events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association.
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode.
Confirmed symptomatic hypoglycaemia: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia.
Nocturnal period: The period between 00:01 and 05:59 a.m. (both included).

重大な又は血糖値確定夜間低血糖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、IDegLira 群で 9.8%及び 24.6 件/100 人・年、IDeg 群で 16.6%及び 50.4 件/100 人・年であった。リラグルチド群では当該低血糖の報告はなかった（表 2.7.4.2-23）。

重大な又は血糖値確定症候性夜間低血糖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、IDegLira 群で 4.7%及び 6.0 件/100 人・年、IDeg 群で 7.7%及び 16.0 件/100 人・年でであった。リラグルチド群では当該低血糖の報告はなかった（表 2.7.4.2-23）。

統計解析結果：

IDeg 群との比較では、比（IDegLira 群／IDeg 群）の推定値は、重大な又は血糖値確定夜間低血糖の単位時間あたりの発現件数では 0.47（95%信頼区間：0.25; 0.89、p=0.0212）、重大な又は血糖値確定症候性夜間低血糖では 0.38（95%信頼区間：0.17; 0.88、p=0.0229）であった。いずれも、その単位時間あたりの発現件数は IDeg 群と比較して IDegLira 群で統計的に有意に少なかった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.226〕。リラグルド群で夜間低血糖の報告がなかったことから、リラグルチド群を含めた統計解析は実施しなかった。

4184 試験

夜間低血糖の発現状況を表 2.7.4.2-24 に示す。低血糖を発現した被験者の一覧は 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7, Listing 16.2.7.7 を参照のこと。

表 2.7.4.2-24　　夜間低血糖（分類別） - SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	105				105			
PYE (years)	54.28				52.27			
Severe or BG confirmed symptomatic hypoglycaemia	4	(3.8)	4	7.37	6	(5.7)	8	15.31
Severe or BG confirmed hypoglycaemia	8	(7.6)	26	47.90	10	(9.5)	19	36.35
ADA	28	(26.7)	152	280.04	34	(32.4)	125	239.16
Severe hypoglycaemia	0				0			
Documented symptomatic hypoglycaemia	13	(12.4)	30	55.27	18	(17.1)	44	84.19
Asymptomatic hypoglycaemia	18	(17.1)	119	219.24	25	(23.8)	74	141.58
Probably symptomatic hypoglycaemia	1	(1.0)	1	1.84	1	(1.0)	1	1.91
Pseudo-hypoglycaemia	1	(1.0)	2	3.68	2	(1.9)	6	11.48
Unclassifiable hypoglycaemia	0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events,
E: Number of events,
R: Rate (number of events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association.
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode
Confirmed symptomatic hypoglycaemia: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia

重大な又は血糖値確定夜間低血糖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、IDegLira 群で 7.6%及び 47.90 件/100 人・年、IDeg 群で 9.5%及び 36.35 件/100 人・年であった。重大な又は血糖値確定症候性夜間低血糖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、IDegLira 群で 3.8%及び 7.37 件/100 人・年、IDeg 群で 5.7%及び 15.31 件/100 人・年であった（表 2.7.4.2-24）。

統計解析結果：

投与群間で統計的な有意差は認められなかった〔4184 試験の治験総括報告書（Module 5.3.5.1）, EOT Table 14.3.1.55〕。

2.7.4.2.1.18.6　要約

「重大な又は血糖値確定低血糖」及び「重大な又は血糖値確定症候性低血糖」の単位時間あたりの発現件数は、4183 試験では IDeg 群と比較して IDegLira 群で統計的に有意に少なかった。IDeg 群の投与量の上限が 50 単位であった 4184 試験では、これらの低血糖の単位時間あたりの発現件数について、IDegLira 群と IDeg 群の間に統計的な有意差は認められなかった。予測されたとおり、これらの低血糖

の単位時間あたりの発現件数は、リラグルチド群と比較して IDegLira 群で統計的に有意に多かった（4183 試験）。

重大な低血糖は少なかった。2 試験で報告された重大な低血糖は 8 件であり、その内訳は、IDegLira で 2 例 2 件（各試験で 1 件）、IDeg 群で 4 例 6 件（いずれも 4183 試験で報告）であった。

夜間低血糖の発現は少なかった。リラグルチド群では、夜間の無症候性低血糖が数件発現したのみであった。夜間低血糖の発現状況は全体の低血糖の結果と一致しており、夜間低血糖の単位時間あたりの発現件数は、4183 試験では IDeg 群と比較して IDegLira 群で統計的に有意に少なく、4184 試験では IDegLira 群と IDeg 群との間に統計的な有意差は認められなかった。

2.7.4.2.1.19　急性胆石症

2.7.4.2.1.19.1　評価方法

急性胆石症に関連する有害事象は、事前規定した MedDRA 検索で特定された有害事象に基づいて評価する。検索に用いた基本語の一覧を付録 2.7.4.7.5、表 2.7.4.7.5-5 に示す。

2.7.4.2.1.19.2　MedDRA 検索により特定された急性胆石症に関連する有害事象

4183 試験

胆石症に関連する有害事象が 11 件（IDegLira 群及びリラグルチド群：いずれも 3 例 4 件、IDeg 群：3 例 3 件）特定された。IDegLira 群の 3 件及びリラグルチド群の 2 件の試験終了時の転帰は「回復」であった。基本語別では、「胆石症」が各投与群の 3 例で認められ、いずれの事象も非重篤で、軽度であった。「胆嚢炎」が IDegLira 群で 1 件、「急性胆嚢炎」がリラグルチド群で 1 件認められた。いずれの事象も重篤で、重度であったが、試験終了までに回復した〔付録 2.7.4.7.5、表 2.7.4.7.5-3 及び 4183 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.1〕。

4184 試験

胆石症に関連する有害事象は、IDeg 群で 2 例 2 件（「急性胆嚢炎」及び「胆石症」）特定されたが、IDegLira 群では認められなかった。「急性胆嚢炎」は重篤で、中等度であった。「胆石症」は非重篤で、軽度であった〔4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.1〕。

2.7.4.2.1.19.3　要約

事前規定した MedDRA 検索の結果、いずれの試験においても胆石症に関連する有害事象の発現に投与群間で明らかな違いは認められなかった。また、いずれの事象も 1 例又は数例からの報告であった。

2.7.4.2.2　　個別有害事象の文章による説明

完了した試験における有害事象の叙述は各試験の治験総括報告書（Module 5）、Section 14.3.3 を参照のこと。

2.7.4.3 臨床検査値の評価

2.7.4.3.1　　血液学的検査

評価方法

4183 試験及び 4184 試験で測定した血液学的検査パラメータは以下のとおりであった。

- ヘモグロビン
- ヘマトクリット
- 血小板数
- 赤血球数
- 白血球数
- 白血球分画（好酸球、好中球、好塩基球、単球及びリンパ球）

いずれの試験においても、スクリーニング（ベースライン値）、投与後 12 週及び 26 週（加えて 4183 試験では投与後 38 週及び 52 週）に検体採取を行った。

血液学的検査パラメータの基準値については、4183 試験及び 4184 試験の各治験総括報告書（Module 5.3.5.1）、Appendix 16.2.8、Listing 16.2.8.1 を参照のこと。統計解析は実施しなかった。

4183 試験

臨床検査値の推移

試験期間中、血液学的検査項目に臨床的に問題となる平均値の変化は認められなかった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 及び Figure 14.3.5.71～14.3.5.94〕。

個々の被験者における変動

試験期間中、いずれの投与群においても、血液学的検査項目に異常値が認められた被験者の割合は低かった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.5.74、EOT Listing 14.3.4.2、Appendix 16.2.8、Listing 16.2.8.1、16.2.8.3 及び 16.2.8.6〕。

4184 試験

臨床検査値の推移

試験期間中、血液学的検査項目に臨床的に問題となる平均値の変化は認められなかった〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 及び Figure 14.3.5.65～14.3.5.88〕。

個々の被験者における変動

試験期間中、いずれの投与群においても、血液学的検査項目に異常値が認められた被験者の割合は、低かった〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Listing 14.3.4.2、EOT Table 14.3.5.68、Appendix 16.2.8、Listing 16.2.8.1、16.2.8.3 及び 16.2.8.6〕。

2.7.4.3.2　　血液生化学的検査

評価方法

4183 試験及び 4184 試験で測定した血液生化学的検査パラメータは以下のとおりであった。

- クレアチニン
- アラニンアミノトランスフェラーゼ（ALT）
- アスパラギン酸アミノトランスフェラーゼ（AST）
- アルカリホスファターゼ
- ナトリウム
- カリウム
- アルブミン
- 総ビリルビン
- 尿素
- クレアチンキナーゼ
- 総カルシウム
- アルブミン補正カルシウム
- リパーゼ
- アミラーゼ

リパーゼ及びアミラーゼは 2.7.4.3.5 に提示し、本項では検討しない。

4184 試験では、スクリーニング（ベースライン値）、投与後 12 週及び 26 週に検体採取を行った。4183 試験では、スクリーニング（ベースライン値）、投与後 4 週、12 週、16 週、26 週、38 週及び 52 週に検体採取を行った。

血液生化学的検査パラメータの基準値については、4183 試験及び 4184 試験の各治験総括報告書（Module 5.3.5.1）、Appendix 16.2.8、Listing 16.2.8.1 を参照のこと。統計解析は実施しなかった。

4183 試験

臨床検査値の推移

試験期間中、血液生化学的検査項目に臨床的に問題となる平均値の変化は認められなかった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 及び Figure 14.3.5.1～14.3.5.30〕。

個々の被験者における変動

試験期間中、いずれの投与群においても、血液生化学的検査項目に異常値が認められた被験者の割合は低かった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.5.4、EOT Listing 14.3.4.1、Appendix 16.2.8、Listing 16.2.8.1、16.2.8.2 及び 16.2.8.6〕。

4184 試験

臨床検査値の推移

試験期間中、血液生化学的検査項目に臨床的に問題となる平均値の変化は認められなかった〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 及び Figure 14.3.5.1～30〕。

個々の被験者における変動

試験期間中、いずれの投与群においても、血液生化学的検査項目に異常値が認められた被験者の割合は低かった〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Listing 14.3.4.1、EOT Table 14.3.5.4、Appendix 16.2.8, Listing 16.2.8.1、16.2.8.2 及び 16.2.8.6〕。

2.7.4.3.3　空腹時脂質プロファイル

評価方法

4183 試験及び 4184 試験で測定した脂質パラメータは以下のとおりであった。

- 総コレステロール
- LDL コレステロール
- 超低比重リポタンパク（VLDL）コレステロール
- HDL コレステロール
- 中性脂肪
- 遊離脂肪酸

4184 試験では無作為割り付け時（ベースライン値）、投与後 4 週、12 週及び 26 週に、4183 試験では無作為割り付け時（ベースライン値）、投与後 12 週、26 週、38 週及び 52 週）に検体採取を行った。

脂質パラメータの基準値については、4183 試験及び 4184 試験の各治験総括報告書（Module 5.3.5.1）、Appendix 16.2.8、Listing 16.2.8.1 を参照のこと。

4183 試験及び 4184 試験では、空腹時脂質プロファイルは有効性エンドポイントとして事前に規定したが、空腹時脂質に関するデータは本臨床概要にのみ提示する。

両試験ともに、投与後 26 週又は 52 週における空腹時脂質は ANCOVA モデルを用いて解析した〔ANCOVA 解析の詳細については 4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Section 9.7 を参照のこと〕。

4183 試験

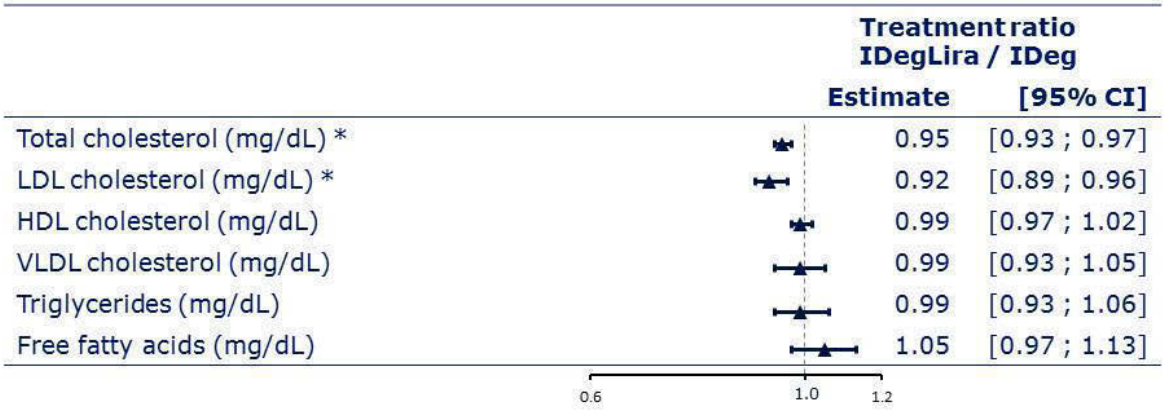
ベースライン及び投与後 52 週の総コレステロール、LDL コレステロール、HDL コレステロール、VLDL コレステロール、中性脂肪及び遊離脂肪酸の幾何平均を表 2.7.4.3-1 に示す。

表 2.7.4.3-1　　ベースライン及び投与後 52 週の空腹時脂質 - 幾何平均 - FAS（4183 試験）

Endpoint	IDegLira		IDeg		liraglutide	
	Week 0	Week 52	Week 0	Week 52	Week 0	Week 52
Total cholesterol (mg/dL)	197.2	180.9	192.2	186.9	194.6	183.3
LDL cholesterol (mg/dL)	106.7	97.0	105.7	104.4	104.5	97.3
HDL cholesterol (mg/dL)	55.6	52.3	57.2	54.0	58.2	57.5
VLDL cholesterol (mg/dL)	25.9	23.8	23.2	22.4	24.1	21.9
Triglycerides (mg/dL)	131.4	120.0	117.8	112.8	121.6	110.6
Free fatty acids (mg/dL)	12.5	9.3	12.7	9.0	13.6	12.6

統計解析結果：

IDeg 群との比較では、総コレステロール及び LDL コレステロールについて、IDegLira 群と IDeg 群との間で統計的な有意差が認められ（比の推定値に基づく）、IDegLira 群に好ましい結果が得られた（図 2.7.4.3-1）。なお、これらの脂質パラメータは、HDL コレステロールを除き、値が低い方が望ましいと考えられる。

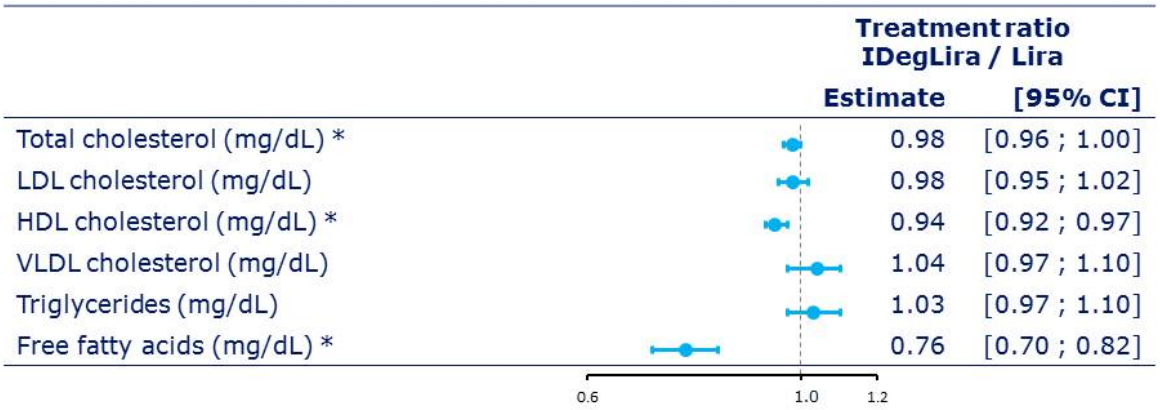


*Statistically significant difference (IDegLira lower), LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein. ANCOVA on log-transformed response after 52 weeks with treatment and pre-trial OAD treatment as factors and corresponding log-transformed baseline value as covariate. Missing values are imputed by LOCF. The dotted line represents a treatment ratio of 1.0.

図 2.7.4.3-1　　空腹時脂質−統計解析（IDegLira vs. IDeg） - FAS（4183 試験）

統計解析結果：

リラグルチド群との比較では、総コレステロール（IDegLira 群に好ましい結果）、遊離脂肪酸（IDegLira 群に好ましい結果）及び HDL コレステロール（リラグルチド群に好ましい結果）に統計的な有意差が認められた（比の推定値に基づく）（図 2.7.4.3-2）。なお、これらの脂質パラメータは、HDL コレステロールを除き、値が低い方が望ましいと考えられる。



*Statistically significant difference (IDegLira lower), LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein. ANCOVA on log-transformed response after 52 weeks with treatment and pre-trial OAD treatment as factors and corresponding log-transformed baseline value as covariate. Missing values are imputed by LOCF. The dotted line represents a treatment ratio of 1.0.

図 2.7.4.3-2　　空腹時脂質−統計解析（IDegLira vs.リラグルチド） - FAS（4183 試験）

4184 試験

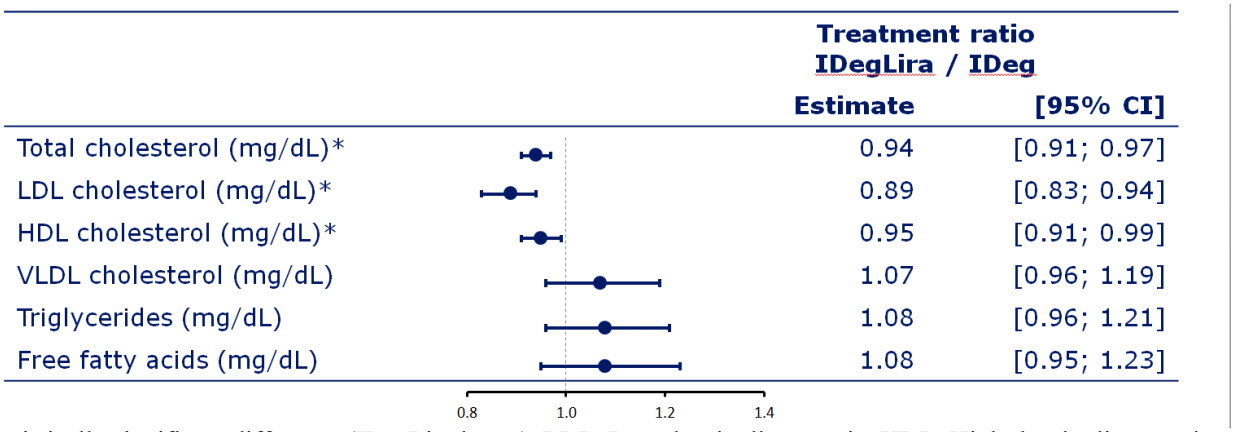
ベースライン及び投与後 26 週の総コレステロール、LDL コレステロール、HDL コレステロール、VLDL コレステロール、中性脂肪及び遊離脂肪酸の幾何平均を表 2.7.4.3-2 に示す。

表 2.7.4.3-2　　ベースライン及び投与後 26 週の空腹時脂質 - 幾何平均 - FAS（4184 試験）

Endpoint	IDegLira		IDeg	
	week 0	week 26	week 0	week 26
Total cholesterol (mg/dL)	184.3	166.3	184.1	176.6
LDL cholesterol (mg/dL)	95.1	81.5	98.9	94.5
HDL cholesterol (mg/dL)	54.8	49.3	54.2	51.3
VLDL cholesterol (mg/dL)	26.3	26.9	25.1	24.4
Triglycerides (mg/dL)	135.1	137.7	127.1	122.9
Free fatty acids (mg/dL)	10.9	9.3	11.2	8.7

統計解析結果：

IDegLira 群と IDeg 群の比の推定値に基づくと、総コレステロール（0.94、IDegLira 群に好ましい結果）、LDL コレステロール（0.89、IDegLira 群に好ましい結果）及び HDL コレステロール（0.95、IDeg 群に好ましい結果）において、投与群間に統計的な有意差が認められた（図 2.7.4.3-3）。なお、これらの脂質パラメータは、HDL コレステロールを除き、値が低い方が望ましいと考えられる。



*Statistically significant difference (IDegLira lower). LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein. ANCOVA on log-transformed response after 26 weeks with treatment and pre-trial anti-diabetic treatment as factors and corresponding log-transformed baseline value as covariate. Missing values are imputed by LOCF. The dotted line represents a treatment ratio of 1.0.

図 2.7.4.3-3　　空腹時脂質 - 統計解析（IDegLira vs.IDeg） - FAS（4184 試験）

2.7.4.3.4　　カルシトニン

評価方法

いずれの試験においても、スクリーニング（ベースライン値）、投与後 12 週及び 26 週（加えて 4183 試験では投与後 38 週及び 52 週）に検体採取を行った。

カルシトニンの基準範囲については、4183 試験及び 4184 試験の各治験総括報告書（Module 5.3.5.1）、Appendix 16.2.8、Listing 16.2.8.1 を参照のこと。

MedDRA 検索により特定したカルシトニンの増加に関連する有害事象は、2.7.4.2.1.10.4 を参照のこと。

4183 試験

臨床検査値の推移

試験期間中、カルシトニンに臨床的に問題となる平均値の変化は認められなかった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 及び Figure 14.3.5.49～14.3.5.62〕。

個々の被験者における変動

カルシトニンについて、ベースラインの「正常」から投与後 52 週に「高値」に変動した被験者は、3 つの投与群のいずれにおいても少なかった（IDegLira 群で 2 例、IDeg 群で 1 例、リラグルチド群で 2 例）〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.5.53〕。カルシトニンの増加に関連する有害事象は少なく（2.7.4.2.1.10.4）、カルシトニン異常高値により試験を中止した被験者はいなかった（2.7.4.2.1.5.1）。

4184 試験

臨床検査値の推移

試験期間中、カルシトニンに臨床的に問題となる平均値の変化は認められなかった〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 及び Figure 14.3.5.45～14.3.5.56〕。

個々の被験者における変動

試験期間中、いずれの投与群においても、カルシトニンに異常値が認められた被験者の割合は、低かった〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.5.48～14.3.5.50 及び 14.3.5.57～14.3.5.62〕。カルシトニンの増加に関連する有害事象は報告されなかった（2.7.4.2.1.10.4）。

2.7.4.3.5　　アミラーゼ及びリパーゼ

評価方法

4184 試験では、スクリーニング（ベースライン値）、投与後 12 週及び 26 週に、4183 試験では、スクリーニング（ベースライン値）、投与後 4 週、12 週、16 週、26 週、38 週及び 52 週に検体採取を行った。

アミラーゼ及びリパーゼの基準範囲については、4183 試験及び 4184 試験の各治験総括報告書（Module 5.3.5.1）、Appendix 16.2.8、Listing 16.2.8.1 を参照のこと。MedDRA 検索により特定したリパーゼ又はアミラーゼの増加に関連する有害事象は、2.7.4.2.1.8.4 を参照のこと。

4183 試験

リパーゼ

臨床検査値の推移

ベースライン（来院 1）から投与後 52 週にかけて、リパーゼの平均は IDegLira 群（変化量：9.84 U/L）及びリラグルチド群（変化量：21.23 U/L）では増加したが、IDeg 群（変化量：-3.66 U/L）では低下した〔表 2.7.4.3-3、4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.5.32〕。

表 2.7.4.3-3　　リパーゼ（U/L）の要約 - SAS（4183 試験）

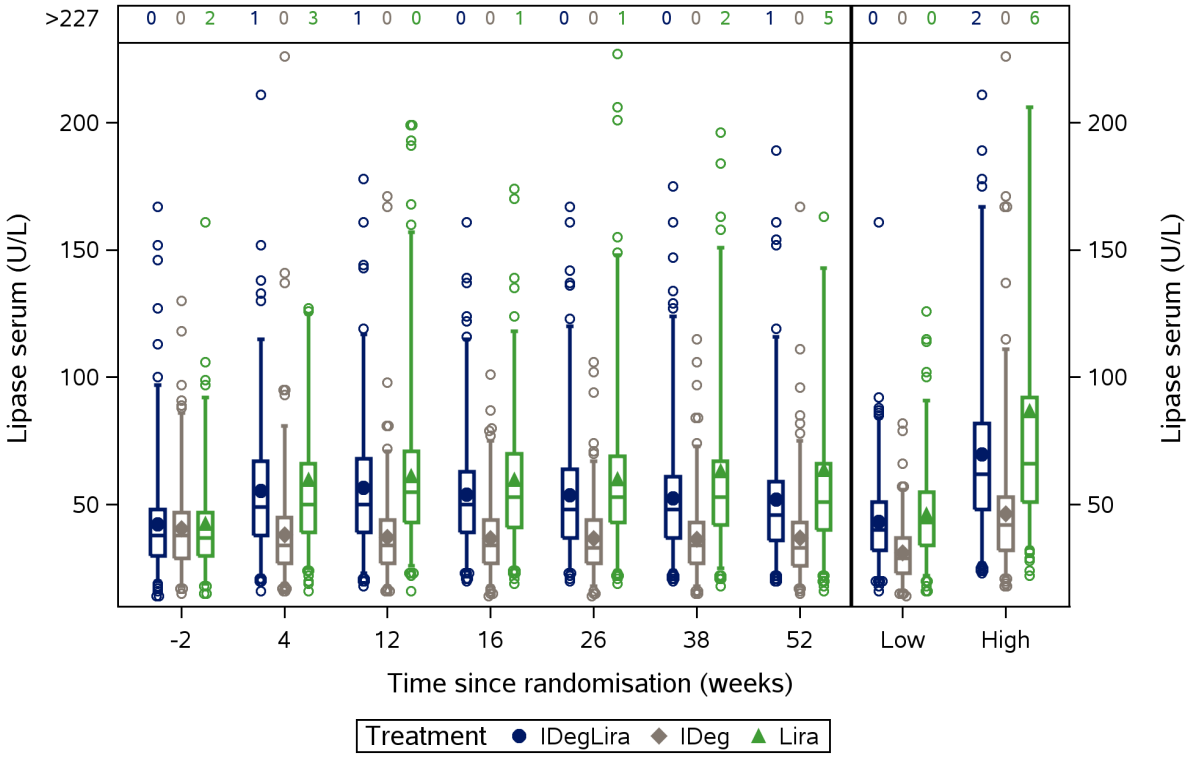
	IDegLira	IDeg	Lira	Total
Number of subjects	275	271	273	819
Visit 1				
N	275	271	273	819
Mean (SD)	42.23 (20.50)	40.67 (16.53)	42.50 (27.69)	41.80 (22.06)
Median	38.00	38.00	37.00	38.00
Min ; Max	14.00 ; 167.00	15.00 ; 130.00	15.00 ; 328.00	14.00 ; 328.00
Visit 54 (Week 52) (LOCF)				
N	275	271	273	819
Mean (SD)	52.06 (26.78)	37.00 (16.65)	63.73 (78.42)	50.97 (49.96)
Median	46.00	33.00	51.00	43.00
Min ; Max	20.00 ; 276.00	15.00 ; 167.00	16.00 ; 1088.00	15.00 ; 1088.00

N: Number of subjects, SD: Standard deviation, LOCF: Last observation carried forward.

個々の被験者における変動

リパーゼについて、ベースラインで「正常」であったが投与後 52 週に「高値」に変動した被験者の割合は、IDegLira 群で 18.5%、IDeg 群で 3.0%、リラグルチド群で 23.8%であった〔図 2.7.4.3-4、及び 4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.5.33 及び 14.3.5.34〕。リパーゼが基準範囲上限の 2 倍又は 3 倍を超える値を示した被験者については、4183 試験の治験総括報告書（Module

5.3.5.1）、EOT Figure14.3.5.42～14.3.5.47、EOT Listing 14.3.4.4 及び 14.3.4.5、Appendix 16.2.8、Listing 16.2.8.4 を参照のこと。リパーゼの増加に関連する有害事象は 2.7.4.2.1.8.4 に示した。



Safety analysis set. Missing values are imputed by LOCF. Normal range (U/L): [13-60]. Legend: Mean (symbol), median (centre line), 25th and 75th percentiles (box), and extreme (circles). Whiskers are from 2.5% -97.5%. Numbers of values above the limit 227 appears in the top panel. High/Low are subject wise highest/lowest value across all post baseline values including values captured at unscheduled visits and retest.

図 2.7.4.3-4　　リパーゼ（U/L） - 箱ひげ図 - SAS（4183 試験）

アミラーゼ

臨床検査値の推移

ベースライン（来院 1）から投与後 52 週にかけて、アミラーゼの平均は、IDegLira 群（変化量：9.29 U/L）、IDeg 群（変化量：4.87 U/L）、リラグルチド群（変化量：8.74 U/L）のいずれも増加した〔表 2.7.4.3-4、及び 4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.5.32〕。

表 2.7.4.3-4　　アミラーゼ（U/L）の要約 - SAS（4183 試験）

	IDegLira	IDeg	Lira	Total
Number of subjects	275	271	273	819
Visit 1				
N	275	271	273	819
Mean (SD)	61.38 (21.51)	60.51 (22.64)	62.62 (26.48)	61.50 (23.62)
Median	57.00	55.00	56.00	57.00
Min ; Max	22.00 ; 141.00	27.00 ; 187.00	20.00 ; 247.00	20.00 ; 247.00
Visit 54 (Week 52) (LOCF)				
N	275	271	273	819
Mean (SD)	70.67 (25.44)	65.38 (23.91)	71.36 (33.89)	69.15 (28.19)
Median	67.00	60.00	64.00	64.00
Min ; Max	29.00 ; 222.00	26.00 ; 185.00	28.00 ; 411.00	26.00 ; 411.00

N: Number of subjects, SD: Standard deviation,
LOCF: Last observation carried forward.

個々の被験者における変動

アミラーゼについて、ベースラインで「正常」であったが投与後 52 週に「高値」に変動した被験者の割合は、IDegLira 群で 6.9%、IDeg 群で 5.2%、リラグルチド群で 6.6%であった（4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.5.33 及び 14.3.5.34）。試験期間中にアミラーゼが基準範囲上限の 2 倍又は 3 倍を超える値を示した被験者は少数であった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Figure 14.3.5.35～14.3.5.40、EOT Listing 14.3.4.6 及び 14.3.4.7、Appendix 16.2.8、Listing 16.2.8.4）。アミラーゼの増加に関連する有害事象は 2.7.4.2.1.8.4 に示した。

4184 試験

リパーゼ

臨床検査値の推移

ベースラインから投与後 26 週にかけて、リパーゼの平均は IDegLira 群では 18.47 U/L 増加した。一方で IDeg 群のリパーゼの変化量は-1.95 U/L であった〔表 2.7.4.3-5 及び 4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.5.32〕。

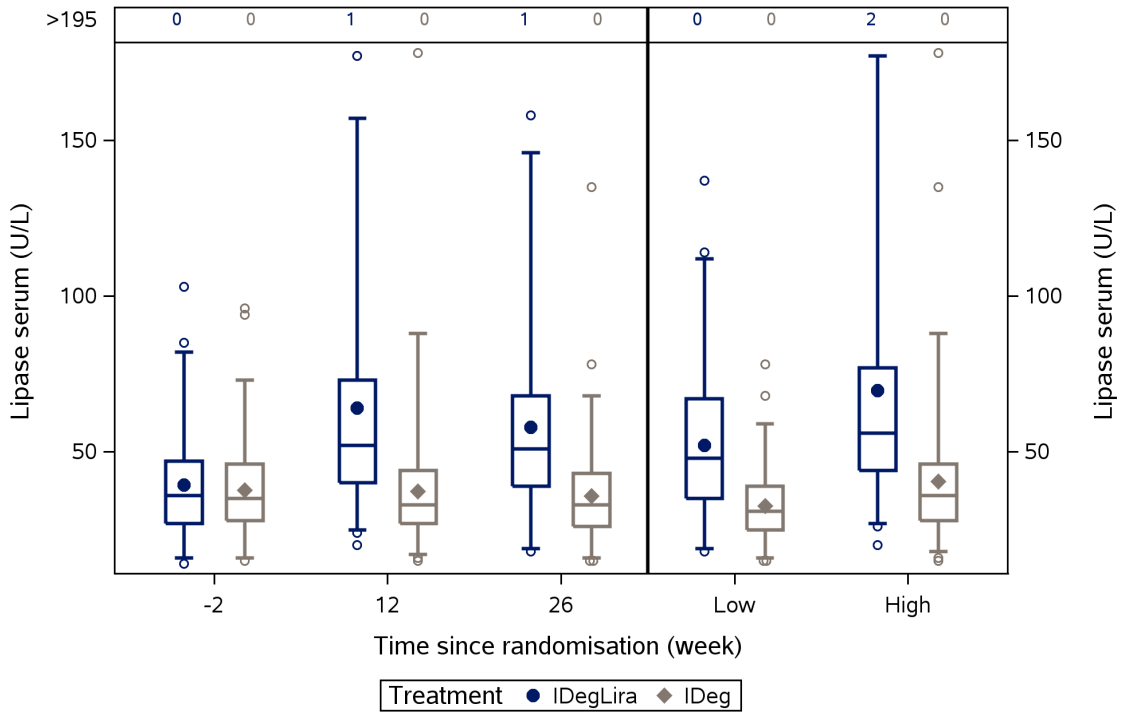
表 2.7.4.3-5　　リパーゼ（U/L）の要約 - SAS（4184 試験）

	IDegLira	IDeg	Total
Number of subjects	105	105	210
Visit 1			
N	105	105	210
Mean (SD)	39.33 (16.61)	37.68 (14.05)	38.50 (15.37)
Median	36.00	35.00	36.00
Min ; Max	14.00 ; 103.00	15.00 ; 96.00	14.00 ; 103.00
Visit 32 (Week 26) (LOCF)			
N	105	105	210
Mean (SD)	57.80 (31.30)	35.72 (15.55)	46.76 (27.02)
Median	51.00	33.00	41.00
Min ; Max	18.00 ; 228.00	15.00 ; 135.00	15.00 ; 228.00

Number of subjects, SD: Standard deviation,
LOCF: Last observation carried forward. Highest/Lowest post baseline value: Subject wise highest/lowest value across all post baseline values including values captured at unscheduled visits and retest.

個々の被験者における変動

リパーゼについて、ベースラインで「正常」であったが投与後 26 週に「高値」に変動した被験者の割合は、IDegLira 群で 24.8%、IDeg 群で 2.9%であった〔図 2.7.4.3-5、及び 4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.5.33 及び 14.3.5.34〕。試験期間中にリパーゼが基準範囲上限の 2 倍又は 3 倍を超える値を示した被験者は少数であった〔4184 試験の治験総括報告書（Module 5.3.5.1）、Listing 14.3.4.4 及び 14.3.4.5、EOT Figure 14.3.5.40～14.3.5.44、Appendix 16.2.8、Listing 16.2.8.4〕。リパーゼの増加に関連する有害事象については 2.7.4.2.1.8.4 に示した。



Safety analysis set. Missing values are imputed by LOCF. Normal range (U/L): [13-60]. Legend: Mean (symbol), median (centre line), 25th and 75th percentiles (box), and extreme (circles). Whiskers are from 2.5% -97.5%. Numbers of values above the limit 195 appears in the top panel. High/Low are subject wise highest/lowest value across all post baseline values including values captured at unscheduled visits and retest.

図 2.7.4.3-5　　リパーゼ（U/L） - 箱ひげ図 - SAS（4184 試験）

アミラーゼ

臨床検査値の推移

ベースラインから投与後 26 週にかけて、アミラーゼの平均は IDegLira 群では 8.40 U/L 増加した。一方、IDeg 群の増加はわずかであった（3.87 U/L）〔表 2.7.4.3-6 及び 4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.5.32〕。

表 2.7.4.3-6　　アミラーゼ（U/L）の要約 - SAS（4184 試験）

	IDegLira	IDeg	Total
Number of subjects	105	105	210
Visit 1			
N	105	105	210
Mean (SD)	62.83 (22.94)	59.63 (24.74)	61.23 (23.85)
Median	59.00	55.00	56.00
Min ; Max	26.00 ; 126.00	25.00 ; 191.00	25.00 ; 191.00
Visit 32 (Week 26) (LOCF)			
N	105	105	210
Mean (SD)	71.23 (23.39)	63.50 (25.57)	67.36 (24.75)
Median	72.00	59.00	63.00
Min ; Max	25.00 ; 142.00	25.00 ; 168.00	25.00 ; 168.00

N: Number of subjects, SD: Standard deviation,
LOCF: Last observation carried forward. Highest/Lowest post baseline value: Subject wise highest/lowest value across all post baseline values including values captured at unscheduled visits and retest.

個々の被験者における変動

アミラーゼについて、ベースラインで「正常」であったが投与後 26 週に「高値」に変動した被験者の割合は、IDegLira 群で 5.7%、IDeg 群で 1.9%であった〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.5.33、14.3.5.34 及び 14.3.5.39〕。試験期間中にアミラーゼが基準範囲上限の 2 倍又は 3 倍を超える値を示した被験者はいなかった〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Figure 14.3.5.35～38、EOT Listing 14.3.4.6 及び 14.3.4.7、Appendix 16.2.8、Listing 16.2.8.4〕。アミラーゼの増加に関連する有害事象は報告されなかった（2.7.4.2.1.8.4）。

2.7.4.3.6　　抗 IDeg 抗体及び抗リラグルチド抗体

評価方法

4183 試験で IDeg 及びリラグルチドに対する抗体を評価した。当該試験では以下の項目を測定した。

- 抗 IDeg 特異抗体
- ヒトインスリンとの交叉反応を有する抗 IDeg 抗体
- 抗リラグルチド抗体
- GLP-1 との交叉反応を有する抗リラグルチド抗体
- *in vitro* で中和作用を有する抗リラグルチド抗体

4183 試験では、無作為割り付け時（ベースライン値）、投与後 12 週、26 週、38 週、52 週及び 53 週に検体採取を行った。

放射免疫測定法（RIA）を用いて抗体を測定した。測定法の詳細については Module 2.7.1.1.4.3 を参照のこと。

以下の抗体産生が認められた被験者を対象に、事後調査来院時の抗体と有害事象の関連について検討した。

- IDeg 特異抗体（0.6% B/T 超*）
- ヒトインスリンとの交叉反応を有する抗 IDeg 抗体（0.7% BT 超*）
- 抗リラグルチド抗体

*：この閾値は、健康被験者 150 例における抗体分布の 95%パーセンタイルから設定した。

4183 試験

抗インスリン抗体

IDegLira 又は IDeg の 52 週間の投与期間中に、臨床的に問題となる IDeg 特異抗体の産生は認められなかった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.6.16〕。IDeg 特異抗体の産生は、IDegLira 群及び IDeg 群で同様であった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Figure 14.3.6.19〕。

ヒトインスリン交叉抗体価（%B/T）は IDeg 群と比較して IDegLira 群で高く、結果として総インスリン抗体価にも違いが認められた〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Figure 14.3.6.20 及び EOT Figure 14.3.6.21〕。

事後調査来院時に抗インスリン抗体が閾値を超えていた被験者における有害事象及び重篤な有害事象（器官別大分類及び基本語別）をそれぞれ付録 2.7.4.7.1、表 2.7.4.7.1.97 及び表 2.7.4.7.1.98 に示す。抗インスリン抗体と有害事象又は重篤な有害事象の間に明らかな関連は認められなかった。

抗リラグルチド抗体

事後調査来院時（53 週）に、IDegLira 群の 17.2%、リラグルチド群の 24.9%に抗リラグルチド抗体の産生が認められた。このうち、数例（IDegLira 群 1 例、リラグルチド群 4 例）に内因性 GLP-1 との交叉抗体が認められ、IDegLira 群の 1 例及びリラグルチド群の 3 例に中和抗体の産生が認められた〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.6.40〕。

事後調査来院時に抗リラグルチド抗体が陽性であった被験者における有害事象及び重篤な有害事象（器官別大分類及び基本語別）をそれぞれ付録 2.7.4.7.1、表 2.7.4.7.1.99 及び表 2.7.4.7.1.100 に示す。抗リラグルチド抗体と有害事象又は重篤な有害事象の間に明らかな関連は認められなかった。

2.7.4.3.7　妊娠検査

4183 試験及び 4184 試験では、妊娠可能な女性はスクリーニング来院及び投与後 26 週又は 52 週に血液妊娠検査を実施した。それ以外の期間については、月経が停止した場合、又は妊娠が疑われた場合に、尿妊娠検査を実施することとした。

4183 試験及び 4184 試験のいずれでも、妊娠の報告はなかった。

2.7.4.3.8　要約

これまでに得られているリラグルチドの所見と一致して、膵酵素（リパーゼ及びアミラーゼ）が増加する被験者の割合は、IDeg 群と比較して、IDegLira 群及びリラグルチド群で高かった。

空腹時脂質については、IDegLira 群と IDeg 群との比較では、総コレステロール及び LDL コレステロールにおいて、いずれの試験でも投与群間に統計的な有意差がみられた（IDegLira 群に好ましい結果）。また、HDL コレステロールにおいて、4184 試験では投与群間に統計的な有意差がみられた（IDeg 群に好ましい結果）が、4183 試験では投与群間に有意差は認められなかった。IDegLira 群とリラグルチド群との比較では、総コレステロール（IDegLira 群に好ましい結果）、遊離脂肪酸（IDegLira 群に好ましい結果）及び HDL コレステロール（リラグルチド群に好ましい結果）に統計的な有意差が認められた。

その他の臨床検査パラメータ（血液学的検査及び血液生化学的検査）は、IDegLira 群と対照群で同様の結果であった。

2.7.4.4 バイタルサイン、身体的所見及び安全性に関連する他の観察項目

2.7.4.4.1 身体所見

評価方法

4183 試験及び 4184 試験では、身体所見として以下の項目について評価した。

- 頭部、耳、眼、鼻、咽喉部、頸部
- 呼吸器系
- 心血管系
- 口腔を含む消化器系
- 筋骨格系
- 中枢及び末梢神経系
- 皮膚
- 一般所見
- リンパ節の触診
- 甲状腺

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

4183 試験及び 4184 試験

両試験とも、身体所見に臨床的に問題となる経時的変化は認められず、IDegLira 群と IDeg 群又はリラグルチド群との間に明らかな違いは認められなかった。各来院時の身体所見の大部分は「正常」又は「異常、臨床的に問題なし」であった。ベースライン時又は試験終了時に「異常、臨床的に問題あり」と評価された被験者の割合は低く、その割合は投与群間で同様であった〔4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.6.1 及び 14.3.6.2、EOT Listing 14.3.7.4〕。

2.7.4.4.2 眼底検査／眼底写真

評価方法

4183 試験及び 4184 試験では、眼底検査／眼底写真をスクリーニング時（ベースライン値）、投与後 26 週又は 52 週に実施した。

眼底検査／眼底写真の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

4183 試験及び 4184 試験

両試験とも、いずれの投与群においても、大部分の被験者はベースライン及び投与終了時の眼底検査所見は「正常」又は「異常、臨床的に問題なし」であった。また、スクリーニング時の「正常」又は「異常、臨床的に問題なし」から投与終了時に「異常、臨床的に問題あり」に変化した被験者の数は、いずれの投与群でも少なかった〔4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.6.14 及び 14.3.6.15、EOT Listing 14.3.7.3〕。

2.7.4.4.3　　心電図

4183 試験及び 4184 試験では、標準的な 12 誘導心電図をスクリーニング時（ベースライン値）及び投与後 26 週又は 52 週に実施した。

心電図の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

4183 試験及び 4184 試験

両試験とも、いずれの投与群でも、大部分の被験者はベースライン時及び投与終了時の心電図所見は「正常」又は「異常、臨床的に問題なし」であった。また、スクリーニング時の「正常」又は「異常、臨床的に問題なし」から投与終了時に「異常、臨床的に問題あり」に変化した被験者の数は、いずれの投与群も少なく、群間で同様であった〔4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.6.12 及び 14.3.6.13、EOT Listing 14.3.7.2〕。

2.7.4.4.4　　脈拍数

評価方法

脈拍数の測定は、4183 試験ではスクリーニング時、無作為割り付け時、投与後 12 週、26 週、38 週及び 52 週に、4184 試験では、スクリーニング時、無作為割り付け時、投与後 4 週、12 週及び 26 週に行った。

ベースラインから投与後 52 週（4183 試験）又は 26 週（4184 試験）までの脈拍数の変化量について、標準的な ANCOVA モデルを用いて解析した〔ANCOVA 解析の詳細については、両試験の治験総括報告書（Module 5.3.5.1）、Section 9.7 を参照のこと〕。

4183 試験

投与後 52 週の脈拍数（平均）は、IDegLira 群及びリラグルチド群では増加（変化量：3.9 拍／分及び 4.2 拍／分）し、また、IDeg 群でもわずかな増加（変化量：0.8 拍／分）がみられた〔図 2.7.4.4-1 及び 4183 試験（Module 5.3.5.1）、EOT Table 14.3.6.5〕。

統計解析結果

IDeg 群との比較では、群差（IDegLira 群－IDeg 群）の推定値は 2.87 拍／分（95%信頼区間：1.43; 4.30、p＜0.0001）であり、投与群間に統計的な有意差が認められた。リラグルチド群との比較では、投与群間に統計的な有意差は認められなかった〔群差（IDegLira 群－リラグルチド群）の推定値：−0.43 拍／分（95%信頼区間：-1.86；1.00、p＝0.5546）〕〔4183 試験（Module 5.3.5.1）、EOT Table 14.3.6.6〕。

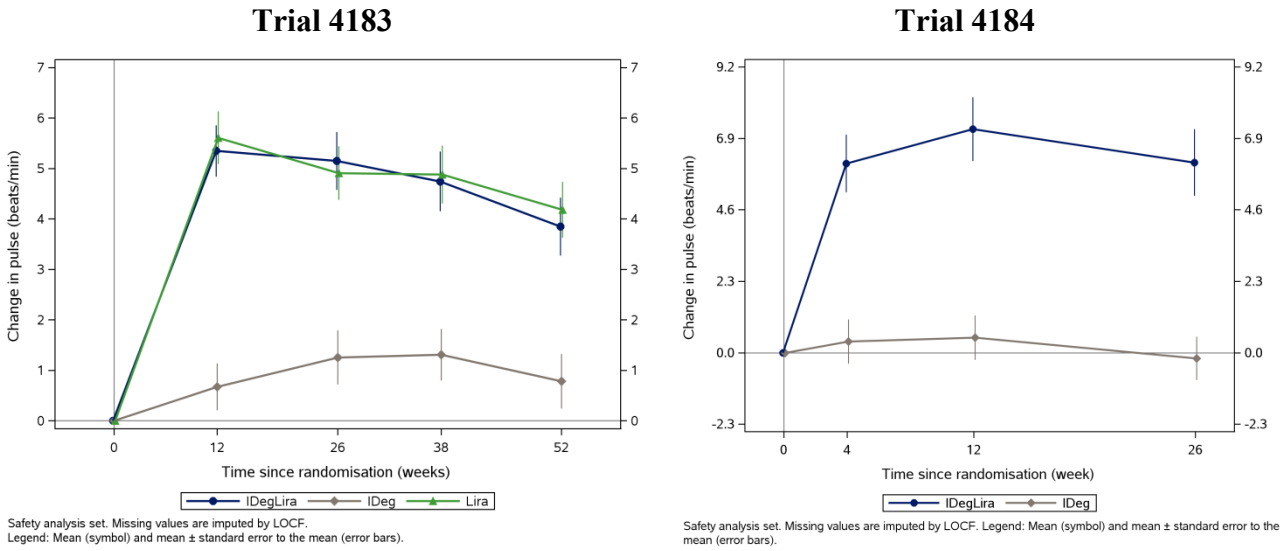


図 2.7.4.4-1　脈拍数（拍／分）のベースラインからの変化量の経時推移 - SAS（4183 試験及び 4184 試験）

4184 試験

投与後 26 週の脈拍数（平均）は、ベースラインと比較して IDegLira 群で増加（変化量：6.1 拍／分）し、IDeg 群では増加はみられなかった（変化量：-0.2 拍／分）〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.6.5〕。

統計解析結果

群差（IDegLira 群－IDeg 群）の推定値は 7.73 拍／分（95%信頼区間：5.45; 10.01、p＜0.0001）であり、投与群間に統計的な有意が認められた〔4184 試験の治験総括報告書（Module 5.3.5.1）, EOT Table 14.3.6.〕。

2.7.4.4.5　　血圧

収縮期血圧及び拡張期血圧は、4184 試験ではスクリーニング時、無作為割り付け時（ベースライン値）、投与後 4 週、12 週及び 26 週に、4183 試験ではスクリーニング時、無作為割り付け時（ベースライン値）、投与後 12 週、26 週、38 週及び 52 週に測定した。

4183 試験及び 4184 試験のいずれにおいても、血圧は有効性エンドポイントとして事前に規定したが、血圧のデータは本臨床概要にのみ提示する。

いずれの試験においても、ベースラインから投与後 26 週又は 52 週までの血圧の変化量について、標準的な ANCOVA モデルを用いて解析した〔ANCOVA 解析の詳細については、両試験の治験総括報告書（Module 5.3.5.1）、Section 9.7 を参照のこと〕。

4183 試験

収縮期血圧

収縮期血圧のベースラインから投与後 52 週までの変化量の平均（SD）は、IDegLira 群で 1.7 mmHg（12.0）、IDeg 群で 3.4 mmHg（14.3）、リラグルチド群で-1.8 mmHg（13.0）であった〔図 2.7.4.4-2 及び 4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 及び Figure 14.2.130～14.2.137、Appendix 16.2.6、Listing 16.2.6.2〕。

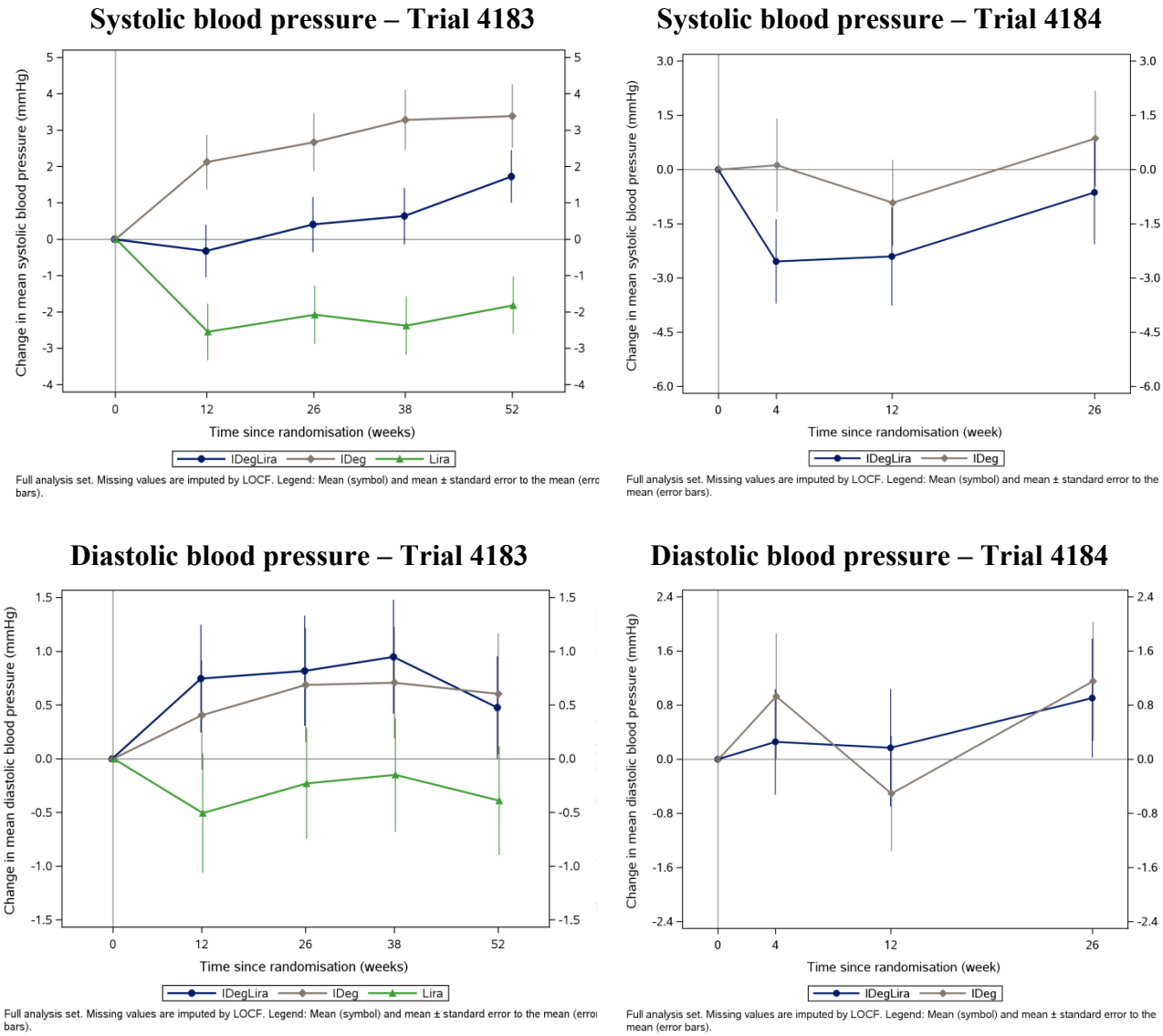


図 2.7.4.4-2　　血圧のベースラインからの変化量の経時推移 - FAS（4183 試験及び 4184 試験）

統計解析結果

IDeg 群との比較では、投与後 52 週の収縮期血圧の変化量について、群差（IDegLira 群－IDeg 群）の推定値は-2.05 mmHg（95%信頼区間：-4.02；-0.08、p=0.0412）であり、投与群間に統計的な有意差が認められた〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.2.132〕。リラグルチド群との比較においても、群差（IDegLira 群－リラグルチド群）の推定値は 2.88 mmHg（95%信頼区間：0.91; 4.85、p=0.0042）であり、投与群間に統計的な有意差が認められた。

拡張期血圧

拡張期血圧のベースラインから投与後 52 週までの変化量の平均（SD）は、IDegLira 群で 0.5 mmHg（7.9）、IDeg 群で 0.6 mmHg（9.3）、リラグルチド群で-0.4 mmHg（8.3）であった〔図 2.7.4.4-2 及び 4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 及び Figure 14.2.138～14.2.145、Appendix 16.2.6、Listing 16.2.6.2）。

統計解析結果

IDeg 群との比較では、投与後 52 週の拡張期血圧の変化量について、群差（IDegLira 群－IDeg 群）の推定値は-0.55 mmHg（95%信頼区間：-1.85; 0.76、p=0.4100）であり、投与群間に統計的な有意差は認められなかった〔4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.2.140〕。リラグルチド群との比較においても、群差（IDegLira 群－リラグルチド群）の推定値は 0.68 mmHg（95%信頼区間：-0.62; 1.98、p=0.3062）であり、投与群間に統計的な有意差は認められなかった。

4184 試験

収縮期血圧

収縮期血圧のベースラインから投与後 26 週までの変化量の平均（SD）は、IDegLira 群で-0.6 mmHg（14.7 mmHg）、IDeg 群で 0.9 mmHg（13.6 mmHg）であった〔図 2.7.4.4-2 及び 4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 及び Figure 14.2.89～96、Appendix 16.2.6、Listing 16.2.6.2〕。

統計解析結果

収縮期血圧のベースラインから投与後 26 週までの変化量について、群差（IDegLira 群－IDeg 群）の推定値は-0.57 mmHg（95%信頼区間：-4.17；3.04、p＝0.7575）であり、投与群間に統計的な有意差は認められなかった〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.2.91〕。

拡張期血圧

拡張期血圧のベースラインから投与後 26 週までの変化量の平均（SD）は、IDegLira 群で 0.9 mmHg（9.0 mmHg）、IDeg 群で 1.2 mmHg（9.0 mmHg）であった。IDegLira 群の拡張期血圧はベースラインの 80.7 mmHg から投与後 26 週に 81.6 mmHg に、IDegLira 群ではベースラインの 77.5 mmHg から投与後 26 週に 78.6 mmHg に変化した〔図 2.7.4.4-2 及び 4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 及び Figure 14.2.97～14.2.104、Appendix 16.2.6、Listing 16.2.6.2〕。

統計解析結果

拡張期血圧のベースラインから投与後 26 週までの変化量について、群差（IDegLira 群－IDeg 群）の推定値は 0.89 mmHg（95%信頼区間：-1.37；3.14、p = 0.4381）であり、投与群間に統計的な有意差は認められなかった〔4184 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.2.99〕。

2.7.4.4.6　　苦情

4183 試験では、各投与群で治験責任医師が苦情に関連すると判断した事象が計 17 件報告された（IDegLira 群：7 例 7 件、IDeg 群：4 例 4 件、リラグルチド群：6 例 6 件）。

4184 試験では、2 例に 2 件（いずれも IDeg 群）の苦情に関連する有害事象が報告された。

詳細は、4183 試験及び 4184 試験の治験総括報告書（Module 5.3.5.1）、Appendix 16.2.7、Listing 16.2.7.8 を参照のこと。

2.7.4.4.7　　要約

IDegLira 群及びリラグルチド群において、脈拍数の平均が 4～6 拍／分増加した。これは、これまでの GLP-1 受容体作動薬の投与で認められた所見と一致している。

いずれの試験でも、IDegLira 群及び対照群において、収縮期血圧のベースラインからのわずかな変化が認められた。IDegLira 群及び IDeg 群では一貫した変化はみられなかった。リラグルチド群では、IDegLira 群と比較して収縮期血圧のわずかな低下が認められた。この差は統計的に有意であり、リラグルチド群に好ましい結果であった。

その他の身体所見（拡張期血圧、眼底検査及び心電図を含む）の結果は、IDegLira 群及び対照群で同様であった。

2.7.4.5 特別な患者集団及び状況下における安全性

2.7.4.5.1 内因性要因

人口統計学的要因及び関連する内因性民族的要因の IDegLira の安全性プロファイルに対する影響の可能性を評価した。以下の要因について検討を行った：

- 年齢
- ベースラインの腎機能
- ベースラインの肝機能
- 性別
- 体容量指数（BMI）

内因性民族的要因の安全性への影響の可能性は、内因性民族的要因の各サブグループにおける有害事象、重篤な有害事象、胃腸障害の有害事象及び低血糖を発現した被験者の割合ならびに単位時間あたりの発現件数を指標として総合的に評価した。検討にあたっては、主に対照群と IDegLira 群とを比較した際の傾向がサブグループ間で異ならないかに着目した。

本項では、年齢、腎機能及び肝機能の影響の可能性について示し、性別及び BMI 別の安全性データについては、付録 2.7.4.7.1、表 2.7.4.7.1-1～2.7.4.7.1-4、表 2.7.4.7.1-13～2.7.4.7.1-22、表 2.7.4.7.1-43～2.7.4.7.1-52、表 2.7.4.7.1-73～2.7.4.7.1-76、表 2.7.4.7.1-85～2.7.4.7.1-88 に示す。

2.7.4.5.1.1 年齢

試験対象集団を以下のサブグループに分けて検討した：

- 65 歳未満
- 65 歳以上
    - 65 歳以上及び 75 歳未満
    - 75 歳以上

4183 試験及び 4184 試験において 75 歳以上の被験者が非常に少なかったため、以下の項では本サブグループについて検討は行わない。

4183 試験

有害事象

いずれの年齢グループでも、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について、投与群間で比較した際の傾向は試験対象集団全体（以降、全集団）の傾向と一致していた（表 2.7.4.5-1 及び表 2.7.4.2-2）。また、重篤な有害事象については、各サブグループに含まれる被験者が少

ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、有害事象と同様の傾向と考えられた（表 2.7.4.5-1）。

いずれの年齢グループでも、胃腸障害の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について、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-1 及び Module 2.7.6.4、表 2.7.6.4.2-1）。

いずれの投与群においても、有害事象及び胃腸障害の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年齢グループ間で同様であった（表 2.7.4.5-1）。

表 2.7.4.5-1　　年齢グループ別の有害事象 - SAS（4183 試験）

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
<65	197				183				202			
>=65	78				88				71			
65<= <75	76				84				66			
>=75	2				4				5			
PYE (years)												
<65	193.01				179.38				202.03			
>=65	74.99				82.43				69.80			
65<= <75	73.16				79.21				64.70			
>=75	1.83				3.22				5.10			
All adverse events												
<65	161	(81.7)	625	323.82	142	(77.6)	558	311.07	167	(82.7)	660	326.68
>=65	68	(87.2)	248	330.71	74	(84.1)	271	328.78	62	(87.3)	225	322.33
65<= <75	66	(86.8)	237	323.93	71	(84.5)	263	332.05	57	(86.4)	199	307.57
>=75	2	(100.0)	11	602.36	3	(75.0)	8	248.47	5	(100.0)	26	509.47
Serious adverse events												
<65	5	(2.5)	5	2.59	5	(2.7)	5	2.79	11	(5.4)	11	5.44
>=65	12	(15.4)	13	17.34	8	(9.1)	11	13.35	3	(4.2)	3	4.30
65<= <75	10	(13.2)	11	15.03	8	(9.5)	11	13.89	3	(4.5)	3	4.64
>=75	2	(100.0)	2	109.52	0				0			
Gastrointestinal adverse events												
<65	70	(35.5)	133	68.91	43	(23.5)	77	42.93	84	(41.6)	170	84.14
>=65	26	(33.3)	54	72.01	19	(21.6)	33	40.04	30	(42.3)	48	68.76
65<= <75	25	(32.9)	47	64.24	18	(21.4)	32	40.40	26	(39.4)	43	66.46
>=75	1	(50.0)	7	383.32	1	(25.0)	1	31.06	4	(80.0)	5	97.97

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), MedDRA version 20.0.

年齢グループ別の有害事象及び重篤な有害事象（器官別大分類及び基本語別）の要約を付録 2.7.4.7.1、表 2.7.4.7.1-23～2.7.4.7.1-26 及び表 2.7.4.7.1-53～2.7.4.7.1-56 に示す。

低血糖

いずれの年齢グループでも、重大な又は血糖値確定低血糖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について、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-2 及び表 2.7.4.2-17）。重大な又は血糖値確定夜間低血糖についても同様の結果であった。

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年齢グループ間で概ね同様であった（表 2.7.4.5-2）。

表 2.7.4.5-2　　年齢グループ別の低血糖 - SAS（4183 試験）

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
<65	197				183				202			
>=65	78				88				71			
65<= <75	76				84				66			
>=75	2				4				5			
PYE (years)												
<65			193.01				179.38				202.03	
>=65			74.99				82.43				69.80	
65<= <75			73.16				79.21				64.70	
>=75			1.83				3.22				5.10	
Severe or BG confirmed hypoglycaemia												
<65	69	(35.0)	320	165.79	101	(55.2)	623	347.30	4	(2.0)	10	4.95
>=65	37	(47.4)	147	196.03	47	(53.4)	246	298.45	2	(2.8)	3	4.30
65<= <75	36	(47.4)	146	199.55	46	(54.8)	241	304.27	2	(3.0)	3	4.64
>=75	1	(50.0)	1	54.76	1	(25.0)	5	155.29	0			
Nocturnal severe or BG confirmed hypoglycaemia												
<65	18	(9.1)	49	25.39	31	(16.9)	85	47.39	0			
>=65	9	(11.5)	17	22.67	14	(15.9)	47	57.02	0			
65<= <75	9	(11.8)	17	23.24	14	(16.7)	47	59.34	0			
>=75	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode, BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL).

4184 試験

有害事象

いずれの年齢グループでも、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について、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-3 及び表 2.7.4.2-4）。また、各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、いずれの年齢グループにおいても重篤な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について投与群間で明らかな違いはみられなかった（表 2.7.4.5-3）。

いずれの年齢グループでも、胃腸障害の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について、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-3 及び Module 2.7.6.5、表 2.7.6.5.2-1）。

有害事象については、65 歳以上のグループで単位時間あたりの発現件数が多くなる傾向が認められた（表 2.7.4.5-3）。胃腸障害の有害事象については、65 歳以上のグループで発現した被験者の割合及び単位時間あたりの発現件数が高くなる傾向がみられた。この傾向は IDeg 群でより顕著であった（表 2.7.4.5-3）。

表 2.7.4.5-3　　年齢グループ別の有害事象 - SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects								
<65	75				85			
>=65	30				20			
65<= <75	28				19			
>=75	2				1			
PYE (years)								
<65	38.80				43.35			
>=65	15.47				8.91			
65<= <75	14.44				8.66			
>=75	1.03				0.25			
All adverse events								
<65	58	(77.3)	187	481.91	65	(76.5)	169	389.82
>=65	24	(80.0)	93	601.00	15	(75.0)	41	460.07
65<= <75	22	(78.6)	69	477.86	14	(73.7)	40	461.76
>=75	2	(100.0)	24	2319.05	1	(100.0)	1	401.37
Serious adverse events								
<65	2	(2.7)	2	5.15	3	(3.5)	5	11.53
>=65	1	(3.3)	2	12.92	1	(5.0)	1	11.22
65<= <75	0				1	(5.3)	1	11.54
>=75	1	(50.0)	2	193.25	0			
Gastrointestinal adverse events								
<65	31	(41.3)	56	144.32	17	(20.0)	28	64.58
>=65	14	(46.7)	32	206.79	7	(35.0)	12	134.65
65<= <75	12	(42.9)	27	186.99	7	(36.8)	12	138.53
>=75	2	(100.0)	5	483.13	0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events,
E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days). MedDRA version 20.0.

年齢グループ別の有害事象及び重篤な有害事象（器官別大分類及び基本語別）の要約を付録 2.7.4.7.1、表 2.7.4.7.1-27～2.7.4.7.1-30 及び表 2.7.4.7.1-57～2.7.4.7.1-60 に示す。

低血糖

65 歳未満のグループでは、重大な又は血糖値確定低血糖を発現した被験者の割合は投与群間で同様であったが、単位時間あたりの発現件数は IDeg 群と比較して IDegLira 群で多かった。65 歳以上のグループでは、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 IDeg 群と比較して IDegLira 群で低かった（表 2.7.4.5-4）。同様の傾向が、重大な又は血糖値確定夜間低血糖でも認められた（表 2.7.4.5-4）。

IDegLira 群では、重大な又は血糖値確定低血糖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について、年齢に依存した明らかな傾向はみられなかった、IDeg 群では、発現した被験者の割合及び単位時間あたりの発現件数が年齢とともに高くなる傾向が認められた（表 2.7.4.5-4）。

重大な又は血糖値確定夜間低血糖は両群ともに少なかった。各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、重大な又は血糖値確定夜間低血糖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について年齢グループ間で明らかな違いは認められなかった（表 2.7.4.5-4）。

表 2.7.4.5-4　　年齢グループ別の低血糖 - SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects								
<65	75				85			
>=65	30				20			
65<= <75	28				19			
>=75	2				1			
PYE (years)								
<65	38.80				43.35			
>=65	15.47				8.91			
65<= <75	14.44				8.66			
>=75	1.03				0.25			
Severe or BG confirmed hypoglycaemia								
<65	20	(26.7)	90	231.94	22	(25.9)	77	177.61
>=65	10	(33.3)	34	219.72	10	(50.0)	32	359.08
65<= <75	10	(35.7)	34	235.47	9	(47.4)	31	357.86
>=75	0				1	(100.0)	1	401.37
Nocturnal severe or BG confirmed hypoglycaemia								
<65	6	(8.0)	22	56.70	6	(7.1)	13	29.99
>=65	2	(6.7)	4	25.85	4	(20.0)	6	67.33
65<= <75	2	(7.1)	4	27.70	4	(21.1)	6	69.26
>=75	0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode, BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL).

2.7.4.5.1.2　　腎機能

除外基準に従い、腎機能障害（CKD-EPI 式による eGFR が 60 mL/min/1.73m^{2}未満）のある被験者はいずれの試験にも含まれなかった。本項では、試験対象集団を以下のサブグループに分けて検討した：

- 正常腎機能：ベースラインの eGFR が 90 mL/min/1.73 m^{2}以上
- 軽度腎機能障害：ベースラインの eGFR が 60 mL/min/1.73 m^{2}以上、90 mL/min/1.73 m^{2}未満

4183 試験

有害事象

いずれの腎機能グループでも、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について、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-5）。また、重篤な有害事象については、各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、有害事象と同様の傾向と考えられた（表 2.7.4.5-5）。

軽度腎機能障害のグループにおいて、胃腸障害の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について、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-5）。正常腎機能のグループでは、本サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、胃腸障害の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について投与群間で明らかな違いはみられなかった（表 2.7.4.5-5）。

いずれの投与群においても、有害事象及び胃腸障害の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腎機能グループ間で明らかな違いはみられなかった（表 2.7.4.5-5）。

表 2.7.4.5-5　　ベースラインの腎機能別の有害事象 - SAS（4183 試験）

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Normal function	24				20				23			
Mild impairment	251				251				250			
PYE (years)												
Normal function	23.25				18.69				21.69			
Mild impairment	244.75				243.12				250.15			
All adverse events												
Normal function	20	(83.3)	85	365.59	16	(80.0)	73	390.67	19	(82.6)	81	373.50
Mild impairment	209	(83.3)	788	321.96	200	(79.7)	756	310.96	210	(84.0)	804	321.40
Serious adverse events												
Normal function	1	(4.2)	1	4.30	0				3	(13.0)	3	13.83
Mild impairment	16	(6.4)	17	6.95	13	(5.2)	16	6.58	11	(4.4)	11	4.40
Gastrointestinal adverse events												
Normal function	6	(25.0)	17	73.12	6	(30.0)	20	107.03	11	(47.8)	23	106.06
Mild impairment	90	(35.9)	170	69.46	56	(22.3)	90	37.02	103	(41.2)	195	77.95

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events,
E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2,
mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]. MedDRA version 20.0.

ベースラインの腎機能別の有害事象及び重篤な有害事象（器官別大分類及び基本語別）の要約を付録 2.7.4.7.1、表 2.7.4.7.1-31、2.7.4.7.1-32、2.7.4.7.1-61 及び 2.7.4.7.1-62 に示す。

低血糖

いずれの腎機能グループでも、重大な又は血糖値確定低血糖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ついて、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-6）。同様の傾向が、重大な又は血糖値確定夜間低血糖でも認められた。

各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、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について腎機能グループ間で明らかな違いは認められなかった（表 2.7.4.5-6）。

表 2.7.4.5-6　　ベースラインの腎機能別の低血糖 - SAS（4183 試験）

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Normal function	24				20				23			
Mild impairment	251				251				250			
PYE (years)												
Normal function	23.25				18.69				21.69			
Mild impairment	244.75				243.12				250.15			
Severe or BG confirmed hypoglycaemia												
Normal function	5	(20.8)	27	116.13	9	(45.0)	61	326.45	0			
Mild impairment	101	(40.2)	440	179.78	139	(55.4)	808	332.34	6	(2.4)	13	5.20
Nocturnal severe or BG confirmed hypoglycaemia												
Normal function	0				4	(20.0)	5	26.76	0			
Mild impairment	27	(10.8)	66	26.97	41	(16.3)	127	52.24	0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode, BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2,
mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2].

4184 試験

有害事象

いずれの腎機能グループでも、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について、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-7）。また、各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、いずれの腎機能グループにおいても重篤な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について投与群間で明らかな違いはみられなかった（表 2.7.4.5-7）。

いずれの腎機能グループでも、胃腸障害の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について、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-7）。

いずれの投与群においても、有害事象及び胃腸障害の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、正常腎機能サブグループと比較して軽度腎機能障害サブグループで低かった（表 2.7.4.5-7）。

表 2.7.4.5-7　　ベースラインの腎機能別の有害事象 - SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects								
Normal function	12				12			
Mild impairment	93				93			
PYE (years)								
Normal function	6.20				6.24			
Mild impairment	48.08				46.03			
All adverse events								
Normal function	12	(100.0)	47	758.58	9	(75.0)	30	481.01
Mild impairment	70	(75.3)	233	484.59	71	(76.3)	180	391.06
Serious adverse events								
Normal function	0				0			
Mild impairment	3	(3.2)	4	8.32	4	(4.3)	6	13.04
Gastrointestinal adverse events								
Normal function	7	(58.3)	17	274.38	4	(33.3)	9	144.30
Mild impairment	38	(40.9)	71	147.66	20	(21.5)	31	67.35

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events,
E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2,
mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]. MedDRA version 20.0.

ベースラインの腎機能別の有害事象及び重篤な有害事象（器官別大分類及び基本語別）の要約を付録 2.7.4.7.1、表 2.7.4.7.1-33、2.7.4.7.1-34、2.7.4.7.1-63 及び 2.7.4.7.1-64 に示す。

低血糖

正常腎機能のグループでは、重大な又は血糖値確定低血糖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 IDeg 群と比較して IDegLira 群で低かった。軽度腎機能障害のグループでは、重大な又は血糖値確定低血糖を発現した被験者の割合は投与群間で同様であったが、単位時間あたりの発現件数は IDeg 群と比較して IDegLira 群で多かった（表 2.7.4.5-8）。同様の傾向が、重大な又は血糖値確定夜間低血糖でも認められた（表 2.7.4.5-8）。

各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、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について腎機能グループ間で一定の傾向はみられなかった。

表 2.7.4.5-8　　ベースラインの腎機能別の低血糖 - SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects								
Normal function	12				12			
Mild impairment	93				93			
PYE (years)								
Normal function	6.20				6.24			
Mild impairment	48.08				46.03			
Severe or BG confirmed hypoglycaemia								
Normal function	3	(25.0)	8	129.12	5	(41.7)	22	352.74
Mild impairment	27	(29.0)	116	241.25	27	(29.0)	87	189.01
Nocturnal Severe or BG confirmed hypoglycaemia								
Normal function	0				1	(8.3)	2	32.07
Mild impairment	8	(8.6)	26	54.07	9	(9.7)	17	36.93

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode, BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2,
mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2].

2.7.4.5.1.3　　肝機能

除外基準に従い、肝機能障害（ALT 又は AST が正常範囲の上限の 2.5 倍以上）のある被験者はいずれの試験にも含まれなかった。本項では、試験対象集団を以下のサブグループに分けて検討した：

試験集団を以下の肝機能サブグループに分けた。

·正常肝機能：ベースラインの ALT 及び AST の両方が基準値上限以下

·肝機能障害：ベースラインの ALT 及び AST のいずれか又は両方が基準値上限を超える

4183 試験

有害事象

いずれの肝機能グループでも、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について、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-9）。また、重篤な有害事象については、各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、有害事象と同様の傾向と考えられた（表 2.7.4.5-9）。

いずれの肝機能グループでも、胃腸障害の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について、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-9）。

いずれの投与群においても、有害事象及び胃腸障害の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肝機能サブグループ間で同様であった（表 2.7.4.5-9）。

表 2.7.4.5-9　　ベースラインの肝機能別の有害事象 - SAS（4183 試験）

	IDegLira			IDeg			Lira		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Normal	226				222				213			
Impairment	49				49				60			
PYE (years)												
Normal	219.62				213.34				212.03			
Impairment	48.38				48.47				59.81			
All adverse events												
Normal	188	(83.2)	660	300.51	176	(79.3)	685	321.08	177	(83.1)	703	331.55
Impairment	41	(83.7)	213	440.31	40	(81.6)	144	297.12	52	(86.7)	182	304.32
Serious adverse events												
Normal	15	(6.6)	16	7.29	11	(5.0)	14	6.56	10	(4.7)	10	4.72
Impairment	2	(4.1)	2	4.13	2	(4.1)	2	4.13	4	(6.7)	4	6.69
Gastrointestinal adverse events												
Normal	77	(34.1)	147	66.93	54	(24.3)	89	41.72	90	(42.3)	162	76.40
Impairment	19	(38.8)	40	82.69	8	(16.3)	21	43.33	24	(40.0)	56	93.64

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower, impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]. MedDRA version 20.0.

ベースラインの肝機能別の有害事象及び重篤な有害事象（器官別大分類及び基本語別）の要約を付録 2.7.4.7.1、表 2.7.4.7.1-35、2.7.4.7.1-36、2.7.4.7.1-65 及び 2.7.4.7.1-66 に示す。

低血糖

いずれの肝機能グループでも、重大な又は血糖値確定低血糖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について、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-10）。同様の傾向が、重大な又は血糖値確定夜間低血糖でも認められた。

IDegLira 群及び IDeg 群において、重大な又は血糖値確定低血糖を発現した被験者の割合は、肝機能障害のグループで低い傾向がみられた（表 2.7.4.5-10）。同様の傾向が、重大な又は血糖値確定夜間低血糖でも認められた。

表 2.7.4.5-10　　ベースラインの肝機能別の低血糖 - SAS（4183 試験）

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Normal	226				222				213			
Impairment	49				49				60			
PYE (years)												
Normal	219.62				213.34				212.03			
Impairment	48.38				48.47				59.81			
Severe or BG confirmed hypoglycaemia												
Normal	90	(39.8)	403	183.49	125	(56.3)	750	351.55	4	(1.9)	8	3.77
Impairment	16	(32.7)	64	132.30	23	(46.9)	119	245.54	2	(3.3)	5	8.36
Nocturnal severe or BG confirmed hypoglycaemia												
Normal	25	(11.1)	61	27.77	38	(17.1)	120	56.25	0			
Impairment	2	(4.1)	5	10.34	7	(14.3)	12	24.76	0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode, BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL), Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower, impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range].

4184 試験

有害事象

正常肝機能のグループでは、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について、投与群間で比較した際の傾向は全集団の傾向と一致していた。肝機能障害のグループでは、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、IDeg 群と比較して IDegLira 群で低かった（表 2.7.4.5-11）。また、各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、いずれの肝機能サブグループにおいても重篤な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について投与群間で明らかな違いはみられなかった（表 2.7.4.5-11）。

いずれの肝機能グループでも、胃腸障害の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について、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-11）。

いずれの投与群においても、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肝機能のグループ間で概ね同様であった。また、少数例に基づく結果であるものの、胃腸障害の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、肝機能障害のグループと比較して正常肝機能のグループで高い傾向がみられた（表 2.7.4.5-11）。

表 2.7.4.5-11　　ベースラインの肝機能別の有害事象 - SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects								
Normal	79				88			
Impairment	26				17			
PYE (years)								
Normal	40.82				43.70			
Impairment	13.46				8.56			
All adverse events								
Normal	64	(81.0)	226	553.63	66	(75.0)	172	393.58
Impairment	18	(69.2)	54	401.29	14	(82.4)	38	443.72
Serious adverse events								
Normal	2	(2.5)	3	7.35	4	(4.5)	6	13.73
Impairment	1	(3.8)	1	7.43	0			
Gastrointestinal adverse events								
Normal	38	(48.1)	70	171.48	22	(25.0)	34	77.80
Impairment	7	(26.9)	18	133.76	2	(11.8)	6	70.06

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower, impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]. MedDRA version 20.0.

ベースラインの肝機能別の有害事象及び重篤な有害事象（器官別大分類及び基本語別）の要約を付録 2.7.4.7.1、表 2.7.4.7.1-37、2.7.4.7.1-38、2.7.4.7.1-67 及び 2.7.4.7.1-68 に示す。

低血糖

正常肝機能のグループでは、重大な又は血糖値確定低血糖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について、投与群間で比較した際の傾向は全集団の傾向と一致していた（表 2.7.4.5-12）。重大な又は血糖値確定夜間低血糖については、本サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、重大な又は血糖値確定低血糖でみられた傾向と同様であった。肝機能障害のグループでは、本サブグループで低血糖を発現した被験者が少なかったことを考慮すると、重大な又は血糖値確定低血糖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に投与群間で明らかな違いは認められなかった（表 2.7.4.5-12）。肝機能障害のグループで、重大な又は血糖値確定夜間低血糖は報告されなかった。

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、各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、肝機能のサブグループ間で同様と考えらえた（表 2.7.4.5-12）。

表 2.7.4.5-12　　ベースラインの肝機能別の低血糖 - SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects								
Normal	79				88			
Impairment	26				17			
PYE (years)								
Normal	40.82				43.70			
Impairment	13.46				8.56			
Severe or BG confirmed hypoglycaemia								
Normal	24	(30.4)	106	259.67	30	(34.1)	92	210.52
Impairment	6	(23.1)	18	133.76	2	(11.8)	17	198.51
Nocturnal severe or BG confirmed hypoglycaemia								
Normal	8	(10.1)	26	63.69	10	(11.4)	19	43.48
Impairment	0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode, BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL), Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower, impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range].

2.7.4.5.1.4　　要約

いずれの試験においても、検討した内因性民族的要因（年齢、腎機能、肝機能）のサブグループにおいて、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について、投与群間で比較した際の傾向は全集団の傾向と概ね一致していた。また、重篤な有害事象については、各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、有害事象と同様の傾向であった。

胃腸障害の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、いずれの年齢グループにおいても IDegLira 群で IDeg 群と比較して高く、リラグルチド群と比較して低かった。これは、全集団の傾向と一致していた。大部分の腎機能サブグループ及び肝機能サブグループでも同様の結果であった。

検討した内因性民族的要因サブグループにおける重大な又は血糖値確定低血糖の発現状況については、一部のサブグループで被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、発現した被験者の割合及び単位時間あたりの発現件数を投与群間で比較した際の傾向は全集団の傾向と一致していた。

また、各投与群における有害事象、重篤な有害事象、胃腸障害の有害事象、重大な又は血糖値確定低血糖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、一部のサブグループで被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、内因性民族的要因（年齢、腎機能、肝機能）のサブグループ間で同様と考えられた。

2.7.4.5.2　　外因性要因

外因性民族的要因の IDegLira の安全性プロファイルへの影響の可能性を評価した。以下の要因について検討を行った：

- 前治療の糖尿病治療
- 抗体産生

外因性民族的要因の安全性への影響の可能性は、前治療の糖尿病治療サブグループにおける有害事象、重篤な有害事象、胃腸障害の有害事象及び低血糖を発現した被験者の割合ならびに単位時間あたりの発現件数を考慮し、総合的に評価した。検討にあたっては、主に対照群と IDegLira 群とを比較した際の傾向がサブグループ間で異ならないかに着目した。

2.7.4.5.2.1　　前治療の糖尿病治療

試験期間中、4183 試験では治験薬と併用して前治療の糖尿病治療薬の投与を継続した。4184 試験では、治験薬と併用してメトホルミンの投与は継続し、それ以外の前治療の糖尿病治療薬は無作為割り付け時に中止した。

4183 試験

有害事象

すべての前治療の経口糖尿病薬グループにおいて、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に、投与群間で明らかな違いはみられなかった（表 2.7.4.5-13）。いずれの投与群でも、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、前治療の経口糖尿病薬グループ間で概ね同様であった（表 2.7.4.5-13）。

重篤な有害事象については、各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、すべての前治療の経口糖尿病薬グループにおいて投与群間で明らかな違いはみられなかった（表 2.7.4.5-13）。

すべての前治療の経口糖尿病薬グループにおいて、IDegLira 群の胃腸障害の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、概して、IDeg 群と比較して多くリラグルチド群と比較して少なかった（表 2.7.4.5-13）。IDegLira 群と IDeg 群では、胃腸障害の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に、前治療の経口糖尿病薬グループ間で明らかな傾向は認められなかった。リラグルチド群においては、胃腸障害の有害事象は、メトホルミン、SU 及び SGLT-2 阻害薬のグループで、他のサブグループと比較して多かった（表 2.7.4.5-13）。

表 2.7.4.5-13　前治療の経口糖尿病薬別の有害事象 - SAS（4183 試験）

	IDegLira			IDeg			Lira		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Metformin	47				46				47			
Alpha-glucosidase inh.	41				40				41			
Thiazolidinedione	43				43				42			
Sulphonylurea	43				42				42			
Sodium-glucose co-transporter 2 inh.	61				61				61			
Glinide	40				39				40			
PYE (years)												
Metformin	46.10				44.82				46.46			
Alpha-glucosidase inh.	38.56				38.39				41.44			
Thiazolidinedione	42.43				39.90				42.66			
Sulphonylurea	42.21				39.93				41.39			
Sodium-glucose co-transporter 2 inh.	59.40				60.03				61.09			
Glinide	39.30				38.73				38.80			
All adverse events												
Metformin	41	(87.2)	137	297.16	36	(78.3)	133	296.75	40	(85.1)	172	370.20
Alpha-glucosidase inh.	28	(68.3)	97	251.57	30	(75.0)	100	260.46	33	(80.5)	97	234.06
Thiazolidinedione	37	(86.0)	137	322.88	33	(76.7)	122	305.73	38	(90.5)	119	278.94
Sulphonylurea	38	(88.4)	162	383.83	35	(83.3)	131	328.06	35	(83.3)	142	343.09
Sodium-glucose co-transporter 2 inh.	53	(86.9)	174	292.94	52	(85.2)	239	398.12	51	(83.6)	217	355.22
Glinide	32	(80.0)	166	422.34	30	(76.9)	104	268.55	32	(80.0)	138	355.71
Serious adverse events												
Metformin	3	(6.4)	3	6.51	4	(8.7)	6	13.39	5	(10.6)	5	10.76
Alpha-glucosidase inh.	3	(7.3)	3	7.78	2	(5.0)	3	7.81	3	(7.3)	3	7.24
Thiazolidinedione	2	(4.7)	2	4.71	2	(4.7)	2	5.01	0			
Sulphonylurea	3	(7.0)	3	7.11	2	(4.8)	2	5.01	3	(7.1)	3	7.25
Sodium-glucose co-transporter 2 inh.	3	(4.9)	3	5.05	2	(3.3)	2	3.33	1	(1.6)	1	1.64
Glinide	3	(7.5)	4	10.18	1	(2.6)	1	2.58	2	(5.0)	2	5.16
Gastrointestinal adverse events												
Metformin	12	(25.5)	29	62.90	11	(23.9)	14	31.24	20	(42.6)	50	107.62
Alpha-glucosidase inh.	12	(29.3)	22	57.06	8	(20.0)	8	20.84	13	(31.7)	17	41.02
Thiazolidinedione	13	(30.2)	22	51.85	9	(20.9)	19	47.61	17	(40.5)	21	49.23
Sulphonylurea	12	(27.9)	28	66.34	11	(26.2)	19	47.58	20	(47.6)	38	91.81
Sodium-glucose co-transporter 2 inh.	26	(42.6)	41	69.03	16	(26.2)	34	56.64	33	(54.1)	72	117.86
Glinide	21	(52.5)	45	114.49	7	(17.9)	16	41.31	11	(27.5)	20	51.55

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), OAD: Oral antidiabetic drug, MedDRA version 20.0.

前治療の経口糖尿病薬別の有害事象及び重篤な有害事象（器官別大分類及び基本語別）の要約を 4183 試験の治験総括報告書（Module 5.3.5.1）、EOT Table 14.3.1.14～14.3.1.19 及び 14.3.1.21～14.3.1.26 に示す。

低血糖

すべての前治療の経口糖尿病薬グループにおいて、IDegLira 群の重大な又は血糖値確定低血糖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、概して、IDeg 群と比較して少なくリラグルチド

群と比較して多かった（表 2.7.4.5-14）。同様に、重大な又は血糖値確定夜間低血糖についても、各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、すべての前治療の経口糖尿病薬グループにおいて、その発現頻度はIDeg 群と比較して IDegLira 群で全般的に少なかった。なお、リラグルチド群では重大な又は血糖値確定夜間低血糖は報告されなかった。

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、他のサブグループと比較して SU のグループで多い傾向がみられた（表 2.7.4.5-14）。この所見は低血糖リスクに関する SU の既知の特性と一致していた。

表 2.7.4.5-14　　前治療の経口糖尿病薬別の低血糖 - SAS（4183 試験）

	IDegLira				IDeg				Lira			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Metformin	47				46				47			
Alpha-glucosidase inh.	41				40				41			
Thiazolidinedione	43				43				42			
Sulphonylurea	43				42				42			
Sodium-glucose co-transporter 2 inh.	61				61				61			
Glinide	40				39				40			
PYE (years)												
Metformin	46.10				44.82				46.46			
Alpha-glucosidase inh.	38.56				38.39				41.44			
Thiazolidinedione	42.43				39.90				42.66			
Sulphonylurea	42.21				39.93				41.39			
Sodium-glucose co-transporter 2 inh.	59.40				60.03				61.09			
Glinide	39.30				38.73				38.80			
Severe or BG confirmed hypoglycaemia												
Metformin	16	(34.0)	40	86.76	21	(45.7)	76	169.57	0			
Alpha-glucosidase inh.	16	(39.0)	60	155.61	23	(57.5)	147	382.88	0			
Thiazolidinedione	23	(53.5)	116	273.38	22	(51.2)	140	350.84	1	(2.4)	4	9.38
Sulphonylurea	23	(53.5)	137	324.59	29	(69.0)	182	455.78	4	(9.5)	7	16.91
Sodium-glucose co-transporter 2 inh.	17	(27.9)	59	99.33	31	(50.8)	190	316.49	0			
Glinide	11	(27.5)	55	139.93	22	(56.4)	134	346.01	1	(2.5)	2	5.16
Nocturnal severe or BG confirmed hypoglycaemia												
Metformin	5	(10.6)	11	23.86	6	(13.0)	9	20.08	0			
Alpha-glucosidase inh.	3	(7.3)	7	18.15	7	(17.5)	32	83.35	0			
Thiazolidinedione	7	(16.3)	12	28.28	8	(18.6)	22	55.13	0			
Sulphonylurea	6	(14.0)	18	42.65	6	(14.3)	20	50.09	0			
Sodium-glucose co-transporter 2 inh.	3	(4.9)	15	25.25	10	(16.4)	32	53.30	0			
Glinide	3	(7.5)	3	7.63	8	(20.5)	17	43.90	0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), inh.: inhibitor, OAD: Oral antidiabetic drug.

4184 試験

有害事象

すべての前治療の糖尿病治療グループにおいて、有害事象の単位時間あたりの発現件数について、投与群間で比較した際の傾向は全集団の傾向と一致していたが、発現した被験者の割合には一貫した傾向はみられなかった（表 2.7.4.5-15）。いずれの投与群においても、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、前治療の糖尿病治療グループ間で概ね同様であった（表 2.7.4.5-15）。

重篤な有害事象については、各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、すべての前治療の糖尿病治療グループにおいて投与群間で明らかな違いはみられなかった（表 2.7.4.5-15）。

すべての前治療の糖尿病治療グループにおいて、胃腸障害の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、IDeg 群と比較して IDegLira 群で多かった（表 2.7.4.5-15）。いずれの投与群においても、胃腸障害の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、前治療の糖尿病治療グループ間で概ね同様であった（表 2.7.4.5-15）。

表 2.7.4.5-15　前治療の糖尿病治療別の有害事象 - SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects								
Metformin and basal insulin	46				46			
Metformin, basal insulin and one other OAD	20				21			
Metformin and pre-mix/ combination insulin	26				25			
Metformin, pre-mix/ combination insulin and one other OAD	13				13			
PYE (years)								
Metformin and basal insulin	23.85				22.70			
Metformin, basal insulin and one other OAD	10.34				10.92			
Metformin and pre-mix/ combination insulin	13.39				11.92			
Metformin, pre-mix/ combination insulin and one other OAD	6.70				6.72			
All adverse events								
Metformin and basal insulin	36	(78.3)	141	591.07	36	(78.3)	97	427.27
Metformin, basal insulin and one other OAD	19	(95.0)	50	483.52	16	(76.2)	45	412.14
Metformin and pre-mix/ combination insulin	18	(69.2)	60	448.25	18	(72.0)	44	369.11
Metformin, pre-mix/ combination insulin and one other OAD	9	(69.2)	29	433.04	10	(76.9)	24	356.92
Serious adverse events								
Metformin and basal insulin	1	(2.2)	2	8.38	3	(6.5)	5	22.02
Metformin, basal insulin and one other OAD	2	(10.0)	2	19.34	0			
Metformin and pre-mix/ combination insulin	0				1	(4.0)	1	8.39
Metformin, pre-mix/ combination insulin and one other OAD	0				0			
Gastrointestinal adverse events								
Metformin and basal insulin	19	(41.3)	40	167.68	10	(21.7)	15	66.07
Metformin, basal insulin and one other OAD	10	(50.0)	15	145.06	5	(23.8)	10	91.59
Metformin and pre-mix/ combination insulin	10	(38.5)	23	171.83	4	(16.0)	8	67.11
Metformin, pre-mix/ combination insulin and one other OAD	6	(46.2)	10	149.33	5	(38.5)	7	104.10

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), OAD: Oral antidiabetic drug, MedDRA version 20.0

前治療の糖尿病治療別の有害事象及び重篤な有害事象（器官別大分類及び基本語別）の要約を付録 2.7.4.7.1、表 2.7.4.7.1-39～2.7.4.7.1-42 及び 2.7.4.7.1-69～2.7.4.7.1-72 に示す。

低血糖

すべての前治療の糖尿病治療グループにおいて、重大な又は血糖値確定低血糖（全体及び夜間）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について、各サブグループで低血糖を発現した被験者の割合が低かったことを考慮すると、投与群間に特定の傾向はみられなかった（表 2.7.4.5-16）。

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、各サブグループに含まれる被験者が少ないこと、発現した被験者が少ないこと及び単位時間あたりの発現件数が少ないことを考慮すると、前治療の糖尿病治療グループ間で同様と考えられた（表 2.7.4.5-16）。

表 2.7.4.5-16　　前治療の糖尿病治療別の低血糖 - SAS（4184 試験）

	IDegLira				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects								
Metformin and basal insulin	46				46			
Metformin, basal insulin and one other OAD	20				21			
Metformin and pre-mix/ combination insulin	26				25			
Metformin, pre-mix/ combination insulin and one other OAD	13				13			
PYE (years)								
Metformin and basal insulin	23.85				22.70			
Metformin, basal insulin and one other OAD	10.34				10.92			
Metformin and pre-mix/ combination insulin	13.39				11.92			
Metformin, pre-mix/ combination insulin and one other OAD	6.70				6.72			
Severe or BG confirmed hypoglycaemia								
Metformin and basal insulin	11	(23.9)	64	268.29	11	(23.9)	28	123.34
Metformin, basal insulin and one other OAD	2	(10.0)	8	77.36	3	(14.3)	7	64.11
Metformin and pre-mix/ combination insulin	9	(34.6)	31	231.60	12	(48.0)	43	360.72
Metformin, pre-mix/ combination insulin and one other OAD	8	(61.5)	21	313.58	6	(46.2)	31	461.02
Nocturnal severe or BG confirmed hypoglycaemia								
Metformin and basal insulin	4	(8.7)	17	71.26	3	(6.5)	4	17.62
Metformin, basal insulin and one other OAD	2	(10.0)	7	67.69	1	(4.8)	1	9.16
Metformin and pre-mix/ combination insulin	1	(3.8)	1	7.47	4	(16.0)	6	50.33
Metformin, pre-mix/ combination insulin and one other OAD	1	(7.7)	1	14.93	2	(15.4)	8	118.97

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events divided by patient years of exposure multiplied by 100), PYE: Patient years of exposure (1 PYE = 365.25 days), Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode, BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL), OAD: Oral antidiabetic drug

2.7.4.5.2.2　抗体産生

抗体の産生と有害事象の発現状況との間に関連は認められず、IDegLira の臨床的安全性に影響を与えるような抗 IDeg 特異抗体、ヒトインスリンと交叉反応を有する抗 IDeg 抗体又は抗リラグルチド抗体の産生を示すような所見はみられなかった。詳細は 2.7.4.3.6 を参照のこと。

2.7.4.5.2.3　要約

いずれの前治療の糖尿病治療グループにおいても、全般的な有害事象又は重篤な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について、重篤な有害事象を発現した被験者数が少ないことを考慮すると、投与群間で明らかな違いはみられなかった。

いずれの前治療の糖尿病治療グループにおいても、IDegLira 群での胃腸障害の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、概して、IDeg 群と比較して多くリラグルチド群と比較して少なかった。

IDegLira 群において、有害事象、重篤な有害事象又は胃腸障害の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について、前治療の糖尿病治療グループ間で明らかな傾向は認められなかった。

4183 試験では、すべての前治療の経口糖尿病薬グループにおいて、IDegLira 群の重大な又は血糖値確定低血糖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、概して、IDeg 群と比較して少なくリラグルチド群と比較して多かった。4184 試験では、いずれの前治療の糖尿病治療薬サブグループにおいても、重大な又は血糖値確定低血糖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について、投与群間に特定の傾向はみられなかった。

4183 試験（前治療の経口糖尿病薬の投与を無作為割り付け後も継続）では、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、他のサブグループと比較して SU のグループで多い傾向がみられた。この所見は低血糖リスクに関する SU の既知の特性と一致していた。

抗体の産生と有害事象及び重篤な有害事象（器官別大分類及び基本語別）の発現状況との間に、臨床的に問題となる関連は認められなかった。

2.7.4.5.3　　薬物相互作用

IDegLira の各成分（IDeg 及びリラグルチド）の初回承認申請時に、薬物相互作用について検討した。その結果、IDeg 及びリラグルチドと併用する薬剤の投与量調節は必要ないことが示された。

前治療の糖尿病治療薬については、2.7.4.5.2.1 を参照のこと。

2.7.4.5.4　　妊娠及び授乳時の使用

IDegLira の各成分（IDeg 及びリラグルチド）の生殖毒性について十分な検討を行っているため、ICH-M3 ガイドラインに基づき、IDegLira の生殖毒性試験は実施していない。また、2018 年 3 月 31 日時点で、IDegLira の臨床開発プログラムにおいて妊婦及び授乳婦を対象とした臨床試験は実施しておらず、IDegLira の乳汁への排泄及び乳児への影響に関する情報は得られていない。

4183 試験及び 4184 試験において妊娠は報告されなかった。

2.7.4.5.5　　過量投与

評価方法

過量投与に関連する有害事象を抽出するため、事前規定した MedDRA 検索を実施した。検索に用いた基本語の一覧を付録 2.7.4.7.5、表 2.7.4.7.5-5 に示す。

投薬過誤については 2.7.4.2.1.13 を参照のこと。

4183 試験

5 例 5 件の過量投与に関連する有害事象が報告された（付録 2.7.4.7.5、表 2.7.4.7.5-1）。各投与群で 1 例ずつの「偶発的過量投与」、IDegLira 群で 1 例の「過量投与」、及びリラグルチド群で 1 例の「自殺企図」（当該事象は重篤）が報告された。重症度は、軽度が 3 件、中等度が 2 件であった。IDeg 群の「偶発的過量投与」を除き、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。試験終了時の転帰はいずれも「回復」であった〔治験総括報告書の 4183 試験（Module 5.3.5.1）, Appendix 16.2.7, Listing 16.2.7.1〕。

4184 試験

本試験で過量投与に関連する有害事象は報告されなかった（付録 2.7.4.7.5、表 2.7.4.7.5-2）。

要約及び結論

過量投与に関連する事象は、4183 試験において 5 例で報告され、4184 試験では報告されなかった。該当被験者はいずれも合併症を生じることなく回復した。

2.7.4.5.6　　薬物乱用

これまでに得られている臨床試験の結果では、IDegLira の乱用性／依存性との関連は示唆されない。また、IDeg 及びリラグルチドの市販後の使用経験では、これらの製剤の乱用性／依存性の可能性は示唆されていない。

2.7.4.5.7　　離脱症状及び反跳現象

IDegLira の各成分（IDeg 及びリラグルチド）の初回承認申請時に、離脱症状及び反跳現象に関連する安全性は評価され、その結果から、これに関連する安全性上の懸念は示されなかった。

2.7.4.5.8　　自動車運転及び機械操作に対する影響又は精神機能の障害

IDegLira の各成分（IDeg 及びリラグルチド）の初回承認申請時に、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する安全性は評価され、その結果から、これに関連する安全性上の懸念は示されなかった。

2.7.4.5.9　　海外試験における安全性情報

2.7.4.5.9.1　　GLP-1 受容体作動薬から IDegLira への切り替え時の安全性の評価

海外で実施した 3851 試験は、GLP-1 受容体作動薬と経口糖尿病薬の併用により十分な血糖コントロールが得られていない 2 型糖尿病患者を対象とした、IDegLira と GLP-1 受容体作動薬（前治療から継続投与）を比較する、26 週間、無作為割り付け、並行群間、非盲検、多施設共同、国際共同、treat-to-target 試験であった。本試験の主要目的は、メトホルミン±ピオグリタゾン±SU 併用下での GLP-1 受容体作動薬による治療で十分な血糖コントロールが得られていない、インスリン治療歴のない 2 型糖尿病患者を対象に、血糖コントロールにおける IDegLira の GLP-1 受容体作動薬（前治療から継続投与）に対する優越性を検証することであった。

有害事象プロファイル

試験期間中、死亡は報告されなかった。

有害事象全体の単位時間あたりの発現件数は、IDegLira 群で 410.1 件/100 人・年、GLP-1 受容体作動薬群（以降、GLP-1 群）で 364.3 件/100 人・年であった。有害事象の大部分は非重篤、軽度及び一過性の事象であり、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。

最も高頻度に報告された有害事象は「鼻咽頭炎」、「上気道感染」、「リパーゼ増加」、「頭痛」及び「下痢」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、IDegLira 群で 8.5 件/100 人・年、GLP-1 群で 4.6 件/100 人・年であり、事象の種類に明らかな傾向は認められなかった。治験薬との因果関係が「あり」又は「可能性あり」と判定された重篤な有害事象はなかった。

試験の中止に至った有害事象は 3 例（0.7%）の被験者で報告された〔IDegLira 群 1 例（0.3%）、GLP-1 群 2 例（1.4%）〕。3 例中 2 例の被験者は回復し、残りの 1 例の転帰は不明であった。

IDegLira 群の 2 件が外部のイベント判定委員会により心血管系事象と確定された（いずれも MACE）。

膵炎の報告はなく、イベント判定委員会の判定対象となった甲状腺に関連する有害事象はなかった。カルシトニンの継続的なモニタリングで安全性上の問題は認められなかった。

イベント判定委員会により 3 件の新生物が確定された（IDegLira 群：2 件、GLP-1 群：1 件）。確定された新生物の単位時間あたりの発現件数は、IDegLira 群で 1.4 件/100 人・年、GLP-1 群で 1.5 件/100 人・年であった。確定された 3 件の新生物のうち 1 件（口唇扁平上皮癌、IDegLira 群）は悪性と分類された。

アレルギー反応の単位時間あたりの発現件数は、IDegLira 群で 6.4 件/100 人・年、GLP-1 群で 10.6 件/100 人・年であった。いずれの事象も、非重篤であり、IDegLira 群の「薬物過敏症」1 件を除き、治験薬との因果関係は「なし」と判定された。「薬物過敏症」は治験薬との因果関係が「あり」と判定され、当該被験者は試験を中止した。

注射部位反応に関する有害事象の単位時間あたりの発現件数は、IDegLira 群で 7.1 件/100 人・年、GLP-1 群で 1.5 件/100 人・年であった。いずれの事象も、非重篤で、軽度であり、発現した被験者は試験終了時までに回復した。事象の大部分は、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。

胃腸障害の有害事象の単位時間あたりの発現件数は、IDegLira 群で 44.7 件/100 人・年、GLP-1 群で 57.7 件/100 人・年であった。いずれの事象も非重篤であり、事象の大部分は軽度であった。

低血糖

確定低血糖の単位時間あたりの発現件数は、IDegLira 群で 281.7 件/100 人・年、GLP-1 群で 12.1 件/100 人・年であった。比の推定値（IDegLira 群／GLP-1 群）は 25.36（95%信頼区間：10.63; 60.51、$p<0.001$）であり、低血糖の単位時間あたりの発現件数は GLP-1 群と比較して IDegLira 群で統計的に有意に多かった。

重大な低血糖は、IDegLira 群の 1 例で報告された。

確定夜間低血糖の単位時間あたりの発現件数は、IDegLira 群で 45.4 件/100 人・年、GLP-1 群で 1.5 件/100 人・年であった。比の推定値（IDegLira 群／GLP-1 群、事後解析）は 32.82（95%信頼区間：4.13; 261.04、$p<0.001$）であり、確定夜間低血糖の単位時間あたりの発現件数は GLP-1 群と比較して IDegLira 群で統計的に有意に多かった。

結論

IDegLira の安全性プロファイルは、各成分（IDeg 及びリラグルチド）のプロファイルと同様であった。詳細については、Module 2.7.6.9 及び治験総括報告書の 3851 試験（Module 5.3.5.1）を参照のこと。

2.7.4.5.9.2　グローバル併合データの安全性情報

本項では、データベースロック時点（2018 年 3 月 31 日）で完了した（治験総括報告書の完成と定義）又は進行中の臨床試験から得られたグローバル併合データについて記述する。

臨床試験における累積曝露

2018 年 3 月 31 日までに完了した IDegLira の臨床試験（ノボ ノルディスク社が治験依頼者の試験）では、2 型糖尿病患者 2,761 例（3697 試験、3912 試験、3851 試験、3951 試験、3952 試験、4119 試験、4056 試験、4185 試験及び 4229 試験）、ならびに健康被験者 97 例（3632 試験、3871 試験及び 4026 試験）が IDegLira の投与を受けた。また、これらの試験では 2 型糖尿病患者 1,910 例、健康被験者 48 例が実対照薬の投与を受け、2 型糖尿病患者 146 例がプラセボの投与を受けた。対象集団及び投与群別の累積曝露の概要を表 2.7.4.5-17 に示す。

2018 年 3 月 31 日時点では 6 つの臨床試験が実施中であった。このうち 5 試験は 2 型糖尿病患者（4 つの第 3a 相試験：4148 試験、4166 試験、4183 試験及び 4184 試験、ならびに 1 つの第 3b 相試験：4228 試験）、1 試験は健康被験者（第 1 相：4139 試験）を対象とした試験である。無作為割り付け予定被験者数に基づくと、実施中の 6 試験では 2 型糖尿病患者 1,175 例及び健康被験者 24 例が IDegLira の投与を受ける見込みである。

表 2.7.4.5-17　2018 年 3 月 31 日までに完了した IDegLira（被験薬として使用）の臨床試験における累積曝露

Product	Population/ Indication	Treatment	Number of subjects (%)	SYE
Clinical pharmacology trials				
	Healthy subjects	IDegLira	23 (23.5)	NA
		IDegLira B3	24 (24.5)	NA
		IDegLira B5	50 (51.0)	NA
		IDegLira V2	50 (51.0)	NA
		IDeg	48 (49.0)	NA
		Liraglutide + IDeg	24 (24.5)	NA
		Liraglutide	48 (49.0)	NA
		Total	98 (100.0)	NA
	Total	IDegLira	97 (99.0)	NA
		Comparator - pooled	48 (49.0)	NA
		Total	98 (100.0)	NA
Exploratory and confirmatory clinical trials				
	T2DM	IDegLira	2552 (53.0)	1610.7
		IDegLira 1WT	209 (4.3)	125.7
		IDeg	611 (12.7)	451.8
		GLP-1	145 (3.0)	68.7
		Liraglutide	412 (8.6)	342.2
		IGlar	489 (10.2)	246.3
		IGlar + IAsp	253 (5.3)	124.2
		Placebo	146 (3.0)	64.9
		Total	4817 (100.0)	3034.6
	Total	IDegLira	2761 (57.3)	1736.4
		Comparator - pooled	1910 (39.7)	1233.2
		Placebo	146 (3.0)	64.9
		Total	4817 (100.0)	3034.6

SYE: Subject years exposure. Exposure in years is calculated as (date of last randomised treatment-date of first randomised treatment+1+7)/365.25. For crossover trials subjects are counted only once in total row in a trial.
IDegLira B5: The IDegLira formulation used in the phase 3a clinical trials,
IDegLira V2: IDegLira formulation with the same concentrations of IDeg and liraglutide as used in IDegLira B5,
IDegLira B3: IDegLira formulation with lower concentration of phenol than used in phase 3.
Comparator: Insulin: IDeg (NN9068-3632, -3871, -3697-main-ext, -3912), IGlar (NN9068-3952, -4229) and IGlar+IAsp (NN9068-4185). GLP-1 RA: Liraglutide (NN9068-3697-main-ext, -3632, -3871) and GLP-1 (NN9068-3851).
NN9068-4119: IDegLira contains IDegLira 80 Dose step and IDegLira 50 Dose step+IAsp.
IDegLira 1WT: IDegLira once weekly titration, IDegLira row under total contains both IDegLira and IDegLira 1WT.
Trials included: NN9068-3632, -3871, -4026, -3697-main-ext, -3912, -3851, -3951, -3952, -4119, -4056, -4185 and -4229.

臨床試験で報告された重篤な有害事象の累積要約表

概して、報告された重篤な有害事象の種類及び各器官別大分類別の発現状況は、IDegLira 群及び対照薬群で同様であった。最も高頻度に報告された重篤な有害事象（器官別大分類）の発現状況を表 2.7.4.5-18 に示す。

2018 年 3 月 31 日までに報告されたすべての重篤な有害事象の累積要約表（器官別大分類及び基本語別）を付録 2.7.4.7.4、表 2.7.4.7.4-1 に示す。

2018 年 3 月 31 日までに、IDegLira（被験薬として使用）の臨床試験において計 567 件の重篤な有害事象が報告された。このうち 286 件は IDegLira 群の被験者での報告であった。残りの 281 件のうち、253 件は実薬対照群、6 件はプラセボ群、17 件は治験薬を投与していない被験者での報告であった。5 件は盲検下で報告された。

表 2.7.4.5-18　IDegLira（被験薬として使用）の臨床試験において最も高頻度に報告された重篤な有害事象（器官別大分類）

System organ class	Number of serious adverse events (% of total)	
	IDegLira	Active comparator[a]
心臓障害	47 (16%)	36 (14%)
感染症および寄生虫症	36 (13%)	35 (14%)
傷害、中毒および処置合併症	28 (10%)	16 (6%)
神経系障害	22 (8%)	19 (8%)
胃腸障害	21 (7%)	18 (7%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	18 (6%)	24 (9%)

[a]Excluding 6 events in subjects receiving placebo.

2.7.4.6 市販後データ

市販後の累積曝露

IDegLira（販売名：Xultophy®）は欧州及び米国を含む海外で既に承認、販売されている。

2018 年 3 月 31 日までにノボ ノルディスク社が顧客に販売した Xultophy®の総量（サンプルを含む）は、約 1,518,000,000 単位である（この「単位」は IDeg の用量と等しく、「用量ステップ」に読み替えられる）。曝露データは、世界保健機関（WHO）が規定した 1 日投与量（40 用量ステップ）に基づき、Xultophy®の総販売数から算出した。推定累積曝露（人・年：PYE）の要約を表 2.7.4.6-1 に示す。

表 2.7.4.6-1　　市販後の曝露（地域別）

	Patient-years of exposure (PYE)			
	Europe	**US**	**Rest of the World**	**Total**
Cumulative period[a]	88,537	10,753	4,702	**103,992**

Note: As the exposure is based on volume distributed to external customers and average daily usage rather than actual patient exposure, the numbers can be over- or underestimated.

[a]Cumulative period: 12 Sep 2014−31 Mar 2018. PYE = patient years of exposure.

市販後データに基づく累積要約表

2018 年 3 月 31 日までに、Xultophy®の使用により 507 例で計 999 件の有害事象が報告された（自発報告）。このうち 86 例で報告された 129 件（13%）は重篤な有害事象であった。2018 年 3 月 31 日までに、市販後の非介入試験及びその他の報告から 2 件の重篤な副作用が報告された。上述の自発的な報告によるすべての事象について検討した結果、新たな安全性上の懸念は認められなかった。

すべての副作用の累積要約表（器官別大分類及び基本語別）は付録 2.7.4.7.4、表 2.7.4.7.4-2 を参照のこと。

2.7.4.7 付録

本 Module に対する付録は、付録 2.7.4.7.1～付録 2.7.4.7.5 として添付した。

参考文献

[1] U.S.Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry, Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. December 2008, Clinical/Medical .

[2] Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. J Clin Invest 1987; 79(3):777-781.

[3] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes cars. 2014;37 (Suppl.1):23. 2014.

ゾルトファイ配合注フレックスタッチ

2.7.4.7 付録
1.内因性及び外因性民族的要因の影響の検討に関する安全性データ

ノボ ノルディスク ファーマ株式会社

目次

ページ

2.7.4.7.1-1 男女別の有害事象の概要－SAS（4183 試験）.....7
2.7.4.7.1-2 男女別の有害事象の概要－SAS（4184 試験）.....8
2.7.4.7.1-3 ベースラインの BMI（kg/m^2）別の有害事象の概要－SAS（4183 試験）.....9
2.7.4.7.1-4 ベースラインの BMI（kg/m^2）別の有害事象の概要－SAS（4184 試験）.....10
2.7.4.7.1-5 ベースラインの年齢（歳）別の有害事象の概要－SAS（4183 試験）.....11
2.7.4.7.1-6 ベースラインの年齢（歳）別の有害事象の概要－SAS（4184 試験）.....13
2.7.4.7.1-7 ベースラインの腎機能別の有害事象の概要－SAS（4183 試験）.....15
2.7.4.7.1-8 ベースラインの腎機能別の有害事象の概要－SAS（4184 試験）.....16
2.7.4.7.1-9 ベースラインの肝機能別の有害事象の概要－SAS（4183 試験）.....17
2.7.4.7.1-10 ベースラインの肝機能別の有害事象の概要－SAS（4184 試験）.....18
2.7.4.7.1-11 前治療の経口糖尿病薬別の有害事象の概要－SAS（4183 試験）.....19
2.7.4.7.1-12 前治療の糖尿病治療別の有害事象の概要－SAS（4184 試験）.....22
2.7.4.7.1-13 男性被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....25
2.7.4.7.1-14 女性被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....39
2.7.4.7.1-15 男性被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....50
2.7.4.7.1-16 女性被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....55
2.7.4.7.1-17 ベースラインの BMI（kg/m^2）が 25 未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....60
2.7.4.7.1-18 ベースラインの BMI（kg/m^2）が 25 以上 30 未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....72
2.7.4.7.1-19 ベースラインの BMI（kg/m^2）が 30 以上の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....85
2.7.4.7.1-20 ベースラインの BMI（kg/m^2）が 25 未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....93
2.7.4.7.1-21 ベースラインの BMI（kg/m^2）が 25 以上 30 未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....96
2.7.4.7.1-22 ベースラインの BMI（kg/m^2）が 30 以上の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....101
2.7.4.7.1-23 ベースラインの年齢が 65 歳未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....105
2.7.4.7.1-24 ベースラインの年齢が 65 歳以上の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....120

2.7.4.7.1-25 ベースラインの年齢が 65 歳以上 75 歳未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....131
2.7.4.7.1-26 ベースラインの年齢が 75 歳以上の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....142
2.7.4.7.1-27 ベースラインの年齢が 65 歳未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....144
2.7.4.7.1-28 ベースラインの年齢が 65 歳以上の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....150
2.7.4.7.1-29 ベースラインの年齢が 65 歳以上 75 歳未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....154
2.7.4.7.1-30 ベースラインの年齢が 75 歳以上の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....158
2.7.4.7.1-31 ベースライン時に正常腎機能を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....160
2.7.4.7.1-32 ベースライン時に軽度腎機能障害を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....166
2.7.4.7.1-33 ベースライン時に正常腎機能を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....184
2.7.4.7.1-34 ベースライン時に軽度腎機能障害を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....187
2.7.4.7.1-35 ベースライン時に正常肝機能を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....194
2.7.4.7.1-36 ベースライン時に肝機能障害を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....211
2.7.4.7.1-37 ベースライン時に正常肝機能を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....219
2.7.4.7.1-38 ベースライン時に肝機能障害を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....226
2.7.4.7.1-39 有害事象（器官別大分類及び基本語別）－前治療：メトホルミン+Basal インスリン－SAS（4184 試験）.....229
2.7.4.7.1-40 有害事象（器官別大分類及び基本語別）－前治療：メトホルミン+Basal インスリン+その他の経口糖尿病薬 1 剤－SAS（4184 試験）.....234
2.7.4.7.1-41 有害事象（器官別大分類及び基本語別）－前治療：メトホルミン +混合／配合インスリン－SAS（4184 試験）.....237
2.7.4.7.1-42 有害事象（器官別大分類及び基本語別）－前治療：メトホルミン +混合／配合インスリン+その他の経口糖尿病薬 1 剤－SAS（4184 試験）.....241
2.7.4.7.1-43 男性被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....243

2.7.4.7.1-44 女性被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....246
2.7.4.7.1-45 男性被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....248
2.7.4.7.1-46 女性被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....249
2.7.4.7.1-47 ベースラインの BMI（kg/m^2）が 25 未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....250
2.7.4.7.1-48 ベースラインの BMI（kg/m^2）が 25 以上 30 未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....252
2.7.4.7.1-49 ベースラインの BMI（kg/m^2）が 30 以上の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....254
2.7.4.7.1-50 ベースラインの BMI（kg/m^2）が 25 未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....255
2.7.4.7.1-51 ベースラインの BMI（kg/m^2）が 25 以上 30 未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....256
2.7.4.7.1-52 ベースラインの BMI（kg/m^2）が 30 以上の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....257
2.7.4.7.1-53 ベースラインの年齢が 65 歳未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....258
2.7.4.7.1-54 ベースラインの年齢が 65 歳以上の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....260
2.7.4.7.1-55 ベースラインの年齢が 65 歳以上 75 歳未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....262
2.7.4.7.1-56 ベースラインの年齢が 75 歳以上の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....264
2.7.4.7.1-57 ベースラインの年齢が 65 歳未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....265
2.7.4.7.1-58 ベースラインの年齢が 65 歳以上の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....266
2.7.4.7.1-59 ベースラインの年齢が 65 歳以上 75 歳未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....267
2.7.4.7.1-60 ベースラインの年齢が 75 歳以上の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....268
2.7.4.7.1-61 ベースライン時に正常腎機能を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....269
2.7.4.7.1-62 ベースライン時に軽度腎機能障害を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....270

2.7.4.7.1-63 ベースライン時に正常腎機能を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 273
2.7.4.7.1-64 ベースライン時に軽度腎機能障害を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 274
2.7.4.7.1-65 ベースライン時に正常肝機能を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験） 275
2.7.4.7.1-66 ベースライン時に肝機能障害を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験） 278
2.7.4.7.1-67 ベースライン時に正常肝機能を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 279
2.7.4.7.1-68 ベースライン時に肝機能障害を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 280
2.7.4.7.1-69 重篤な有害事象（器官別大分類及び基本語別）－前治療：メトホルミン+Basal インスリン－SAS（4184 試験） 281
2.7.4.7.1-70 重篤な有害事象（器官別大分類及び基本語別）－前治療：メトホルミン+Basal インスリン+その他の経口糖尿病薬 1 剤－SAS（4184 試験） 282
2.7.4.7.1-71 重篤な有害事象（器官別大分類及び基本語別）－前治療：メトホルミン +混合／配合インスリン－SAS（4184 試験） 283
2.7.4.7.1-72 重篤な有害事象（器官別大分類及び基本語別）－前治療：メトホルミン +混合／配合インスリン+その他の経口糖尿病薬 1 剤－SAS（4184 試験） 283
2.7.4.7.1-73 男女別の低血糖－SAS（4183 試験） 284
2.7.4.7.1-74 男女別の低血糖－SAS（4184 試験） 287
2.7.4.7.1-75 ベースラインの BMI（kg/m^2）別の低血糖－SAS（4183 試験） 290
2.7.4.7.1-76 ベースラインの BMI（kg/m^2）別の低血糖－SAS（4184 試験） 293
2.7.4.7.1-77 ベースラインの年齢（歳）別の低血糖－SAS（4183 試験） 296
2.7.4.7.1-78 ベースラインの年齢（歳）別の低血糖－SAS（4184 試験） 299
2.7.4.7.1-79 ベースラインの腎機能別の低血糖－SAS（4183 試験） 302
2.7.4.7.1-80 ベースラインの腎機能別の低血糖－SAS（4184 試験） 305
2.7.4.7.1-81 ベースラインの肝機能別の低血糖－SAS（4183 試験） 308
2.7.4.7.1-82 ベースラインの肝機能別の低血糖－SAS（4184 試験） 311
2.7.4.7.1-83 前治療の経口糖尿病薬別の低血糖－SAS（4183 試験） 314
2.7.4.7.1-84 前治療の糖尿病治療別の低血糖－SAS（4184 試験） 320
2.7.4.7.1-85 男女別の夜間低血糖－SAS（4183 試験） 326
2.7.4.7.1-86 男女別の夜間低血糖－SAS（4184 試験） 329
2.7.4.7.1-87 ベースラインの BMI（kg/m^2）別の夜間低血糖－SAS（4183 試験） 332
2.7.4.7.1-88 ベースラインの BMI（kg/m^2）別の夜間低血糖－SAS（4184 試験） 335
2.7.4.7.1-89 ベースラインの年齢（歳）別の夜間低血糖－SAS（4183 試験） 338
2.7.4.7.1-90 ベースラインの年齢（歳）別の夜間低血糖－SAS（4184 試験） 341

2.7.4.7.1-91 ベースラインの腎機能別の夜間低血糖－SAS（4183 試験）.....344
2.7.4.7.1-92 ベースラインの腎機能別の夜間低血糖－SAS（4184 試験）.....347
2.7.4.7.1-93 ベースラインの肝機能別の夜間低血糖－SAS（4183 試験）.....350
2.7.4.7.1-94 ベースラインの肝機能別の夜間低血糖－SAS（4184 試験）.....353
2.7.4.7.1-95 前治療の経口糖尿病薬別の夜間低血糖－SAS（4183 試験）.....356
2.7.4.7.1-96 前治療の糖尿病治療別の夜間低血糖－SAS（4184 試験）.....362
2.7.4.7.1-97 事後調査来院時の抗インスリン抗体価が閾値を超えていた被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....368
2.7.4.7.1-98 事後調査来院時の抗インスリン抗体価が閾値を超えていた被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....377
2.7.4.7.1-99 事後調査来院時に抗リラグルチド抗体が陽性であった被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....378
2.7.4.7.1-100 事後調査来院時に抗リラグルチド抗体が陽性であった被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....386

2.7.4.7 付録 1

2.7.4.7.1-1 男女別の有害事象の概要－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
Male	194				195				192				581			
Female	81				76				81				238			
PYE (years)																
Male	189.96				188.09				192.61				570.66			
Female	78.04				73.72				79.23				230.99			
All adverse events																
Male	156	(80.4)	570	300.06	151	(77.4)	504	267.96	153	(79.7)	551	286.07	460	(79.2)	1625	284.76
Female	73	(90.1)	303	388.26	65	(85.5)	325	440.86	76	(93.8)	334	421.55	214	(89.9)	962	416.47
Serious adverse events																
Male	15	(7.7)	16	8.42	10	(5.1)	13	6.91	5	(2.6)	5	2.60	30	(5.2)	34	5.96
Female	2	(2.5)	2	2.56	3	(3.9)	3	4.07	9	(11.1)	9	11.36	14	(5.9)	14	6.06
Gastrointestinal adverse events																
Male	54	(27.8)	117	61.59	38	(19.5)	59	31.37	75	(39.1)	135	70.09	167	(28.7)	311	54.50
Female	42	(51.9)	70	89.70	24	(31.6)	51	69.18	39	(48.1)	83	104.76	105	(44.1)	204	88.32

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

nn9068/nn9068-exploratory/lsueot011_20180717_er
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2.7.4.7.1-2 男女別の有害事象の概要－SAS（4184 試験）

	IDegLira			IDeg			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Male	70				63				133			
Female	35				42				77			
PYE (years)												
Male	36.19				31.53				67.73			
Female	18.09				20.73				38.82			
All adverse events												
Male	53	(75.7)	157	433.80	48	(76.2)	119	377.36	101	(75.9)	276	407.52
Female	29	(82.9)	123	680.07	32	(76.2)	91	438.96	61	(79.2)	214	551.30
Serious adverse events												
Male	2	(2.9)	2	5.53	3	(4.8)	5	15.86	5	(3.8)	7	10.34
Female	1	(2.9)	2	11.06	1	(2.4)	1	4.82	2	(2.6)	3	7.73
Gastrointestinal adverse events												
Male	28	(40.0)	49	135.39	14	(22.2)	22	69.76	42	(31.6)	71	104.83
Female	17	(48.6)	39	215.63	10	(23.8)	18	86.83	27	(35.1)	57	146.84

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-3 ベースラインの BMI（kg/m^2）別の有害事象の概要－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
<25	122				117				118				357			
25<= <30	112				107				109				328			
>=30	41				47				46				134			
PYE (years)																
<25	117.94				111.20				117.32				346.46			
25<= <30	110.64				105.69				109.04				325.37			
>=30	39.42				44.91				45.48				129.82			
All adverse events																
<25	103	(84.4)	340	288.29	87	(74.4)	352	316.54	97	(82.2)	360	306.85	287	(80.4)	1052	303.64
25<= <30	89	(79.5)	394	356.09	87	(81.3)	336	317.91	93	(85.3)	370	339.33	269	(82.0)	1100	338.07
>=30	37	(90.2)	139	352.62	42	(89.4)	141	313.93	39	(84.8)	155	340.80	118	(88.1)	435	335.09
Serious adverse events																
<25	12	(9.8)	13	11.02	5	(4.3)	7	6.29	4	(3.4)	4	3.41	21	(5.9)	24	6.93
25<= <30	5	(4.5)	5	4.52	5	(4.7)	6	5.68	7	(6.4)	7	6.42	17	(5.2)	18	5.53
>=30	0				3	(6.4)	3	6.68	3	(6.5)	3	6.60	6	(4.5)	6	4.62
Gastrointestinal adverse events																
<25	42	(34.4)	73	61.90	29	(24.8)	47	42.26	49	(41.5)	89	75.86	120	(33.6)	209	60.32
25<= <30	40	(35.7)	79	71.40	22	(20.6)	41	38.79	52	(47.7)	104	95.38	114	(34.8)	224	68.84
>=30	14	(34.1)	35	88.79	11	(23.4)	22	48.98	13	(28.3)	25	54.97	38	(28.4)	82	63.17

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

2.7.4.7.1-4 ベースラインの BMI（kg/m^2）別の有害事象の概要－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
<25	26				28				54			
25<= <30	64				53				117			
>=30	15				24				39			
PYE (years)												
<25	13.42				13.74				27.16			
25<= <30	33.06				26.07				59.13			
>=30	7.79				12.46				20.25			
All adverse events												
<25	21	(80.8)	64	476.77	19	(67.9)	40	291.21	40	(74.1)	104	382.92
25<= <30	50	(78.1)	175	529.35	40	(75.5)	93	356.70	90	(76.9)	268	453.22
>=30	11	(73.3)	41	526.00	21	(87.5)	77	618.12	32	(82.1)	118	582.66
Serious adverse events												
<25	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
25<= <30	3	(4.7)	4	12.10	1	(1.9)	1	3.84	4	(3.4)	5	8.46
>=30	0				2	(8.3)	4	32.11	2	(5.1)	4	19.75
Gastrointestinal adverse events												
<25	11	(42.3)	28	208.59	3	(10.7)	7	50.96	14	(25.9)	35	128.87
25<= <30	26	(40.6)	45	136.12	12	(22.6)	17	65.20	38	(32.5)	62	104.85
>=30	8	(53.3)	15	192.44	9	(37.5)	16	128.44	17	(43.6)	31	153.07

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

2.7.4.7.1-5 ベースラインの年齢（歳）別の有害事象の概要－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
<65	197				183				202				582			
>=65	78				88				71				237			
65<= <75	76				84				66				226			
>=75	2				4				5				11			
PYE (years)																
<65	193.01				179.38				202.03				574.43			
>=65	74.99				82.43				69.80				227.22			
65<= <75	73.16				79.21				64.70				217.07			
>=75	1.83				3.22				5.10				10.15			
All adverse events																
<65	161	(81.7)	625	323.82	142	(77.6)	558	311.07	167	(82.7)	660	326.68	470	(80.8)	1843	320.84
>=65	68	(87.2)	248	330.71	74	(84.1)	271	328.78	62	(87.3)	225	322.33	204	(86.1)	744	327.44
65<= <75	66	(86.8)	237	323.93	71	(84.5)	263	332.05	57	(86.4)	199	307.57	194	(85.8)	699	322.02
>=75	2	(100.0)	11	602.36	3	(75.0)	8	248.47	5	(100.0)	26	509.47	10	(90.9)	45	443.38
Serious adverse events																
<65	5	(2.5)	5	2.59	5	(2.7)	5	2.79	11	(5.4)	11	5.44	21	(3.6)	21	3.66
>=65	12	(15.4)	13	17.34	8	(9.1)	11	13.35	3	(4.2)	3	4.30	23	(9.7)	27	11.88
65<= <75	10	(13.2)	11	15.03	8	(9.5)	11	13.89	3	(4.5)	3	4.64	21	(9.3)	25	11.52
>=75	2	(100.0)	2	109.52	0				0				2	(18.2)	2	19.71

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by age (years) at baseline - treatment emergent - trial 4183 - overview - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Gastrointestinal adverse events																
<65	70	(35.5)	133	68.91	43	(23.5)	77	42.93	84	(41.6)	170	84.14	197	(33.8)	380	66.15
>=65	26	(33.3)	54	72.01	19	(21.6)	33	40.04	30	(42.3)	48	68.76	75	(31.6)	135	59.41
65<= <75	25	(32.9)	47	64.24	18	(21.4)	32	40.40	26	(39.4)	43	66.46	69	(30.5)	122	56.20
>=75	1	(50.0)	7	383.32	1	(25.0)	1	31.06	4	(80.0)	5	97.97	6	(54.5)	13	128.09

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-6 ベースラインの年齢（歳）別の有害事象の概要－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
<65	75				85				160			
>=65	30				20				50			
65<= <75	28				19				47			
>=75	2				1				3			
PYE (years)												
<65	38.80				43.35				82.16			
>=65	15.47				8.91				24.39			
65<= <75	14.44				8.66				23.10			
>=75	1.03				0.25				1.28			
All adverse events												
<65	58	(77.3)	187	481.91	65	(76.5)	169	389.82	123	(76.9)	356	433.31
>=65	24	(80.0)	93	601.00	15	(75.0)	41	460.07	39	(78.0)	134	549.49
65<= <75	22	(78.6)	69	477.86	14	(73.7)	40	461.76	36	(76.6)	109	471.82
>=75	2	(100.0)	24	2319.05	1	(100.0)	1	401.37	3	(100.0)	25	1946.96
Serious adverse events												
<65	2	(2.7)	2	5.15	3	(3.5)	5	11.53	5	(3.1)	7	8.52
>=65	1	(3.3)	2	12.92	1	(5.0)	1	11.22	2	(4.0)	3	12.30
65<= <75	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
>=75	1	(50.0)	2	193.25	0				1	(33.3)	2	155.76

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by age (years) at baseline - treatment emergent - trial 4184 - overview - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Gastrointestinal adverse events												
<65	31	(41.3)	56	144.32	17	(20.0)	28	64.58	48	(30.0)	84	102.24
>=65	14	(46.7)	32	206.79	7	(35.0)	12	134.65	21	(42.0)	44	180.43
65<= <75	12	(42.9)	27	186.99	7	(36.8)	12	138.53	19	(40.4)	39	168.82
>=75	2	(100.0)	5	483.13	0				2	(66.7)	5	389.39

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-7 ベースラインの腎機能別の有害事象の概要－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
Normal function	24				20				23				67			
Mild impairment	251				251				250				752			
PYE (years)																
Normal function	23.25				18.69				21.69				63.62			
Mild impairment	244.75				243.12				250.15				738.02			
All adverse events																
Normal function	20	(83.3)	85	365.59	16	(80.0)	73	390.67	19	(82.6)	81	373.50	55	(82.1)	239	375.66
Mild impairment	209	(83.3)	788	321.96	200	(79.7)	756	310.96	210	(84.0)	804	321.40	619	(82.3)	2348	318.15
Serious adverse events																
Normal function	1	(4.2)	1	4.30	0				3	(13.0)	3	13.83	4	(6.0)	4	6.29
Mild impairment	16	(6.4)	17	6.95	13	(5.2)	16	6.58	11	(4.4)	11	4.40	40	(5.3)	44	5.96
Gastrointestinal adverse events																
Normal function	6	(25.0)	17	73.12	6	(30.0)	20	107.03	11	(47.8)	23	106.06	23	(34.3)	60	94.31
Mild impairment	90	(35.9)	170	69.46	56	(22.3)	90	37.02	103	(41.2)	195	77.95	249	(33.1)	455	61.65

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2; mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2],
MedDRA version 20.0

2.7.4.7.1-8 ベースラインの腎機能別の有害事象の概要－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Normal function	12				12				24			
Mild impairment	93				93				186			
PYE (years)												
Normal function	6.20				6.24				12.43			
Mild impairment	48.08				46.03				94.11			
All adverse events												
Normal function	12	(100.0)	47	758.58	9	(75.0)	30	481.01	21	(87.5)	77	619.34
Mild impairment	70	(75.3)	233	484.59	71	(76.3)	180	391.06	141	(75.8)	413	438.84
Serious adverse events												
Normal function	0				0				0			
Mild impairment	3	(3.2)	4	8.32	4	(4.3)	6	13.04	7	(3.8)	10	10.63
Gastrointestinal adverse events												
Normal function	7	(58.3)	17	274.38	4	(33.3)	9	144.30	11	(45.8)	26	209.13
Mild impairment	38	(40.9)	71	147.66	20	(21.5)	31	67.35	58	(31.2)	102	108.38

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2;
mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2],
MedDRA version 20.0

2.7.4.7.1-9 ベースラインの肝機能別の有害事象の概要－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
Normal	226				222				213				661			
Impairment	49				49				60				158			
PYE (years)																
Normal	219.62				213.34				212.03				645.00			
Impairment	48.38				48.47				59.81				156.65			
All adverse events																
Normal	188	(83.2)	660	300.51	176	(79.3)	685	321.08	177	(83.1)	703	331.55	541	(81.8)	2048	317.52
Impairment	41	(83.7)	213	440.31	40	(81.6)	144	297.12	52	(86.7)	182	304.32	133	(84.2)	539	344.09
Serious adverse events																
Normal	15	(6.6)	16	7.29	11	(5.0)	14	6.56	10	(4.7)	10	4.72	36	(5.4)	40	6.20
Impairment	2	(4.1)	2	4.13	2	(4.1)	2	4.13	4	(6.7)	4	6.69	8	(5.1)	8	5.11
Gastrointestinal adverse events																
Normal	77	(34.1)	147	66.93	54	(24.3)	89	41.72	90	(42.3)	162	76.40	221	(33.4)	398	61.71
Impairment	19	(38.8)	40	82.69	8	(16.3)	21	43.33	24	(40.0)	56	93.64	51	(32.3)	117	74.69

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower;
impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range],
MedDRA version 20.0

2.7.4.7.1-10 ベースラインの肝機能別の有害事象の概要－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Normal	79				88				167			
Impairment	26				17				43			
PYE (years)												
Normal	40.82				43.70				84.52			
Impairment	13.46				8.56				22.02			
All adverse events												
Normal	64	(81.0)	226	553.63	66	(75.0)	172	393.58	130	(77.8)	398	470.88
Impairment	18	(69.2)	54	401.29	14	(82.4)	38	443.72	32	(74.4)	92	417.79
Serious adverse events												
Normal	2	(2.5)	3	7.35	4	(4.5)	6	13.73	6	(3.6)	9	10.65
Impairment	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Gastrointestinal adverse events												
Normal	38	(48.1)	70	171.48	22	(25.0)	34	77.80	60	(35.9)	104	123.04
Impairment	7	(26.9)	18	133.76	2	(11.8)	6	70.06	9	(20.9)	24	108.99

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower; impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range],
MedDRA version 20.0

2.7.4.7.1-11 前治療の経口糖尿病薬別の有害事象の概要－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
Metformin	47				46				47				140			
Alpha-glucosidase inhibitor	41				40				41				122			
Thiazolidinedione	43				43				42				128			
Sulphonylurea	43				42				42				127			
Sodium-glucose co-transporter 2 inhibitors	61				61				61				183			
Glinide	40				39				40				119			
PYE (years)																
Metformin	46.10				44.82				46.46				137.38			
Alpha-glucosidase inhibitor	38.56				38.39				41.44				118.39			
Thiazolidinedione	42.43				39.90				42.66				125.00			
Sulphonylurea	42.21				39.93				41.39				123.53			
Sodium-glucose co-transporter 2 inhibitors	59.40				60.03				61.09				180.52			
Glinide	39.30				38.73				38.80				116.83			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), OAD: Oral anti-diabetic drug,
MedDRA version 20.0

Adverse events by pre-trial OAD treatment - treatment emergent - trial 4183 - overview - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
All adverse events																
Metformin	41	(87.2)	137	297.16	36	(78.3)	133	296.75	40	(85.1)	172	370.20	117	(83.6)	442	321.73
Alpha-glucosidase inhibitor	28	(68.3)	97	251.57	30	(75.0)	100	260.46	33	(80.5)	97	234.06	91	(74.6)	294	248.33
Thiazolidinedione	37	(86.0)	137	322.88	33	(76.7)	122	305.73	38	(90.5)	119	278.94	108	(84.4)	378	302.41
Sulphonylurea	38	(88.4)	162	383.83	35	(83.3)	131	328.06	35	(83.3)	142	343.09	108	(85.0)	435	352.15
Sodium-glucose co-transporter 2 inhibitors	53	(86.9)	174	292.94	52	(85.2)	239	398.12	51	(83.6)	217	355.22	156	(85.2)	630	348.99
Glinide	32	(80.0)	166	422.34	30	(76.9)	104	268.55	32	(80.0)	138	355.71	94	(79.0)	408	349.23
Serious adverse events																
Metformin	3	(6.4)	3	6.51	4	(8.7)	6	13.39	5	(10.6)	5	10.76	12	(8.6)	14	10.19
Alpha-glucosidase inhibitor	3	(7.3)	3	7.78	2	(5.0)	3	7.81	3	(7.3)	3	7.24	8	(6.6)	9	7.60
Thiazolidinedione	2	(4.7)	2	4.71	2	(4.7)	2	5.01	0				4	(3.1)	4	3.20
Sulphonylurea	3	(7.0)	3	7.11	2	(4.8)	2	5.01	3	(7.1)	3	7.25	8	(6.3)	8	6.48
Sodium-glucose co-transporter 2 inhibitors	3	(4.9)	3	5.05	2	(3.3)	2	3.33	1	(1.6)	1	1.64	6	(3.3)	6	3.32
Glinide	3	(7.5)	4	10.18	1	(2.6)	1	2.58	2	(5.0)	2	5.16	6	(5.0)	7	5.99

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), OAD: Oral anti-diabetic drug,
MedDRA version 20.0

Adverse events by pre-trial OAD treatment - treatment emergent – trial 4183 - overview - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Gastrointestinal adverse events																
Metformin	12	(25.5)	29	62.90	11	(23.9)	14	31.24	20	(42.6)	50	107.62	43	(30.7)	93	67.69
Alpha-glucosidase inhibitor	12	(29.3)	22	57.06	8	(20.0)	8	20.84	13	(31.7)	17	41.02	33	(27.0)	47	39.70
Thiazolidinedione	13	(30.2)	22	51.85	9	(20.9)	19	47.61	17	(40.5)	21	49.23	39	(30.5)	62	49.60
Sulphonylurea	12	(27.9)	28	66.34	11	(26.2)	19	47.58	20	(47.6)	38	91.81	43	(33.9)	85	68.81
Sodium-glucose co-transporter 2 inhibitors	26	(42.6)	41	69.03	16	(26.2)	34	56.64	33	(54.1)	72	117.86	75	(41.0)	147	81.43
Glinide	21	(52.5)	45	114.49	7	(17.9)	16	41.31	11	(27.5)	20	51.55	39	(32.8)	81	69.33

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), OAD: Oral anti-diabetic drug,
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2.7.4.7.1-12 前治療の糖尿病治療別の有害事象の概要－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Metformin and basal insulin	46				46				92			
Metformin, basal insulin and one other OAD	20				21				41			
Metformin and pre-mix/ combination insulin	26				25				51			
Metformin, pre-mix/ combination insulin and one other OAD	13				13				26			
PYE (years)												
Metformin and basal insulin	23.85				22.70				46.56			
Metformin, basal insulin and one other OAD	10.34				10.92				21.26			
Metformin and pre-mix/ combination insulin	13.39				11.92				25.31			
Metformin, pre-mix/ combination insulin and one other OAD	6.70				6.72				13.42			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
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Adverse events by pre-trial diabetes treatment - treatment emergent – trial 4184 - overview - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
All adverse events												
Metformin and basal insulin	36	(78.3)	141	591.07	36	(78.3)	97	427.27	72	(78.3)	238	511.20
Metformin, basal insulin and one other OAD	19	(95.0)	50	483.52	16	(76.2)	45	412.14	35	(85.4)	95	446.86
Metformin and pre-mix/ combination insulin	18	(69.2)	60	448.25	18	(72.0)	44	369.11	36	(70.6)	104	410.97
Metformin, pre-mix/ combination insulin and one other OAD	9	(69.2)	29	433.04	10	(76.9)	24	356.92	19	(73.1)	53	394.91
Serious adverse events												
Metformin and basal insulin	1	(2.2)	2	8.38	3	(6.5)	5	22.02	4	(4.3)	7	15.04
Metformin, basal insulin and one other OAD	2	(10.0)	2	19.34	0				2	(4.9)	2	9.41
Metformin and pre-mix/ combination insulin	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Metformin, pre-mix/ combination insulin and one other OAD	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), OAD: Oral anti-diabetic drug,
MedDRA version 20.0

Adverse events by pre-trial diabetes treatment - treatment emergent – trial 4184 - overview - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Gastrointestinal adverse events												
Metformin and basal insulin	19	(41.3)	40	167.68	10	(21.7)	15	66.07	29	(31.5)	55	118.13
Metformin, basal insulin and one other OAD	10	(50.0)	15	145.06	5	(23.8)	10	91.59	15	(36.6)	25	117.59
Metformin and pre-mix/ combination insulin	10	(38.5)	23	171.83	4	(16.0)	8	67.11	14	(27.5)	31	122.50
Metformin, pre-mix/ combination insulin and one other OAD	6	(46.2)	10	149.33	5	(38.5)	7	104.10	11	(42.3)	17	126.67

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
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2.7.4.7.1-13 男性被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	194				195				192				581			
PYE (years)	189.96				188.09				192.61				570.66			
Events	156	(80.4)	570	300.06	151	(77.4)	504	267.96	153	(79.7)	551	286.07	460	(79.2)	1625	284.76
Infections and infestations	108	(55.7)	196	103.18	87	(44.6)	160	85.07	94	(49.0)	181	93.97	289	(49.7)	537	94.10
Viral upper respiratory tract infection	72	(37.1)	113	59.49	60	(30.8)	99	52.64	59	(30.7)	109	56.59	191	(32.9)	321	56.25
Influenza	9	(4.6)	9	4.74	9	(4.6)	9	4.79	3	(1.6)	3	1.56	21	(3.6)	21	3.68
Pharyngitis	7	(3.6)	9	4.74	10	(5.1)	11	5.85	4	(2.1)	4	2.08	21	(3.6)	24	4.21
Gastroenteritis	7	(3.6)	7	3.68	2	(1.0)	2	1.06	8	(4.2)	9	4.67	17	(2.9)	18	3.15
Bronchitis	4	(2.1)	6	3.16	4	(2.1)	5	2.66	5	(2.6)	5	2.60	13	(2.2)	16	2.80
Conjunctivitis	1	(0.5)	1	0.53	3	(1.5)	3	1.60	5	(2.6)	5	2.60	9	(1.5)	9	1.58
Helicobacter infection	1	(0.5)	1	0.53	3	(1.5)	3	1.60	4	(2.1)	4	2.08	8	(1.4)	8	1.40
Periodontitis	5	(2.6)	5	2.63	2	(1.0)	3	1.60	1	(0.5)	1	0.52	8	(1.4)	9	1.58
Herpes zoster	4	(2.1)	4	2.11	3	(1.5)	3	1.60	0				7	(1.2)	7	1.23
Tonsillitis	1	(0.5)	1	0.53	4	(2.1)	4	2.13	2	(1.0)	2	1.04	7	(1.2)	7	1.23
Sinusitis	5	(2.6)	6	3.16	0				1	(0.5)	1	0.52	6	(1.0)	7	1.23
Tinea pedis	1	(0.5)	1	0.53	1	(0.5)	1	0.53	4	(2.1)	4	2.08	6	(1.0)	6	1.05
Gingivitis	2	(1.0)	2	1.05	1	(0.5)	1	0.53	2	(1.0)	3	1.56	5	(0.9)	6	1.05
Nasopharyngitis	2	(1.0)	4	2.11	1	(0.5)	2	1.06	2	(1.0)	2	1.04	5	(0.9)	8	1.40
Upper respiratory tract infection	1	(0.5)	1	0.53	1	(0.5)	1	0.53	3	(1.6)	4	2.08	5	(0.9)	6	1.05
Otitis externa	2	(1.0)	2	1.05	0				2	(1.0)	3	1.56	4	(0.7)	5	0.88
Cellulitis	0				1	(0.5)	1	0.53	2	(1.0)	2	1.04	3	(0.5)	3	0.53
Hordeolum	1	(0.5)	1	0.53	0				2	(1.0)	2	1.04	3	(0.5)	3	0.53
Oral herpes	2	(1.0)	2	1.05	0				1	(0.5)	1	0.52	3	(0.5)	3	0.53
Pneumonia	1	(0.5)	1	0.53	1	(0.5)	1	0.53	1	(0.5)	1	0.52	3	(0.5)	3	0.53
Pulpitis dental	1	(0.5)	1	0.53	0				2	(1.0)	2	1.04	3	(0.5)	3	0.53
Cystitis	1	(0.5)	1	0.53	1	(0.5)	1	0.53	0				2	(0.3)	2	0.35
Gastroenteritis viral	1	(0.5)	1	0.53	1	(0.5)	1	0.53	0				2	(0.3)	2	0.35
Gingival abscess	2	(1.0)	2	1.05	0				0				2	(0.3)	2	0.35
Otitis media	0				1	(0.5)	1	0.53	1	(0.5)	1	0.52	2	(0.3)	2	0.35

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Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Paronychia	1	(0.5)	1	0.53	0				1	(0.5)	1	0.52	2	(0.3)	2	0.35
Purulence	2	(1.0)	2	1.05	0				0				2	(0.3)	2	0.35
Rhinitis	1	(0.5)	1	0.53	0				1	(0.5)	1	0.52	2	(0.3)	2	0.35
Urinary tract infection	0				2	(1.0)	2	1.06	0				2	(0.3)	2	0.35
Acute sinusitis	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Beta haemolytic streptococcal infection	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Bronchitis bacterial	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Dermatitis infected	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Dermatophytosis of nail	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Eczema impetiginous	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Empyema	1	(0.5)	2	1.05	0				0				1	(0.2)	2	0.35
Enterocolitis bacterial	0				0				1	(0.5)	2	1.04	1	(0.2)	2	0.35
Folliculitis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Furuncle	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Helicobacter gastritis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Herpes virus infection	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Herpes zoster meningitis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Infectious colitis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Localised infection	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Mycoplasma infection	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Oesophageal candidiasis	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Peritonsillitis	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Pharyngotonsillitis	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Pneumonia haemophilus	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Pneumonia mycoplasmal	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Pyelonephritis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Skin infection	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Sycosis barbae	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Ureteritis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Urethritis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Gastrointestinal disorders	54	(27.8)	117	61.59	38	(19.5)	59	31.37	75	(39.1)	135	70.09	167	(28.7)	311	54.50
Constipation	14	(7.2)	15	7.90	4	(2.1)	4	2.13	24	(12.5)	25	12.98	42	(7.2)	44	7.71

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Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Diarrhoea	12	(6.2)	16	8.42	6	(3.1)	8	4.25	12	(6.3)	16	8.31	30	(5.2)	40	7.01
Gastrooesophageal reflux disease	12	(6.2)	12	6.32	5	(2.6)	5	2.66	8	(4.2)	8	4.15	25	(4.3)	25	4.38
Nausea	5	(2.6)	9	4.74	3	(1.5)	3	1.60	14	(7.3)	16	8.31	22	(3.8)	28	4.91
Chronic gastritis	6	(3.1)	6	3.16	5	(2.6)	5	2.66	5	(2.6)	6	3.12	16	(2.8)	17	2.98
Abdominal discomfort	3	(1.5)	4	2.11	3	(1.5)	3	1.60	7	(3.6)	7	3.63	13	(2.2)	14	2.45
Dental caries	4	(2.1)	4	2.11	3	(1.5)	3	1.60	4	(2.1)	5	2.60	11	(1.9)	12	2.10
Dyspepsia	6	(3.1)	7	3.68	0				5	(2.6)	5	2.60	11	(1.9)	12	2.10
Large intestine polyp	5	(2.6)	5	2.63	2	(1.0)	2	1.06	3	(1.6)	3	1.56	10	(1.7)	10	1.75
Vomiting	1	(0.5)	3	1.58	1	(0.5)	1	0.53	6	(3.1)	6	3.12	8	(1.4)	10	1.75
Abdominal pain	2	(1.0)	2	1.05	2	(1.0)	2	1.06	3	(1.6)	4	2.08	7	(1.2)	8	1.40
Gastric polyps	1	(0.5)	1	0.53	3	(1.5)	3	1.60	3	(1.6)	3	1.56	7	(1.2)	7	1.23
Gastritis	2	(1.0)	2	1.05	2	(1.0)	2	1.06	3	(1.6)	3	1.56	7	(1.2)	7	1.23
Abdominal pain upper	3	(1.5)	4	2.11	2	(1.0)	2	1.06	1	(0.5)	1	0.52	6	(1.0)	7	1.23
Colitis	3	(1.5)	3	1.58	1	(0.5)	1	0.53	2	(1.0)	2	1.04	6	(1.0)	6	1.05
Periodontal disease	1	(0.5)	1	0.53	2	(1.0)	2	1.06	3	(1.6)	3	1.56	6	(1.0)	6	1.05
Stomatitis	4	(2.1)	5	2.63	1	(0.5)	1	0.53	1	(0.5)	1	0.52	6	(1.0)	7	1.23
Abdominal distension	3	(1.5)	3	1.58	1	(0.5)	1	0.53	1	(0.5)	1	0.52	5	(0.9)	5	0.88
Toothache	1	(0.5)	1	0.53	0				3	(1.6)	3	1.56	4	(0.7)	4	0.70
Faeces soft	0				1	(0.5)	1	0.53	2	(1.0)	3	1.56	3	(0.5)	4	0.70
Hiatus hernia	1	(0.5)	1	0.53	2	(1.0)	2	1.06	0				3	(0.5)	3	0.53
Anal fissure	0				2	(1.0)	2	1.06	0				2	(0.3)	2	0.35
Barrett's oesophagus	2	(1.0)	2	1.05	0				0				2	(0.3)	2	0.35
Eructation	0				0				2	(1.0)	2	1.04	2	(0.3)	2	0.35
Gastric ulcer	1	(0.5)	1	0.53	1	(0.5)	1	0.53	0				2	(0.3)	2	0.35
Gastrointestinal disorder	0				0				2	(1.0)	3	1.56	2	(0.3)	3	0.53
Hyperchlorhydria	1	(0.5)	1	0.53	0				1	(0.5)	1	0.52	2	(0.3)	2	0.35
Proctitis	2	(1.0)	2	1.05	0				0				2	(0.3)	2	0.35
Brunner's gland hyperplasia	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Diverticulum intestinal	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Dry mouth	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Duodenitis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Enteritis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Flatulence	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Food poisoning	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Functional gastrointestinal disorder	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Gastritis erosive	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Gastroduodenitis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Haemorrhoidal haemorrhage	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Hypoaesthesia oral	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Inguinal hernia	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Mouth ulceration	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Oral discomfort	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Pancreatic atrophy	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Pancreatic cyst	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Pancreatitis acute	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Parotid gland enlargement	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Periodontal inflammation	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Musculoskeletal and connective tissue disorders	31	(16.0)	39	20.53	29	(14.9)	38	20.20	27	(14.1)	42	21.81	87	(15.0)	119	20.85
Back pain	7	(3.6)	7	3.68	3	(1.5)	3	1.60	11	(5.7)	13	6.75	21	(3.6)	23	4.03
Arthralgia	4	(2.1)	4	2.11	2	(1.0)	3	1.60	4	(2.1)	5	2.60	10	(1.7)	12	2.10
Muscle spasms	3	(1.5)	5	2.63	2	(1.0)	2	1.06	4	(2.1)	6	3.12	9	(1.5)	13	2.28
Myalgia	5	(2.6)	5	2.63	3	(1.5)	3	1.60	1	(0.5)	1	0.52	9	(1.5)	9	1.58
Periarthritis	2	(1.0)	2	1.05	4	(2.1)	4	2.13	1	(0.5)	1	0.52	7	(1.2)	7	1.23
Osteoarthritis	3	(1.5)	3	1.58	1	(0.5)	1	0.53	1	(0.5)	1	0.52	5	(0.9)	5	0.88
Spinal osteoarthritis	3	(1.5)	3	1.58	2	(1.0)	2	1.06	0				5	(0.9)	5	0.88
Intervertebral disc protrusion	2	(1.0)	2	1.05	2	(1.0)	2	1.06	0				4	(0.7)	4	0.70
Musculoskeletal stiffness	1	(0.5)	1	0.53	1	(0.5)	1	0.53	2	(1.0)	2	1.04	4	(0.7)	4	0.70
Arthritis	1	(0.5)	1	0.53	1	(0.5)	1	0.53	1	(0.5)	1	0.52	3	(0.5)	3	0.53
Flank pain	1	(0.5)	1	0.53	2	(1.0)	2	1.06	0				3	(0.5)	3	0.53
Musculoskeletal pain	1	(0.5)	1	0.53	1	(0.5)	1	0.53	1	(0.5)	1	0.52	3	(0.5)	3	0.53
Pain in extremity	0				2	(1.0)	2	1.06	1	(0.5)	1	0.52	3	(0.5)	3	0.53
Tenosynovitis	0				1	(0.5)	1	0.53	2	(1.0)	2	1.04	3	(0.5)	3	0.53
Joint swelling	1	(0.5)	1	0.53	1	(0.5)	1	0.53	0				2	(0.3)	2	0.35

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Neck pain	0				1	(0.5)	1	0.53	1	(0.5)	1	0.52	2	(0.3)	2	0.35
Trigger finger	0				1	(0.5)	1	0.53	1	(0.5)	1	0.52	2	(0.3)	2	0.35
Bone pain	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Cervical spinal stenosis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Fasciitis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Groin pain	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Intervertebral disc disorder	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Joint contracture	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Lumbar spinal stenosis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Osteitis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Osteoporosis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Plantar fasciitis	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Rhabdomyolysis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Rheumatoid arthritis	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Spinal column stenosis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Spondylolisthesis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Synovial cyst	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Tendon pain	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Eye disorders	32	(16.5)	37	19.48	18	(9.2)	22	11.70	26	(13.5)	33	17.13	76	(13.1)	92	16.12
Diabetic retinopathy	14	(7.2)	14	7.37	10	(5.1)	12	6.38	9	(4.7)	9	4.67	33	(5.7)	35	6.13
Cataract	4	(2.1)	4	2.11	2	(1.0)	2	1.06	4	(2.1)	4	2.08	10	(1.7)	10	1.75
Asthenopia	1	(0.5)	1	0.53	2	(1.0)	2	1.06	2	(1.0)	2	1.04	5	(0.9)	5	0.88
Vitreous floaters	1	(0.5)	1	0.53	1	(0.5)	1	0.53	2	(1.0)	2	1.04	4	(0.7)	4	0.70
Conjunctivitis allergic	1	(0.5)	1	0.53	1	(0.5)	1	0.53	1	(0.5)	1	0.52	3	(0.5)	3	0.53
Glaucoma	1	(0.5)	1	0.53	0				2	(1.0)	2	1.04	3	(0.5)	3	0.53
Macular fibrosis	2	(1.0)	2	1.05	0				1	(0.5)	1	0.52	3	(0.5)	3	0.53
Dry eye	1	(0.5)	1	0.53	1	(0.5)	1	0.53	0				2	(0.3)	2	0.35
Keratitis	0				0				2	(1.0)	2	1.04	2	(0.3)	2	0.35
Retinal detachment	1	(0.5)	1	0.53	0				1	(0.5)	1	0.52	2	(0.3)	2	0.35
Retinal haemorrhage	1	(0.5)	1	0.53	1	(0.5)	1	0.53	0				2	(0.3)	2	0.35
Age-related macular degeneration	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Astigmatism	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18

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Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Blepharitis	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Chorioretinopathy	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Conjunctival haemorrhage	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Conjunctivochalasis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Diabetic retinal oedema	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Erythema of eyelid	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Exposure keratitis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Eye haemorrhage	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Eye inflammation	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Macular degeneration	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Macular hole	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Macular oedema	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Ocular discomfort	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Posterior capsule opacification	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Retinal degeneration	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Retinal tear	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Retinopathy proliferative	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Vision blurred	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Vitreous haemorrhage	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Investigations	22	(11.3)	32	16.85	19	(9.7)	29	15.42	21	(10.9)	25	12.98	62	(10.7)	86	15.07
Weight increased	4	(2.1)	4	2.11	12	(6.2)	12	6.38	1	(0.5)	1	0.52	17	(2.9)	17	2.98
Lipase increased	4	(2.1)	6	3.16	0				11	(5.7)	11	5.71	15	(2.6)	17	2.98
Blood proinsulin decreased	4	(2.1)	4	2.11	2	(1.0)	2	1.06	0				6	(1.0)	6	1.05
Free fatty acids decreased	3	(1.5)	4	2.11	2	(1.0)	2	1.06	1	(0.5)	1	0.52	6	(1.0)	7	1.23
Insulin C-peptide decreased	3	(1.5)	3	1.58	2	(1.0)	2	1.06	0				5	(0.9)	5	0.88
Amylase increased	2	(1.0)	2	1.05	0				2	(1.0)	2	1.04	4	(0.7)	4	0.70
Blood creatine phosphokinase increased	0				3	(1.5)	4	2.13	1	(0.5)	1	0.52	4	(0.7)	5	0.88
Blood calcitonin increased	1	(0.5)	1	0.53	0				2	(1.0)	2	1.04	3	(0.5)	3	0.53
Blood triglycerides increased	1	(0.5)	1	0.53	0				2	(1.0)	2	1.04	3	(0.5)	3	0.53
Helicobacter test positive	1	(0.5)	1	0.53	1	(0.5)	1	0.53	1	(0.5)	1	0.52	3	(0.5)	3	0.53

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	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Alanine aminotransferase increased	0				1	(0.5)	1	0.53	1	(0.5)	1	0.52	2	(0.3)	2	0.35
Blood creatine phosphokinase MM increased	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Blood potassium increased	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Blood pressure increased	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
C-reactive protein increased	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Carotid intima-media thickness increased	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Electrocardiogram QT prolonged	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Gamma-glutamyltransferase increased	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Glomerular filtration rate decreased	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Hepatic enzyme increased	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Pancreatic enzymes increased	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Rheumatoid factor increased	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Urine ketone body present	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Weight decreased	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
White blood cell count increased	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Skin and subcutaneous tissue disorders	23	(11.9)	25	13.16	19	(9.7)	25	13.29	15	(7.8)	17	8.83	57	(9.8)	67	11.74
Eczema	12	(6.2)	13	6.84	3	(1.5)	3	1.60	4	(2.1)	4	2.08	19	(3.3)	20	3.50
Dermatitis contact	2	(1.0)	2	1.05	1	(0.5)	1	0.53	4	(2.1)	5	2.60	7	(1.2)	8	1.40
Pruritus	1	(0.5)	1	0.53	2	(1.0)	3	1.60	1	(0.5)	1	0.52	4	(0.7)	5	0.88
Rash	2	(1.0)	2	1.05	2	(1.0)	2	1.06	0				4	(0.7)	4	0.70
Urticaria	1	(0.5)	1	0.53	3	(1.5)	4	2.13	0				4	(0.7)	5	0.88
Asteatosis	0				0				2	(1.0)	2	1.04	2	(0.3)	2	0.35
Dermal cyst	1	(0.5)	1	0.53	0				1	(0.5)	1	0.52	2	(0.3)	2	0.35
Dermatitis	0				2	(1.0)	2	1.06	0				2	(0.3)	2	0.35
Dermatitis atopic	0				2	(1.0)	2	1.06	0				2	(0.3)	2	0.35

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	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Haemorrhage subcutaneous	1	(0.5)	1	0.53	1	(0.5)	3	1.60	0				2	(0.3)	4	0.70
Hyperkeratosis	0				2	(1.0)	2	1.06	0				2	(0.3)	2	0.35
Miliaria	1	(0.5)	1	0.53	1	(0.5)	1	0.53	0				2	(0.3)	2	0.35
Acne	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Blister	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Chronic pigmented purpura	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Drug eruption	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Dyshidrotic eczema	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Ingrowing nail	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Psoriasis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Scab	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Solar dermatitis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Injury, poisoning and procedural complications	18	(9.3)	20	10.53	20	(10.3)	25	13.29	17	(8.9)	20	10.38	55	(9.5)	65	11.39
Contusion	5	(2.6)	5	2.63	3	(1.5)	4	2.13	4	(2.1)	4	2.08	12	(2.1)	13	2.28
Ligament sprain	1	(0.5)	2	1.05	3	(1.5)	3	1.60	3	(1.6)	3	1.56	7	(1.2)	8	1.40
Arthropod bite	2	(1.0)	2	1.05	1	(0.5)	1	0.53	1	(0.5)	1	0.52	4	(0.7)	4	0.70
Arthropod sting	1	(0.5)	1	0.53	0				2	(1.0)	2	1.04	3	(0.5)	3	0.53
Rib fracture	0				2	(1.0)	2	1.06	1	(0.5)	1	0.52	3	(0.5)	3	0.53
Accidental overdose	0				1	(0.5)	1	0.53	1	(0.5)	1	0.52	2	(0.3)	2	0.35
Heat illness	1	(0.5)	1	0.53	0				1	(0.5)	1	0.52	2	(0.3)	2	0.35
Laceration	1	(0.5)	1	0.53	0				1	(0.5)	1	0.52	2	(0.3)	2	0.35
Spinal compression fracture	1	(0.5)	1	0.53	0				1	(0.5)	1	0.52	2	(0.3)	2	0.35
Wound	0				2	(1.0)	2	1.06	0				2	(0.3)	2	0.35
Avulsion fracture	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Clavicle fracture	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Epicondylitis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Excoriation	0				0				1	(0.5)	2	1.04	1	(0.2)	2	0.35
Femoral neck fracture	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Foreign body in eye	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Head injury	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Heat stroke	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Incorrect dose administered	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18

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	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Limb injury	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Lip injury	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Median nerve injury	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Meniscus injury	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Muscle injury	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Muscle strain	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Overdose	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Scratch	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Stab wound	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Subcutaneous haematoma	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Suture related complication	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Thermal burn	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Thoracic vertebral fracture	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Tooth injury	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Nervous system disorders	11	(5.7)	15	7.90	24	(12.3)	28	14.89	17	(8.9)	19	9.86	52	(9.0)	62	10.86
Headache	2	(1.0)	5	2.63	3	(1.5)	3	1.60	7	(3.6)	7	3.63	12	(2.1)	15	2.63
Dizziness	2	(1.0)	2	1.05	6	(3.1)	7	3.72	1	(0.5)	1	0.52	9	(1.5)	10	1.75
Hypoaesthesia	1	(0.5)	2	1.05	4	(2.1)	4	2.13	2	(1.0)	2	1.04	7	(1.2)	8	1.40
Diabetic neuropathy	1	(0.5)	1	0.53	3	(1.5)	3	1.60	2	(1.0)	2	1.04	6	(1.0)	6	1.05
Carotid arteriosclerosis	0				3	(1.5)	3	1.60	0				3	(0.5)	3	0.53
Facial paralysis	1	(0.5)	1	0.53	1	(0.5)	1	0.53	0				2	(0.3)	2	0.35
Balance disorder	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Carotid artery stenosis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Cerebral infarction	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Cervicobrachial syndrome	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Dysgeusia	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Head discomfort	0				0				1	(0.5)	2	1.04	1	(0.2)	2	0.35
Hypoglycaemic unconsciousness	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Intercostal neuralgia	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Loss of consciousness	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Lumbar radiculopathy	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Migraine	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18

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Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Neuralgia	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Neuropathy peripheral	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Presyncope	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Sciatica	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Thalamic infarction	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Thrombotic cerebral infarction	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
General disorders and administration site conditions	10	(5.2)	11	5.79	18	(9.2)	19	10.10	17	(8.9)	19	9.86	45	(7.7)	49	8.59
Malaise	0				2	(1.0)	2	1.06	5	(2.6)	6	3.12	7	(1.2)	8	1.40
Oedema peripheral	1	(0.5)	1	0.53	5	(2.6)	6	3.19	1	(0.5)	1	0.52	7	(1.2)	8	1.40
Injection site erythema	1	(0.5)	1	0.53	0				3	(1.6)	3	1.56	4	(0.7)	4	0.70
Injection site bruising	0				2	(1.0)	2	1.06	1	(0.5)	1	0.52	3	(0.5)	3	0.53
Oedema	0				2	(1.0)	2	1.06	1	(0.5)	1	0.52	3	(0.5)	3	0.53
Asthenia	0				2	(1.0)	2	1.06	0				2	(0.3)	2	0.35
Fatigue	0				1	(0.5)	1	0.53	1	(0.5)	1	0.52	2	(0.3)	2	0.35
Injection site pruritus	1	(0.5)	1	0.53	0				1	(0.5)	1	0.52	2	(0.3)	2	0.35
Injection site reaction	2	(1.0)	2	1.05	0				0				2	(0.3)	2	0.35
Injection site swelling	1	(0.5)	1	0.53	1	(0.5)	1	0.53	0				2	(0.3)	2	0.35
Administration site mass	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Chest discomfort	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Fat tissue increased	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Feeling abnormal	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Hunger	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Inflammation	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Injection site discolouration	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Injection site induration	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Injection site mass	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Injection site pain	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Peripheral swelling	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Pyrexia	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18

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Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Thirst	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Respiratory, thoracic and mediastinal disorders	12	(6.2)	16	8.42	17	(8.7)	22	11.70	7	(3.6)	7	3.63	36	(6.2)	45	7.89
Upper respiratory tract inflammation	3	(1.5)	5	2.63	4	(2.1)	5	2.66	2	(1.0)	2	1.04	9	(1.5)	12	2.10
Asthma	2	(1.0)	2	1.05	5	(2.6)	5	2.66	1	(0.5)	1	0.52	8	(1.4)	8	1.40
Sleep apnoea syndrome	2	(1.0)	2	1.05	3	(1.5)	3	1.60	1	(0.5)	1	0.52	6	(1.0)	6	1.05
Oropharyngeal pain	1	(0.5)	1	0.53	2	(1.0)	2	1.06	1	(0.5)	1	0.52	4	(0.7)	4	0.70
Rhinitis allergic	1	(0.5)	1	0.53	1	(0.5)	1	0.53	2	(1.0)	2	1.04	4	(0.7)	4	0.70
Cough	1	(0.5)	1	0.53	2	(1.0)	3	1.60	0				3	(0.5)	4	0.70
Emphysema	1	(0.5)	1	0.53	1	(0.5)	1	0.53	0				2	(0.3)	2	0.35
Rhinorrhoea	1	(0.5)	1	0.53	1	(0.5)	1	0.53	0				2	(0.3)	2	0.35
Chronic obstructive pulmonary disease	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Pulmonary fibrosis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Respiratory disorder	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Vascular disorders	11	(5.7)	11	5.79	14	(7.2)	14	7.44	4	(2.1)	5	2.60	29	(5.0)	30	5.26
Hypertension	9	(4.6)	9	4.74	11	(5.6)	11	5.85	3	(1.6)	3	1.56	23	(4.0)	23	4.03
Orthostatic hypotension	1	(0.5)	1	0.53	0				1	(0.5)	1	0.52	2	(0.3)	2	0.35
Peripheral arterial occlusive disease	0				2	(1.0)	2	1.06	0				2	(0.3)	2	0.35
Arteriosclerosis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Hypotension	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Varicose vein	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Metabolism and nutrition disorders	5	(2.6)	5	2.63	9	(4.6)	10	5.32	12	(6.3)	14	7.27	26	(4.5)	29	5.08
Decreased appetite	1	(0.5)	1	0.53	1	(0.5)	1	0.53	9	(4.7)	9	4.67	11	(1.9)	11	1.93
Hyperuricaemia	1	(0.5)	1	0.53	3	(1.5)	3	1.60	1	(0.5)	1	0.52	5	(0.9)	5	0.88
Dehydration	0				1	(0.5)	1	0.53	1	(0.5)	2	1.04	2	(0.3)	3	0.53
Dyslipidaemia	0				1	(0.5)	1	0.53	1	(0.5)	1	0.52	2	(0.3)	2	0.35
Gout	0				2	(1.0)	2	1.06	0				2	(0.3)	2	0.35

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Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hyperlipidaemia	1	(0.5)	1	0.53	1	(0.5)	1	0.53	0				2	(0.3)	2	0.35
Hyperlipasaemia	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Hypertriglyceridaemia	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Hypokalaemia	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Obesity	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Cardiac disorders	5	(2.6)	5	2.63	7	(3.6)	7	3.72	7	(3.6)	7	3.63	19	(3.3)	19	3.33
Atrial fibrillation	0				2	(1.0)	2	1.06	2	(1.0)	2	1.04	4	(0.7)	4	0.70
Angina pectoris	2	(1.0)	2	1.05	0				0				2	(0.3)	2	0.35
Myocardial ischaemia	0				2	(1.0)	2	1.06	0				2	(0.3)	2	0.35
Ventricular extrasystoles	2	(1.0)	2	1.05	0				0				2	(0.3)	2	0.35
Acute myocardial infarction	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Atrioventricular block complete	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Atrioventricular block first degree	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Coronary artery stenosis	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Palpitations	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Sinus arrhythmia	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Sinus node dysfunction	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Supraventricular tachycardia	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Tachycardia	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Hepatobiliary disorders	6	(3.1)	9	4.74	8	(4.1)	12	6.38	5	(2.6)	8	4.15	19	(3.3)	29	5.08
Gallbladder polyp	1	(0.5)	1	0.53	4	(2.1)	4	2.13	2	(1.0)	2	1.04	7	(1.2)	7	1.23
Cholelithiasis	2	(1.0)	2	1.05	2	(1.0)	2	1.06	2	(1.0)	2	1.04	6	(1.0)	6	1.05
Hepatic steatosis	3	(1.5)	3	1.58	1	(0.5)	1	0.53	1	(0.5)	1	0.52	5	(0.9)	5	0.88
Hepatic cyst	1	(0.5)	1	0.53	1	(0.5)	1	0.53	1	(0.5)	1	0.52	3	(0.5)	3	0.53
Non-alcoholic fatty liver	1	(0.5)	1	0.53	1	(0.5)	1	0.53	1	(0.5)	1	0.52	3	(0.5)	3	0.53
Cholecystitis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Cholecystitis acute	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Chronic hepatitis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Hepatic calcification	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Liver disorder	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18

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Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Renal and urinary disorders	8	(4.1)	8	4.21	5	(2.6)	7	3.72	4	(2.1)	5	2.60	17	(2.9)	20	3.50
Renal cyst	4	(2.1)	4	2.11	2	(1.0)	2	1.06	0				6	(1.0)	6	1.05
Nephrolithiasis	1	(0.5)	1	0.53	3	(1.5)	3	1.60	1	(0.5)	1	0.52	5	(0.9)	5	0.88
Calculus urinary	0				0				2	(1.0)	2	1.04	2	(0.3)	2	0.35
Ureterolithiasis	2	(1.0)	2	1.05	0				0				2	(0.3)	2	0.35
Chronic kidney disease	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Hydronephrosis	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Nephrocalcinosis	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Nephrotic syndrome	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Urinary retention	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Psychiatric disorders	4	(2.1)	4	2.11	5	(2.6)	5	2.66	4	(2.1)	4	2.08	13	(2.2)	13	2.28
Insomnia	4	(2.1)	4	2.11	4	(2.1)	4	2.13	1	(0.5)	1	0.52	9	(1.5)	9	1.58
Sleep disorder	0				0				2	(1.0)	2	1.04	2	(0.3)	2	0.35
Anxiety	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Depression	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Ear and labyrinth disorders	6	(3.1)	6	3.16	4	(2.1)	5	2.66	2	(1.0)	2	1.04	12	(2.1)	13	2.28
Vertigo	3	(1.5)	3	1.58	2	(1.0)	3	1.60	1	(0.5)	1	0.52	6	(1.0)	7	1.23
Tinnitus	1	(0.5)	1	0.53	2	(1.0)	2	1.06	1	(0.5)	1	0.52	4	(0.7)	4	0.70
Sudden hearing loss	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Vertigo positional	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	(2.1)	4	2.11	5	(2.6)	7	3.72	3	(1.6)	3	1.56	12	(2.1)	14	2.45
Colon adenoma	0				0				2	(1.0)	2	1.04	2	(0.3)	2	0.35
Acrochordon	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Adrenal neoplasm	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Basal cell carcinoma	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Benign neoplasm of bladder	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Benign neoplasm of thyroid gland	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Gastric cancer stage I	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18

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Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Lung adenocarcinoma	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Lung neoplasm malignant	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Metastases to lymph nodes	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Oligodendroglioma	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Skin papilloma	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Thyroid neoplasm	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Endocrine disorders	3	(1.5)	3	1.58	4	(2.1)	5	2.66	1	(0.5)	1	0.52	8	(1.4)	9	1.58
Thyroid cyst	2	(1.0)	2	1.05	3	(1.5)	3	1.60	1	(0.5)	1	0.52	6	(1.0)	6	1.05
Thyroid mass	1	(0.5)	1	0.53	2	(1.0)	2	1.06	0				3	(0.5)	3	0.53
Immune system disorders	3	(1.5)	4	2.11	1	(0.5)	1	0.53	2	(1.0)	2	1.04	6	(1.0)	7	1.23
Seasonal allergy	2	(1.0)	2	1.05	1	(0.5)	1	0.53	2	(1.0)	2	1.04	5	(0.9)	5	0.88
Allergy to arthropod sting	1	(0.5)	2	1.05	0				0				1	(0.2)	2	0.35
Reproductive system and breast disorders	3	(1.5)	3	1.58	2	(1.0)	2	1.06	0				5	(0.9)	5	0.88
Balanoposthitis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Benign prostatic hyperplasia	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Gynaecomastia	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Prostatic calcification	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Pruritus genital	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Blood and lymphatic system disorders	0				1	(0.5)	1	0.53	1	(0.5)	1	0.52	2	(0.3)	2	0.35
Iron deficiency anaemia	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Polycythaemia	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Surgical and medical procedures	0				1	(0.5)	1	0.53	1	(0.5)	1	0.52	2	(0.3)	2	0.35
Cataract operation	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Large intestinal polypectomy	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18

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PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-14 女性被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	81			76			81			238		
PYE (years)	78.04			73.72			79.23			230.99		
Events	73 (90.1)	303	388.26	65 (85.5)	325	440.86	76 (93.8)	334	421.55	214 (89.9)	962	416.47
Infections and infestations	47 (58.0)	95	121.73	52 (68.4)	114	154.64	53 (65.4)	90	113.59	152 (63.9)	299	129.44
Viral upper respiratory tract infection	34 (42.0)	53	67.91	31 (40.8)	62	84.10	35 (43.2)	46	58.06	100 (42.0)	161	69.70
Pharyngitis	4 (4.9)	4	5.13	5 (6.6)	7	9.50	5 (6.2)	5	6.31	14 (5.9)	16	6.93
Cystitis	3 (3.7)	5	6.41	7 (9.2)	9	12.21	3 (3.7)	3	3.79	13 (5.5)	17	7.36
Gastroenteritis	5 (6.2)	5	6.41	5 (6.6)	6	8.14	3 (3.7)	3	3.79	13 (5.5)	14	6.06
Influenza	6 (7.4)	6	7.69	0			6 (7.4)	6	7.57	12 (5.0)	12	5.20
Periodontitis	1 (1.2)	1	1.28	4 (5.3)	7	9.50	4 (4.9)	4	5.05	9 (3.8)	12	5.20
Bronchitis	3 (3.7)	3	3.84	2 (2.6)	2	2.71	3 (3.7)	3	3.79	8 (3.4)	8	3.46
Conjunctivitis	2 (2.5)	2	2.56	1 (1.3)	1	1.36	1 (1.2)	1	1.26	4 (1.7)	4	1.73
Nasopharyngitis	1 (1.2)	3	3.84	2 (2.6)	3	4.07	1 (1.2)	1	1.26	4 (1.7)	7	3.03
Herpes zoster	0			2 (2.6)	2	2.71	1 (1.2)	1	1.26	3 (1.3)	3	1.30
Otitis externa	2 (2.5)	2	2.56	0			1 (1.2)	1	1.26	3 (1.3)	3	1.30
Helicobacter gastritis	0			0			2 (2.5)	2	2.52	2 (0.8)	2	0.87
Herpes virus infection	1 (1.2)	1	1.28	0			1 (1.2)	1	1.26	2 (0.8)	2	0.87
Pneumonia	0			0			2 (2.5)	2	2.52	2 (0.8)	2	0.87
Tinea infection	0			2 (2.6)	2	2.71	0			2 (0.8)	2	0.87
Upper respiratory tract infection	0			1 (1.3)	2	2.71	1 (1.2)	1	1.26	2 (0.8)	3	1.30
Abdominal abscess	0			1 (1.3)	1	1.36	0			1 (0.4)	1	0.43
Acute sinusitis	0			1 (1.3)	2	2.71	0			1 (0.4)	2	0.87
Body tinea	1 (1.2)	1	1.28	0			0			1 (0.4)	1	0.43
Cellulitis	0			0			1 (1.2)	1	1.26	1 (0.4)	1	0.43
Conjunctivitis viral	0			1 (1.3)	1	1.36	0			1 (0.4)	1	0.43
Dermatitis infected	1 (1.2)	1	1.28	0			0			1 (0.4)	1	0.43
Eczema infected	0			1 (1.3)	1	1.36	0			1 (0.4)	1	0.43
Enteritis infectious	1 (1.2)	1	1.28	0			0			1 (0.4)	1	0.43
Folliculitis	0			1 (1.3)	1	1.36	0			1 (0.4)	1	0.43

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Fungal cystitis	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Gastroenteritis bacterial	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Gastroenteritis norovirus	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Gastroenteritis viral	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Genital herpes	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Gingivitis	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Helicobacter infection	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Hordeolum	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Infected dermal cyst	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Oral herpes	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Respiratory tract infection	1	(1.2)	2	2.56	0				0				1	(0.4)	2	0.87
Sinusitis	0				0				1	(1.2)	3	3.79	1	(0.4)	3	1.30
Skin infection	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Tinea capitis	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Tinea pedis	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Tonsillitis	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Urinary tract infection	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Vaginal infection	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Gastrointestinal disorders	42	(51.9)	70	89.70	24	(31.6)	51	69.18	39	(48.1)	83	104.76	105	(44.1)	204	88.32
Constipation	13	(16.0)	13	16.66	8	(10.5)	8	10.85	14	(17.3)	17	21.46	35	(14.7)	38	16.45
Diarrhoea	3	(3.7)	4	5.13	6	(7.9)	6	8.14	12	(14.8)	15	18.93	21	(8.8)	25	10.82
Nausea	4	(4.9)	4	5.13	2	(2.6)	4	5.43	9	(11.1)	14	17.67	15	(6.3)	22	9.52
Dental caries	5	(6.2)	5	6.41	4	(5.3)	4	5.43	3	(3.7)	3	3.79	12	(5.0)	12	5.20
Abdominal distension	5	(6.2)	5	6.41	2	(2.6)	2	2.71	2	(2.5)	2	2.52	9	(3.8)	9	3.90
Abdominal pain upper	4	(4.9)	4	5.13	3	(3.9)	3	4.07	2	(2.5)	2	2.52	9	(3.8)	9	3.90
Stomatitis	6	(7.4)	6	7.69	2	(2.6)	3	4.07	0				8	(3.4)	9	3.90
Chronic gastritis	2	(2.5)	2	2.56	3	(3.9)	3	4.07	2	(2.5)	2	2.52	7	(2.9)	7	3.03
Vomiting	1	(1.2)	1	1.28	2	(2.6)	2	2.71	4	(4.9)	6	7.57	7	(2.9)	9	3.90
Dyspepsia	0				1	(1.3)	1	1.36	5	(6.2)	7	8.83	6	(2.5)	8	3.46
Periodontal disease	3	(3.7)	4	5.13	1	(1.3)	1	1.36	2	(2.5)	2	2.52	6	(2.5)	7	3.03
Abdominal discomfort	0				3	(3.9)	4	5.43	2	(2.5)	2	2.52	5	(2.1)	6	2.60
Gastritis	3	(3.7)	3	3.84	0				1	(1.2)	1	1.26	4	(1.7)	4	1.73
Gastric polyps	1	(1.2)	1	1.28	0				2	(2.5)	2	2.52	3	(1.3)	3	1.30

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Gastrooesophageal reflux disease	1	(1.2)	1	1.28	2	(2.6)	2	2.71	0				3	(1.3)	3	1.30
Large intestine polyp	1	(1.2)	1	1.28	1	(1.3)	1	1.36	1	(1.2)	1	1.26	3	(1.3)	3	1.30
Abdominal pain	1	(1.2)	1	1.28	1	(1.3)	3	4.07	0				2	(0.8)	4	1.73
Enterocolitis	2	(2.5)	3	3.84	0				0				2	(0.8)	3	1.30
Faeces soft	1	(1.2)	1	1.28	0				1	(1.2)	1	1.26	2	(0.8)	2	0.87
Abdominal pain lower	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Autoimmune pancreatitis	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Colitis	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Duodenal polyp	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Enteritis	1	(1.2)	2	2.56	0				0				1	(0.4)	2	0.87
Eructation	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Faecaloma	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Food poisoning	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Gastric ulcer	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Gastritis erosive	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Gingival swelling	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Haematochezia	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Haemorrhoids	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Hiatus hernia	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Hyperchlorhydria	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Melaena	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Oesophageal polyp	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Pancreatic cyst	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Parotid gland enlargement	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Toothache	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Musculoskeletal and connective tissue disorders	22	(27.2)	24	30.75	22	(28.9)	33	44.76	14	(17.3)	18	22.72	58	(24.4)	75	32.47
Back pain	5	(6.2)	5	6.41	9	(11.8)	9	12.21	2	(2.5)	3	3.79	16	(6.7)	17	7.36
Arthralgia	3	(3.7)	3	3.84	4	(5.3)	4	5.43	1	(1.2)	1	1.26	8	(3.4)	8	3.46
Osteoarthritis	0				5	(6.6)	5	6.78	1	(1.2)	1	1.26	6	(2.5)	6	2.60
Spinal osteoarthritis	1	(1.2)	1	1.28	2	(2.6)	2	2.71	2	(2.5)	2	2.52	5	(2.1)	5	2.16
Musculoskeletal stiffness	2	(2.5)	2	2.56	0				2	(2.5)	3	3.79	4	(1.7)	5	2.16

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Adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Tenosynovitis	2	(2.5)	2	2.56	1	(1.3)	1	1.36	1	(1.2)	1	1.26	4	(1.7)	4	1.73
Intervertebral disc protrusion	1	(1.2)	1	1.28	0				2	(2.5)	2	2.52	3	(1.3)	3	1.30
Periarthritis	1	(1.2)	1	1.28	1	(1.3)	1	1.36	1	(1.2)	1	1.26	3	(1.3)	3	1.30
Trigger finger	0				3	(3.9)	4	5.43	0				3	(1.3)	4	1.73
Musculoskeletal pain	1	(1.2)	1	1.28	1	(1.3)	2	2.71	0				2	(0.8)	3	1.30
Myalgia	1	(1.2)	1	1.28	0				1	(1.2)	1	1.26	2	(0.8)	2	0.87
Osteoporosis	1	(1.2)	1	1.28	1	(1.3)	1	1.36	0				2	(0.8)	2	0.87
Pain in extremity	2	(2.5)	2	2.56	0				0				2	(0.8)	2	0.87
Arthritis	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Intervertebral disc disorder	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Joint swelling	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Lumbar spinal stenosis	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Muscle spasms	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Musculoskeletal chest pain	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Myalgia intercostal	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Neck pain	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Nodal osteoarthritis	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Spinal column stenosis	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Tendonitis	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Eye disorders	13	(16.0)	15	19.22	10	(13.2)	15	20.35	13	(16.0)	15	18.93	36	(15.1)	45	19.48
Diabetic retinopathy	3	(3.7)	3	3.84	2	(2.6)	2	2.71	2	(2.5)	2	2.52	7	(2.9)	7	3.03
Conjunctivitis allergic	3	(3.7)	4	5.13	1	(1.3)	1	1.36	1	(1.2)	1	1.26	5	(2.1)	6	2.60
Dry eye	2	(2.5)	2	2.56	1	(1.3)	1	1.36	1	(1.2)	1	1.26	4	(1.7)	4	1.73
Asthenopia	0				1	(1.3)	1	1.36	2	(2.5)	2	2.52	3	(1.3)	3	1.30
Cataract	0				2	(2.6)	2	2.71	1	(1.2)	1	1.26	3	(1.3)	3	1.30
Vision blurred	0				2	(2.6)	2	2.71	1	(1.2)	1	1.26	3	(1.3)	3	1.30
Diabetic retinal oedema	1	(1.2)	1	1.28	0				1	(1.2)	1	1.26	2	(0.8)	2	0.87
Glaucoma	1	(1.2)	1	1.28	0				1	(1.2)	1	1.26	2	(0.8)	2	0.87
Retinal haemorrhage	1	(1.2)	1	1.28	0				1	(1.2)	1	1.26	2	(0.8)	2	0.87
Retinopathy	0				0				2	(2.5)	2	2.52	2	(0.8)	2	0.87
Blepharitis	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Blepharitis allergic	0				1	(1.3)	2	2.71	0				1	(0.4)	2	0.87

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Adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Blepharospasm	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Conjunctival haemorrhage	0				1	(1.3)	2	2.71	0				1	(0.4)	2	0.87
Cystoid macular oedema	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Posterior capsule opacification	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Retinal exudates	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Visual impairment	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Vitreous floaters	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Nervous system disorders	10	(12.3)	14	17.94	12	(15.8)	21	28.49	14	(17.3)	16	20.19	36	(15.1)	51	22.08
Headache	5	(6.2)	6	7.69	4	(5.3)	9	12.21	8	(9.9)	10	12.62	17	(7.1)	25	10.82
Dizziness	1	(1.2)	4	5.13	2	(2.6)	2	2.71	2	(2.5)	2	2.52	5	(2.1)	8	3.46
Hypoaesthesia	1	(1.2)	1	1.28	2	(2.6)	2	2.71	1	(1.2)	1	1.26	4	(1.7)	4	1.73
Diabetic neuropathy	1	(1.2)	1	1.28	1	(1.3)	1	1.36	0				2	(0.8)	2	0.87
Dysgeusia	0				0				2	(2.5)	2	2.52	2	(0.8)	2	0.87
Facial paralysis	0				1	(1.3)	1	1.36	1	(1.2)	1	1.26	2	(0.8)	2	0.87
Migraine	0				2	(2.6)	2	2.71	0				2	(0.8)	2	0.87
Somnolence	1	(1.2)	1	1.28	1	(1.3)	2	2.71	0				2	(0.8)	3	1.30
Carpal tunnel syndrome	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Head discomfort	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Tongue biting	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Skin and subcutaneous tissue disorders	9	(11.1)	10	12.81	13	(17.1)	15	20.35	13	(16.0)	16	20.19	35	(14.7)	41	17.75
Eczema	4	(4.9)	5	6.41	3	(3.9)	3	4.07	5	(6.2)	6	7.57	12	(5.0)	14	6.06
Pruritus	2	(2.5)	2	2.56	1	(1.3)	1	1.36	2	(2.5)	2	2.52	5	(2.1)	5	2.16
Dermatitis allergic	1	(1.2)	1	1.28	2	(2.6)	2	2.71	0				3	(1.3)	3	1.30
Dermatitis contact	0				0				2	(2.5)	2	2.52	2	(0.8)	2	0.87
Skin mass	0				0				2	(2.5)	2	2.52	2	(0.8)	2	0.87
Asteatosis	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Dermatitis atopic	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Dry skin	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Granuloma annulare	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Hand dermatitis	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43

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Adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hyperkeratosis	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Ingrowing nail	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Miliaria	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Nail hypertrophy	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Onychoclasis	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Onycholysis	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Pigmentation disorder	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Rash	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Seborrhoeic dermatitis	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Swelling face	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Respiratory, thoracic and mediastinal disorders	16	(19.8)	20	25.63	7	(9.2)	8	10.85	9	(11.1)	13	16.41	32	(13.4)	41	17.75
Upper respiratory tract inflammation	3	(3.7)	3	3.84	2	(2.6)	2	2.71	4	(4.9)	5	6.31	9	(3.8)	10	4.33
Rhinitis allergic	6	(7.4)	6	7.69	1	(1.3)	1	1.36	0				7	(2.9)	7	3.03
Cough	2	(2.5)	2	2.56	2	(2.6)	3	4.07	1	(1.2)	1	1.26	5	(2.1)	6	2.60
Oropharyngeal pain	1	(1.2)	1	1.28	1	(1.3)	1	1.36	3	(3.7)	3	3.79	5	(2.1)	5	2.16
Asthma	2	(2.5)	2	2.56	0				2	(2.5)	2	2.52	4	(1.7)	4	1.73
Bronchitis chronic	1	(1.2)	2	2.56	0				0				1	(0.4)	2	0.87
Dysphonia	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Pharyngeal oedema	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Pleuritic pain	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Productive cough	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Rhinorrhoea	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Sleep apnoea syndrome	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Sneezing	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Investigations	8	(9.9)	11	14.10	8	(10.5)	14	18.99	13	(16.0)	14	17.67	29	(12.2)	39	16.88
Weight increased	0				7	(9.2)	7	9.50	0				7	(2.9)	7	3.03
Lipase increased	2	(2.5)	2	2.56	0				4	(4.9)	4	5.05	6	(2.5)	6	2.60
Blood proinsulin decreased	1	(1.2)	1	1.28	1	(1.3)	1	1.36	1	(1.2)	1	1.26	3	(1.3)	3	1.30
Free fatty acids decreased	1	(1.2)	1	1.28	2	(2.6)	3	4.07	0				3	(1.3)	4	1.73
Helicobacter test positive	2	(2.5)	2	2.56	0				1	(1.2)	1	1.26	3	(1.3)	3	1.30

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Adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Alanine aminotransferase increased	1	(1.2)	1	1.28	0				1	(1.2)	1	1.26	2	(0.8)	2	0.87
Electrocardiogram T wave amplitude decreased	2	(2.5)	2	2.56	0				0				2	(0.8)	2	0.87
Insulin C-peptide decreased	0				2	(2.6)	2	2.71	0				2	(0.8)	2	0.87
Amylase increased	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Aspartate aminotransferase increased	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Carbohydrate antigen 125 increased	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Cardiac murmur	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Eosinophil count increased	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Gamma-glutamyltransferase increased	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Intraocular pressure increased	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Occult blood positive	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Pancreatic enzymes increased	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Waist circumference increased	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
General disorders and administration site conditions	8	(9.9)	8	10.25	7	(9.2)	8	10.85	12	(14.8)	15	18.93	27	(11.3)	31	13.42
Oedema peripheral	3	(3.7)	3	3.84	2	(2.6)	2	2.71	0				5	(2.1)	5	2.16
Malaise	2	(2.5)	2	2.56	1	(1.3)	1	1.36	1	(1.2)	1	1.26	4	(1.7)	4	1.73
Injection site induration	0				0				3	(3.7)	4	5.05	3	(1.3)	4	1.73
Fatigue	0				0				2	(2.5)	2	2.52	2	(0.8)	2	0.87
Injection site reaction	0				0				2	(2.5)	2	2.52	2	(0.8)	2	0.87
Oedema	0				1	(1.3)	1	1.36	1	(1.2)	1	1.26	2	(0.8)	2	0.87
Pyrexia	0				1	(1.3)	1	1.36	1	(1.2)	1	1.26	2	(0.8)	2	0.87
Chest discomfort	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Chills	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Feeling hot	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43

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Adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Infusion site bruising	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Injection site bruising	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Injection site haemorrhage	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Injection site pain	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Injection site pruritus	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Pain	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Sense of oppression	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Injury, poisoning and procedural complications	4	(4.9)	4	5.13	9	(11.8)	12	16.28	11	(13.6)	16	20.19	24	(10.1)	32	13.85
Contusion	0				3	(3.9)	3	4.07	5	(6.2)	6	7.57	8	(3.4)	9	3.90
Arthropod sting	0				1	(1.3)	2	2.71	1	(1.2)	1	1.26	2	(0.8)	3	1.30
Ligament sprain	0				1	(1.3)	2	2.71	1	(1.2)	1	1.26	2	(0.8)	3	1.30
Skin abrasion	0				0				2	(2.5)	2	2.52	2	(0.8)	2	0.87
Accidental overdose	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Arthropod bite	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Bone contusion	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Chest injury	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Foreign body in eye	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Hand fracture	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Heat illness	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Lower limb fracture	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Lumbar vertebral fracture	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Pubis fracture	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Rib fracture	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Spinal compression fracture	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Tooth fracture	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Tooth injury	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Wrong drug administered	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Hepatobiliary disorders	4	(4.9)	4	5.13	4	(5.3)	5	6.78	7	(8.6)	7	8.83	15	(6.3)	16	6.93
Hepatic steatosis	3	(3.7)	3	3.84	2	(2.6)	2	2.71	2	(2.5)	2	2.52	7	(2.9)	7	3.03
Cholelithiasis	1	(1.2)	1	1.28	1	(1.3)	1	1.36	1	(1.2)	1	1.26	3	(1.3)	3	1.30
Hepatic function abnormal	0				1	(1.3)	1	1.36	1	(1.2)	1	1.26	2	(0.8)	2	0.87

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Adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Drug-induced liver injury	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Gallbladder polyp	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Hepatic cyst	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Hepatic mass	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Metabolism and nutrition disorders	5	(6.2)	5	6.41	4	(5.3)	4	5.43	3	(3.7)	3	3.79	12	(5.0)	12	5.20
Decreased appetite	0				2	(2.6)	2	2.71	2	(2.5)	2	2.52	4	(1.7)	4	1.73
Dyslipidaemia	2	(2.5)	2	2.56	1	(1.3)	1	1.36	1	(1.2)	1	1.26	4	(1.7)	4	1.73
Overweight	2	(2.5)	2	2.56	1	(1.3)	1	1.36	0				3	(1.3)	3	1.30
Hypoglycaemia	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Reproductive system and breast disorders	2	(2.5)	2	2.56	5	(6.6)	7	9.50	3	(3.7)	7	8.83	10	(4.2)	16	6.93
Ovarian cyst	1	(1.2)	1	1.28	1	(1.3)	1	1.36	1	(1.2)	1	1.26	3	(1.3)	3	1.30
Pruritus genital	1	(1.2)	1	1.28	2	(2.6)	2	2.71	0				3	(1.3)	3	1.30
Menopausal symptoms	0				1	(1.3)	1	1.36	1	(1.2)	1	1.26	2	(0.8)	2	0.87
Cervical cyst	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Cervical polyp	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Endometrial hyperplasia	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Menorrhagia	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Menstruation irregular	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Uterine disorder	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Uterine haemorrhage	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Uterine prolapse	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Vascular disorders	4	(4.9)	4	5.13	2	(2.6)	2	2.71	3	(3.7)	3	3.79	9	(3.8)	9	3.90
Arteriosclerosis	1	(1.2)	1	1.28	1	(1.3)	1	1.36	1	(1.2)	1	1.26	3	(1.3)	3	1.30
Hypertension	1	(1.2)	1	1.28	1	(1.3)	1	1.36	1	(1.2)	1	1.26	3	(1.3)	3	1.30
Hot flush	1	(1.2)	1	1.28	0				1	(1.2)	1	1.26	2	(0.8)	2	0.87
Internal haemorrhage	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Cardiac disorders	2	(2.5)	2	2.56	2	(2.6)	2	2.71	4	(4.9)	4	5.05	8	(3.4)	8	3.46
Palpitations	1	(1.2)	1	1.28	1	(1.3)	1	1.36	2	(2.5)	2	2.52	4	(1.7)	4	1.73

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Adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Supraventricular extrasystoles	0				0				2	(2.5)	2	2.52	2	(0.8)	2	0.87
Cardiac disorder	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Cardiomegaly	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Psychiatric disorders	2	(2.5)	2	2.56	4	(5.3)	4	5.43	2	(2.5)	2	2.52	8	(3.4)	8	3.46
Insomnia	2	(2.5)	2	2.56	2	(2.6)	2	2.71	1	(1.2)	1	1.26	5	(2.1)	5	2.16
Depression	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Neurosis	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Suicide attempt	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Ear and labyrinth disorders	3	(3.7)	5	6.41	1	(1.3)	1	1.36	3	(3.7)	3	3.79	7	(2.9)	9	3.90
Vertigo	2	(2.5)	4	5.13	0				2	(2.5)	2	2.52	4	(1.7)	6	2.60
Vertigo positional	1	(1.2)	1	1.28	0				1	(1.2)	1	1.26	2	(0.8)	2	0.87
Otorrhoea	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Renal and urinary disorders	2	(2.5)	2	2.56	2	(2.6)	2	2.71	2	(2.5)	2	2.52	6	(2.5)	6	2.60
Renal cyst	1	(1.2)	1	1.28	0				2	(2.5)	2	2.52	3	(1.3)	3	1.30
Diabetic nephropathy	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Nephrolithiasis	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Renal impairment	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Blood and lymphatic system disorders	2	(2.5)	2	2.56	0				3	(3.7)	3	3.79	5	(2.1)	5	2.16
Iron deficiency anaemia	1	(1.2)	1	1.28	0				2	(2.5)	2	2.52	3	(1.3)	3	1.30
Anaemia	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Splenomegaly	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(2.5)	2	2.56	1	(1.3)	1	1.36	2	(2.5)	2	2.52	5	(2.1)	5	2.16
Benign neoplasm of thyroid gland	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Breast cancer	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43

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	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Colon adenoma	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Skin papilloma	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Uterine leiomyoma	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Endocrine disorders	1	(1.2)	1	1.28	2	(2.6)	2	2.71	1	(1.2)	1	1.26	4	(1.7)	4	1.73
Thyroid cyst	0				2	(2.6)	2	2.71	0				2	(0.8)	2	0.87
Hyperthyroidism	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Silent thyroiditis	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Surgical and medical procedures	1	(1.2)	1	1.28	1	(1.3)	2	2.71	1	(1.2)	1	1.26	3	(1.3)	4	1.73
Tooth extraction	1	(1.2)	1	1.28	1	(1.3)	2	2.71	0				2	(0.8)	3	1.30
Cardiac ablation	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Congenital, familial and genetic disorders	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Epidermolysis	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Immune system disorders	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Hypersensitivity	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-15 男性被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	70				63				133			
PYE (years)	36.19				31.53				67.73			
Events	53	(75.7)	157	433.80	48	(76.2)	119	377.36	101	(75.9)	276	407.52
Infections and infestations	21	(30.0)	34	93.94	23	(36.5)	32	101.48	44	(33.1)	66	97.45
Viral upper respiratory tract infection	14	(20.0)	20	55.26	16	(25.4)	19	60.25	30	(22.6)	39	57.58
Gastroenteritis	4	(5.7)	6	16.58	2	(3.2)	2	6.34	6	(4.5)	8	11.81
Bronchitis	0				4	(6.3)	4	12.68	4	(3.0)	4	5.91
Pharyngitis	2	(2.9)	2	5.53	1	(1.6)	2	6.34	3	(2.3)	4	5.91
Influenza	1	(1.4)	1	2.76	1	(1.6)	1	3.17	2	(1.5)	2	2.95
Adenoviral conjunctivitis	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Cellulitis	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Gingivitis	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Herpes zoster	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Tinea pedis	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Tonsillitis	1	(1.4)	2	5.53	0				1	(0.8)	2	2.95
Upper respiratory tract infection	0				1	(1.6)	2	6.34	1	(0.8)	2	2.95
Gastrointestinal disorders	28	(40.0)	49	135.39	14	(22.2)	22	69.76	42	(31.6)	71	104.83
Diarrhoea	12	(17.1)	14	38.68	4	(6.3)	5	15.86	16	(12.0)	19	28.05
Nausea	6	(8.6)	7	19.34	2	(3.2)	2	6.34	8	(6.0)	9	13.29
Constipation	6	(8.6)	7	19.34	1	(1.6)	1	3.17	7	(5.3)	8	11.81
Abdominal discomfort	3	(4.3)	3	8.29	2	(3.2)	2	6.34	5	(3.8)	5	7.38
Vomiting	2	(2.9)	3	8.29	2	(3.2)	2	6.34	4	(3.0)	5	7.38
Chronic gastritis	1	(1.4)	2	5.53	1	(1.6)	1	3.17	2	(1.5)	3	4.43
Faeces soft	1	(1.4)	1	2.76	1	(1.6)	1	3.17	2	(1.5)	2	2.95
Gastritis	1	(1.4)	1	2.76	1	(1.6)	1	3.17	2	(1.5)	2	2.95
Gastrooesophageal reflux disease	1	(1.4)	1	2.76	1	(1.6)	1	3.17	2	(1.5)	2	2.95
Hiatus hernia	2	(2.9)	2	5.53	0				2	(1.5)	2	2.95
Abdominal distension	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Abdominal pain	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Dental caries	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Duodenal ulcer	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Dyspepsia	1	(1.4)	2	5.53	0				1	(0.8)	2	2.95
Enteritis	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Gastritis erosive	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Gastrointestinal motility disorder	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Hyperchlorhydria	1	(1.4)	2	5.53	0				1	(0.8)	2	2.95
Large intestine polyp	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Oesophageal disorder	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Periodontal disease	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Eye disorders	12	(17.1)	14	38.68	11	(17.5)	13	41.22	23	(17.3)	27	39.87
Diabetic retinopathy	10	(14.3)	11	30.39	9	(14.3)	10	31.71	19	(14.3)	21	31.01
Blepharospasm	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Cataract	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Cataract nuclear	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Posterior capsule opacification	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Retinal detachment	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Retinal haemorrhage	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Musculoskeletal and connective tissue disorders	9	(12.9)	12	33.16	8	(12.7)	9	28.54	17	(12.8)	21	31.01
Back pain	4	(5.7)	4	11.05	3	(4.8)	3	9.51	7	(5.3)	7	10.34
Arthralgia	2	(2.9)	2	5.53	1	(1.6)	1	3.17	3	(2.3)	3	4.43
Musculoskeletal pain	2	(2.9)	2	5.53	0				2	(1.5)	2	2.95
Periarthritis	0				2	(3.2)	2	6.34	2	(1.5)	2	2.95
Flank pain	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Muscle spasms	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Musculoskeletal stiffness	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Neck pain	1	(1.4)	2	5.53	0				1	(0.8)	2	2.95
Tenosynovitis	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Trigger finger	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Metabolism and nutrition disorders	13	(18.6)	13	35.92	2	(3.2)	2	6.34	15	(11.3)	15	22.15
Decreased appetite	6	(8.6)	6	16.58	0				6	(4.5)	6	8.86
Dyslipidaemia	2	(2.9)	2	5.53	1	(1.6)	1	3.17	3	(2.3)	3	4.43

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Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Gout	2	(2.9)	2	5.53	1	(1.6)	1	3.17	3	(2.3)	3	4.43
Hyperuricaemia	3	(4.3)	3	8.29	0				3	(2.3)	3	4.43
Nervous system disorders	4	(5.7)	4	11.05	5	(7.9)	8	25.37	9	(6.8)	12	17.72
Diabetic neuropathy	1	(1.4)	1	2.76	1	(1.6)	1	3.17	2	(1.5)	2	2.95
Dizziness	1	(1.4)	1	2.76	1	(1.6)	2	6.34	2	(1.5)	3	4.43
Headache	1	(1.4)	1	2.76	1	(1.6)	1	3.17	2	(1.5)	2	2.95
Carpal tunnel syndrome	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Hypoaesthesia	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Loss of consciousness	0				1	(1.6)	2	6.34	1	(0.8)	2	2.95
Sciatica	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Skin and subcutaneous tissue disorders	3	(4.3)	4	11.05	6	(9.5)	6	19.03	9	(6.8)	10	14.77
Eczema	2	(2.9)	2	5.53	3	(4.8)	3	9.51	5	(3.8)	5	7.38
Dermatitis	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Hyperkeratosis	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Miliaria	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Penile ulceration	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Rash	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
General disorders and administration site conditions	2	(2.9)	2	5.53	5	(7.9)	5	15.86	7	(5.3)	7	10.34
Administration site induration	0				2	(3.2)	2	6.34	2	(1.5)	2	2.95
Induration	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Inflammation	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Injection site discomfort	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Oedema peripheral	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Pyrexia	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Injury, poisoning and procedural complications	6	(8.6)	9	24.87	1	(1.6)	1	3.17	7	(5.3)	10	14.77
Contusion	1	(1.4)	1	2.76	1	(1.6)	1	3.17	2	(1.5)	2	2.95
Fall	2	(2.9)	2	5.53	0				2	(1.5)	2	2.95
Arthropod bite	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Excoriation	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48

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Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hip fracture	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Laceration	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Ligament sprain	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Tooth injury	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Investigations	4	(5.7)	4	11.05	3	(4.8)	3	9.51	7	(5.3)	7	10.34
Lipase increased	2	(2.9)	2	5.53	0				2	(1.5)	2	2.95
Electrocardiogram T wave inversion	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Free fatty acids decreased	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Gamma-glutamyltransferase increased	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Glomerular filtration rate decreased	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Weight decreased	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Respiratory, thoracic and mediastinal disorders	3	(4.3)	4	11.05	3	(4.8)	3	9.51	6	(4.5)	7	10.34
Upper respiratory tract inflammation	1	(1.4)	2	5.53	2	(3.2)	2	6.34	3	(2.3)	4	5.91
Oropharyngeal pain	2	(2.9)	2	5.53	0				2	(1.5)	2	2.95
Bronchitis chronic	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Renal and urinary disorders	2	(2.9)	4	11.05	2	(3.2)	2	6.34	4	(3.0)	6	8.86
Nephrolithiasis	1	(1.4)	1	2.76	1	(1.6)	1	3.17	2	(1.5)	2	2.95
Renal cyst	1	(1.4)	1	2.76	1	(1.6)	1	3.17	2	(1.5)	2	2.95
Haematuria	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Ureterolithiasis	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Vascular disorders	2	(2.9)	2	5.53	2	(3.2)	2	6.34	4	(3.0)	4	5.91
Hypertension	1	(1.4)	1	2.76	2	(3.2)	2	6.34	3	(2.3)	3	4.43
Arteriosclerosis	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Psychiatric disorders	1	(1.4)	1	2.76	2	(3.2)	2	6.34	3	(2.3)	3	4.43
Insomnia	1	(1.4)	1	2.76	2	(3.2)	2	6.34	3	(2.3)	3	4.43
Ear and labyrinth disorders	0				2	(3.2)	3	9.51	2	(1.5)	3	4.43
Vertigo	0				2	(3.2)	3	9.51	2	(1.5)	3	4.43

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Adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hepatobiliary disorders	0				2	(3.2)	2	6.34	2	(1.5)	2	2.95
Cholecystitis acute	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Hepatic steatosis	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Blood and lymphatic system disorders	0				1	(1.6)	3	9.51	1	(0.8)	3	4.43
Leukopenia	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Lymphopenia	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Neutropenia	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Immune system disorders	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Seasonal allergy	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Pancreatic carcinoma	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48

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PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-16 女性被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	35				42				77			
PYE (years)	18.09				20.73				38.82			
Events	29	(82.9)	123	680.07	32	(76.2)	91	438.96	61	(79.2)	214	551.30
Infections and infestations	14	(40.0)	23	127.17	15	(35.7)	20	96.47	29	(37.7)	43	110.78
Viral upper respiratory tract infection	7	(20.0)	7	38.70	8	(19.0)	11	53.06	15	(19.5)	18	46.37
Pharyngitis	3	(8.6)	4	22.12	0				3	(3.9)	4	10.30
Sinusitis	3	(8.6)	3	16.59	0				3	(3.9)	3	7.73
Bronchitis	1	(2.9)	1	5.53	1	(2.4)	1	4.82	2	(2.6)	2	5.15
Cystitis	1	(2.9)	1	5.53	1	(2.4)	1	4.82	2	(2.6)	2	5.15
Herpes zoster	1	(2.9)	1	5.53	1	(2.4)	1	4.82	2	(2.6)	2	5.15
Periodontitis	2	(5.7)	2	11.06	0				2	(2.6)	2	5.15
Upper respiratory tract infection	1	(2.9)	1	5.53	1	(2.4)	1	4.82	2	(2.6)	2	5.15
Abscess	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Herpes simplex	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Hordeolum	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Infected dermal cyst	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Influenza	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Otitis externa	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Upper respiratory tract infection bacterial	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Urinary tract infection	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Gastrointestinal disorders	17	(48.6)	39	215.63	10	(23.8)	18	86.83	27	(35.1)	57	146.84
Abdominal discomfort	5	(14.3)	5	27.65	3	(7.1)	3	14.47	8	(10.4)	8	20.61
Vomiting	7	(20.0)	8	44.23	0				7	(9.1)	8	20.61
Constipation	3	(8.6)	3	16.59	3	(7.1)	3	14.47	6	(7.8)	6	15.46
Nausea	4	(11.4)	5	27.65	2	(4.8)	3	14.47	6	(7.8)	8	20.61
Diarrhoea	3	(8.6)	6	33.17	1	(2.4)	1	4.82	4	(5.2)	7	18.03
Dyspepsia	2	(5.7)	2	11.06	1	(2.4)	1	4.82	3	(3.9)	3	7.73
Gastrooesophageal reflux disease	2	(5.7)	2	11.06	1	(2.4)	1	4.82	3	(3.9)	3	7.73
Chronic gastritis	2	(5.7)	2	11.06	0				2	(2.6)	2	5.15
Abdominal pain	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58

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Adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Dental caries	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Enteritis	1	(2.9)	2	11.06	0				1	(1.3)	2	5.15
Epigastric discomfort	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Food poisoning	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Gastritis	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Gastritis erosive	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Glossitis	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Hiatus hernia	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Stomatitis	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Varices oesophageal	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Eye disorders	10	(28.6)	10	55.29	9	(21.4)	10	48.24	19	(24.7)	20	51.52
Diabetic retinopathy	7	(20.0)	7	38.70	8	(19.0)	8	38.59	15	(19.5)	15	38.64
Cataract	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Conjunctival haemorrhage	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Dry eye	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Pingueculitis	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Retinopathy	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Injury, poisoning and procedural complications	4	(11.4)	5	27.65	9	(21.4)	10	48.24	13	(16.9)	15	38.64
Contusion	1	(2.9)	1	5.53	2	(4.8)	2	9.65	3	(3.9)	3	7.73
Laceration	1	(2.9)	1	5.53	1	(2.4)	1	4.82	2	(2.6)	2	5.15
Fall	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Foot fracture	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Fractured coccyx	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Heat illness	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Heat stroke	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Postoperative fever	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Thermal burn	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Tibia fracture	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Tooth fracture	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Wrong drug administered	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58

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PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
General disorders and administration site conditions	7	(20.0)	8	44.23	5	(11.9)	5	24.12	12	(15.6)	13	33.49
Malaise	2	(5.7)	3	16.59	1	(2.4)	1	4.82	3	(3.9)	4	10.30
Pyrexia	2	(5.7)	2	11.06	1	(2.4)	1	4.82	3	(3.9)	3	7.73
Inflammation	0				2	(4.8)	2	9.65	2	(2.6)	2	5.15
Oedema peripheral	1	(2.9)	1	5.53	1	(2.4)	1	4.82	2	(2.6)	2	5.15
Generalised oedema	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Injection site induration	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Musculoskeletal and connective tissue disorders	5	(14.3)	6	33.17	6	(14.3)	6	28.94	11	(14.3)	12	30.91
Back pain	1	(2.9)	2	11.06	2	(4.8)	2	9.65	3	(3.9)	4	10.30
Intervertebral disc protrusion	1	(2.9)	1	5.53	1	(2.4)	1	4.82	2	(2.6)	2	5.15
Arthralgia	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Arthritis	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Muscle spasms	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Myalgia	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Osteoarthritis	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Tenosynovitis	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Nervous system disorders	5	(14.3)	7	38.70	6	(14.3)	6	28.94	11	(14.3)	13	33.49
Dizziness	1	(2.9)	1	5.53	3	(7.1)	3	14.47	4	(5.2)	4	10.30
Headache	2	(5.7)	2	11.06	0				2	(2.6)	2	5.15
Hypoaesthesia	1	(2.9)	1	5.53	1	(2.4)	1	4.82	2	(2.6)	2	5.15
Carpal tunnel syndrome	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Dysgeusia	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Lacunar infarction	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Migraine	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Neuropathy peripheral	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Respiratory, thoracic and mediastinal disorders	3	(8.6)	5	27.65	3	(7.1)	3	14.47	6	(7.8)	8	20.61
Cough	1	(2.9)	1	5.53	1	(2.4)	1	4.82	2	(2.6)	2	5.15
Atelectasis	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Pleural effusion	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Respiratory tract inflammation	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Sputum increased	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Sputum retention	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Upper respiratory tract inflammation	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Investigations	3	(8.6)	3	16.59	2	(4.8)	2	9.65	5	(6.5)	5	12.88
Helicobacter test positive	1	(2.9)	1	5.53	2	(4.8)	2	9.65	3	(3.9)	3	7.73
Electrocardiogram ST-T segment depression	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Oxygen saturation decreased	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Skin and subcutaneous tissue disorders	1	(2.9)	1	5.53	4	(9.5)	4	19.29	5	(6.5)	5	12.88
Acne	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Eczema	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Pustular psoriasis	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Skin irritation	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Skin swelling	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Metabolism and nutrition disorders	2	(5.7)	2	11.06	1	(2.4)	1	4.82	3	(3.9)	3	7.73
Decreased appetite	2	(5.7)	2	11.06	0				2	(2.6)	2	5.15
Dehydration	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(5.7)	2	11.06	1	(2.4)	1	4.82	3	(3.9)	3	7.73
Adenocarcinoma	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Renal cell carcinoma	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Uterine leiomyoma	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Renal and urinary disorders	2	(5.7)	3	16.59	1	(2.4)	1	4.82	3	(3.9)	4	10.30
Nephrolithiasis	1	(2.9)	1	5.53	1	(2.4)	1	4.82	2	(2.6)	2	5.15
Acute kidney injury	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Renal cyst	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Vascular disorders	3	(8.6)	3	16.59	0				3	(3.9)	3	7.73
Hypertension	2	(5.7)	2	11.06	0				2	(2.6)	2	5.15
Orthostatic hypotension	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Cardiac disorders	2	(5.7)	3	16.59	0				2	(2.6)	3	7.73
Acute myocardial infarction	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Cardiac failure congestive	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Supraventricular extrasystoles	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Hepatobiliary disorders	1	(2.9)	1	5.53	1	(2.4)	1	4.82	2	(2.6)	2	5.15
Cholelithiasis	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Hepatic cirrhosis	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Ear and labyrinth disorders	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Vertigo	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Endocrine disorders	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Thyroid mass	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Reproductive system and breast disorders	0				1	(2.4)	3	14.47	1	(1.3)	3	7.73
Uterine cyst	0				1	(2.4)	2	9.65	1	(1.3)	2	5.15
Uterine mass	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58

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2.7.4.7.1-17 ベースラインの BMI（kg/m^2）が 25 未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	122				117				118				357			
PYE (years)	117.94				111.20				117.32				346.46			
Events	103	(84.4)	340	288.29	87	(74.4)	352	316.54	97	(82.2)	360	306.85	287	(80.4)	1052	303.64
Infections and infestations	60	(49.2)	104	88.18	59	(50.4)	116	104.31	61	(51.7)	97	82.68	180	(50.4)	317	91.50
Viral upper respiratory tract infection	43	(35.2)	65	55.11	39	(33.3)	71	63.85	39	(33.1)	59	50.29	121	(33.9)	195	56.28
Pharyngitis	5	(4.1)	6	5.09	4	(3.4)	4	3.60	5	(4.2)	5	4.26	14	(3.9)	15	4.33
Gastroenteritis	5	(4.1)	5	4.24	2	(1.7)	2	1.80	3	(2.5)	3	2.56	10	(2.8)	10	2.89
Bronchitis	1	(0.8)	3	2.54	5	(4.3)	5	4.50	2	(1.7)	2	1.70	8	(2.2)	10	2.89
Cystitis	2	(1.6)	4	3.39	5	(4.3)	5	4.50	1	(0.8)	1	0.85	8	(2.2)	10	2.89
Influenza	1	(0.8)	1	0.85	3	(2.6)	3	2.70	4	(3.4)	4	3.41	8	(2.2)	8	2.31
Periodontitis	3	(2.5)	3	2.54	4	(3.4)	6	5.40	0				7	(2.0)	9	2.60
Helicobacter infection	1	(0.8)	1	0.85	1	(0.9)	1	0.90	3	(2.5)	3	2.56	5	(1.4)	5	1.44
Herpes zoster	1	(0.8)	1	0.85	4	(3.4)	4	3.60	0				5	(1.4)	5	1.44
Sinusitis	2	(1.6)	3	2.54	0				1	(0.8)	1	0.85	3	(0.8)	4	1.15
Tonsillitis	1	(0.8)	1	0.85	1	(0.9)	1	0.90	1	(0.8)	1	0.85	3	(0.8)	3	0.87
Upper respiratory tract infection	0				1	(0.9)	2	1.80	2	(1.7)	2	1.70	3	(0.8)	4	1.15
Conjunctivitis	0				2	(1.7)	2	1.80	0				2	(0.6)	2	0.58
Gingival abscess	2	(1.6)	2	1.70	0				0				2	(0.6)	2	0.58
Helicobacter gastritis	0				1	(0.9)	1	0.90	1	(0.8)	1	0.85	2	(0.6)	2	0.58
Oral herpes	1	(0.8)	1	0.85	0				1	(0.8)	1	0.85	2	(0.6)	2	0.58
Otitis externa	2	(1.6)	2	1.70	0				0				2	(0.6)	2	0.58
Pneumonia	0				1	(0.9)	1	0.90	1	(0.8)	1	0.85	2	(0.6)	2	0.58
Rhinitis	1	(0.8)	1	0.85	0				1	(0.8)	1	0.85	2	(0.6)	2	0.58
Tinea pedis	0				0				2	(1.7)	2	1.70	2	(0.6)	2	0.58
Acute sinusitis	0				1	(0.9)	2	1.80	0				1	(0.3)	2	0.58
Bronchitis bacterial	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Cellulitis	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Eczema impetiginous	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29

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PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline < 25 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Folliculitis	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Gastroenteritis bacterial	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Gingivitis	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Herpes virus infection	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Herpes zoster meningitis	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Hordeolum	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Infected dermal cyst	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Infectious colitis	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Nasopharyngitis	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Otitis media	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Paronychia	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Peritonsillitis	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Pneumonia haemophilus	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Pneumonia mycoplasmal	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Tinea capitis	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Ureteritis	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Urethritis	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Vaginal infection	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Gastrointestinal disorders	42	(34.4)	73	61.90	29	(24.8)	47	42.26	49	(41.5)	89	75.86	120	(33.6)	209	60.32
Constipation	10	(8.2)	10	8.48	4	(3.4)	4	3.60	16	(13.6)	16	13.64	30	(8.4)	30	8.66
Diarrhoea	5	(4.1)	5	4.24	6	(5.1)	6	5.40	8	(6.8)	9	7.67	19	(5.3)	20	5.77
Nausea	2	(1.6)	5	4.24	2	(1.7)	2	1.80	12	(10.2)	15	12.79	16	(4.5)	22	6.35
Chronic gastritis	6	(4.9)	6	5.09	4	(3.4)	4	3.60	4	(3.4)	5	4.26	14	(3.9)	15	4.33
Gastrooesophageal reflux disease	7	(5.7)	7	5.94	3	(2.6)	3	2.70	3	(2.5)	3	2.56	13	(3.6)	13	3.75
Abdominal discomfort	0				4	(3.4)	5	4.50	5	(4.2)	5	4.26	9	(2.5)	10	2.89
Abdominal pain upper	5	(4.1)	6	5.09	2	(1.7)	2	1.80	2	(1.7)	2	1.70	9	(2.5)	10	2.89
Abdominal distension	4	(3.3)	4	3.39	1	(0.9)	1	0.90	3	(2.5)	3	2.56	8	(2.2)	8	2.31
Dental caries	3	(2.5)	3	2.54	3	(2.6)	3	2.70	2	(1.7)	2	1.70	8	(2.2)	8	2.31
Periodontal disease	3	(2.5)	3	2.54	2	(1.7)	2	1.80	2	(1.7)	2	1.70	7	(2.0)	7	2.02
Stomatitis	6	(4.9)	6	5.09	1	(0.9)	1	0.90	0				7	(2.0)	7	2.02
Large intestine polyp	4	(3.3)	4	3.39	0				2	(1.7)	2	1.70	6	(1.7)	6	1.73

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PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline < 25 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Dyspepsia	1	(0.8)	1	0.85	1	(0.9)	1	0.90	3	(2.5)	3	2.56	5	(1.4)	5	1.44
Vomiting	0				2	(1.7)	2	1.80	3	(2.5)	3	2.56	5	(1.4)	5	1.44
Colitis	2	(1.6)	2	1.70	0				2	(1.7)	2	1.70	4	(1.1)	4	1.15
Gastritis	2	(1.6)	2	1.70	0				2	(1.7)	2	1.70	4	(1.1)	4	1.15
Gastric polyps	0				1	(0.9)	1	0.90	2	(1.7)	2	1.70	3	(0.8)	3	0.87
Abdominal pain	0				2	(1.7)	2	1.80	0				2	(0.6)	2	0.58
Enteritis	1	(0.8)	2	1.70	1	(0.9)	1	0.90	0				2	(0.6)	3	0.87
Eructation	1	(0.8)	1	0.85	0				1	(0.8)	1	0.85	2	(0.6)	2	0.58
Hiatus hernia	1	(0.8)	1	0.85	1	(0.9)	1	0.90	0				2	(0.6)	2	0.58
Hyperchlorhydria	0				1	(0.9)	1	0.90	1	(0.8)	1	0.85	2	(0.6)	2	0.58
Abdominal pain lower	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Anal fissure	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Autoimmune pancreatitis	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Barrett's oesophagus	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Dry mouth	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Enterocolitis	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Faeces soft	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Flatulence	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Gastric ulcer	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Gastritis erosive	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Gastrointestinal disorder	0				0				1	(0.8)	2	1.70	1	(0.3)	2	0.58
Haemorrhoidal haemorrhage	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Hypoaesthesia oral	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Melaena	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Mouth ulceration	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Oral discomfort	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Pancreatic cyst	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Pancreatitis acute	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Periodontal inflammation	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Toothache	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Musculoskeletal and connective tissue disorders	25	(20.5)	29	24.59	18	(15.4)	28	25.18	19	(16.1)	29	24.72	62	(17.4)	86	24.82

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline < 25 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Back pain	10	(8.2)	10	8.48	4	(3.4)	4	3.60	7	(5.9)	9	7.67	21	(5.9)	23	6.64
Muscle spasms	2	(1.6)	2	1.70	1	(0.9)	1	0.90	4	(3.4)	6	5.11	7	(2.0)	9	2.60
Intervertebral disc protrusion	2	(1.6)	2	1.70	2	(1.7)	2	1.80	2	(1.7)	2	1.70	6	(1.7)	6	1.73
Arthralgia	2	(1.6)	2	1.70	1	(0.9)	2	1.80	1	(0.8)	1	0.85	4	(1.1)	5	1.44
Tenosynovitis	2	(1.6)	2	1.70	1	(0.9)	1	0.90	1	(0.8)	1	0.85	4	(1.1)	4	1.15
Musculoskeletal pain	1	(0.8)	1	0.85	1	(0.9)	2	1.80	1	(0.8)	1	0.85	3	(0.8)	4	1.15
Musculoskeletal stiffness	1	(0.8)	1	0.85	0				2	(1.7)	2	1.70	3	(0.8)	3	0.87
Myalgia	3	(2.5)	3	2.54	0				0				3	(0.8)	3	0.87
Trigger finger	0				2	(1.7)	3	2.70	1	(0.8)	1	0.85	3	(0.8)	4	1.15
Flank pain	0				2	(1.7)	2	1.80	0				2	(0.6)	2	0.58
Joint swelling	1	(0.8)	1	0.85	1	(0.9)	1	0.90	0				2	(0.6)	2	0.58
Osteoporosis	0				2	(1.7)	2	1.80	0				2	(0.6)	2	0.58
Pain in extremity	1	(0.8)	1	0.85	1	(0.9)	1	0.90	0				2	(0.6)	2	0.58
Periarthritis	0				1	(0.9)	1	0.90	1	(0.8)	1	0.85	2	(0.6)	2	0.58
Spinal osteoarthritis	1	(0.8)	1	0.85	1	(0.9)	1	0.90	0				2	(0.6)	2	0.58
Arthritis	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Bone pain	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Cervical spinal stenosis	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Intervertebral disc disorder	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Lumbar spinal stenosis	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Myalgia intercostal	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Neck pain	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Osteitis	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Osteoarthritis	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Rheumatoid arthritis	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Spondylolisthesis	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Synovial cyst	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Tendon pain	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Eye disorders	15	(12.3)	19	16.11	12	(10.3)	14	12.59	17	(14.4)	23	19.60	44	(12.3)	56	16.16
Diabetic retinopathy	4	(3.3)	4	3.39	7	(6.0)	7	6.29	5	(4.2)	5	4.26	16	(4.5)	16	4.62
Cataract	3	(2.5)	3	2.54	0				3	(2.5)	3	2.56	6	(1.7)	6	1.73

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline < 25 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Vitreous floaters	2	(1.6)	2	1.70	1	(0.9)	1	0.90	2	(1.7)	2	1.70	5	(1.4)	5	1.44
Glaucoma	1	(0.8)	1	0.85	0				3	(2.5)	3	2.56	4	(1.1)	4	1.15
Asthenopia	0				2	(1.7)	2	1.80	1	(0.8)	1	0.85	3	(0.8)	3	0.87
Conjunctivitis allergic	2	(1.6)	3	2.54	0				0				2	(0.6)	3	0.87
Retinopathy	0				0				2	(1.7)	2	1.70	2	(0.6)	2	0.58
Blepharitis allergic	0				1	(0.9)	2	1.80	0				1	(0.3)	2	0.58
Conjunctivochalasis	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Diabetic retinal oedema	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Dry eye	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Eye haemorrhage	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Keratitis	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Macular degeneration	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Macular fibrosis	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Macular hole	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Posterior capsule opacification	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Retinal detachment	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Retinal haemorrhage	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Retinal tear	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Retinopathy proliferative	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Vision blurred	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Vitreous haemorrhage	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Investigations	13	(10.7)	17	14.41	9	(7.7)	19	17.09	13	(11.0)	16	13.64	35	(9.8)	52	15.01
Lipase increased	4	(3.3)	5	4.24	0				6	(5.1)	6	5.11	10	(2.8)	11	3.17
Weight increased	0				7	(6.0)	7	6.29	1	(0.8)	1	0.85	8	(2.2)	8	2.31
Amylase increased	2	(1.6)	2	1.70	0				3	(2.5)	3	2.56	5	(1.4)	5	1.44
Blood proinsulin decreased	2	(1.6)	2	1.70	2	(1.7)	2	1.80	1	(0.8)	1	0.85	5	(1.4)	5	1.44
Insulin C-peptide decreased	1	(0.8)	1	0.85	3	(2.6)	3	2.70	0				4	(1.1)	4	1.15
Free fatty acids decreased	0				3	(2.6)	3	2.70	0				3	(0.8)	3	0.87
Helicobacter test positive	1	(0.8)	1	0.85	0				2	(1.7)	2	1.70	3	(0.8)	3	0.87
Pancreatic enzymes increased	0				0				2	(1.7)	2	1.70	2	(0.6)	2	0.58

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline < 25 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Blood creatine phosphokinase MM increased	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Blood creatine phosphokinase increased	0				1	(0.9)	2	1.80	0				1	(0.3)	2	0.58
Blood potassium increased	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Blood pressure increased	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Blood triglycerides increased	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Cardiac murmur	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Carotid intima-media thickness increased	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Electrocardiogram QT prolonged	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Electrocardiogram T wave amplitude decreased	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Glomerular filtration rate decreased	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Nervous system disorders	10	(8.2)	13	11.02	14	(12.0)	25	22.48	11	(9.3)	12	10.23	35	(9.8)	50	14.43
Headache	3	(2.5)	3	2.54	3	(2.6)	8	7.19	6	(5.1)	7	5.97	12	(3.4)	18	5.20
Dizziness	3	(2.5)	6	5.09	4	(3.4)	5	4.50	0				7	(2.0)	11	3.17
Carotid arteriosclerosis	0				3	(2.6)	3	2.70	0				3	(0.8)	3	0.87
Hypoaesthesia	0				2	(1.7)	2	1.80	1	(0.8)	1	0.85	3	(0.8)	3	0.87
Diabetic neuropathy	1	(0.8)	1	0.85	1	(0.9)	1	0.90	0				2	(0.6)	2	0.58
Migraine	0				1	(0.9)	1	0.90	1	(0.8)	1	0.85	2	(0.6)	2	0.58
Cerebral infarction	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Dysgeusia	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Intercostal neuralgia	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Loss of consciousness	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Presyncope	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Sciatica	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Somnolence	0				1	(0.9)	2	1.80	0				1	(0.3)	2	0.58
Thalamic infarction	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29

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	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Thrombotic cerebral infarction	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Tongue biting	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Injury, poisoning and procedural complications	9	(7.4)	10	8.48	12	(10.3)	14	12.59	12	(10.2)	14	11.93	33	(9.2)	38	10.97
Contusion	3	(2.5)	3	2.54	1	(0.9)	1	0.90	4	(3.4)	5	4.26	8	(2.2)	9	2.60
Arthropod bite	1	(0.8)	1	0.85	2	(1.7)	2	1.80	0				3	(0.8)	3	0.87
Arthropod sting	0				1	(0.9)	2	1.80	2	(1.7)	2	1.70	3	(0.8)	4	1.15
Heat illness	1	(0.8)	1	0.85	0				2	(1.7)	2	1.70	3	(0.8)	3	0.87
Ligament sprain	0				2	(1.7)	2	1.80	1	(0.8)	1	0.85	3	(0.8)	3	0.87
Laceration	1	(0.8)	1	0.85	0				1	(0.8)	1	0.85	2	(0.6)	2	0.58
Rib fracture	0				1	(0.9)	1	0.90	1	(0.8)	1	0.85	2	(0.6)	2	0.58
Avulsion fracture	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Clavicle fracture	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Foreign body in eye	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Head injury	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Heat stroke	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Incorrect dose administered	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Limb injury	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Lower limb fracture	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Skin abrasion	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Spinal compression fracture	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Thoracic vertebral fracture	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Tooth injury	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Skin and subcutaneous tissue disorders	14	(11.5)	16	13.57	10	(8.5)	13	11.69	9	(7.6)	9	7.67	33	(9.2)	38	10.97
Eczema	7	(5.7)	8	6.78	2	(1.7)	2	1.80	1	(0.8)	1	0.85	10	(2.8)	11	3.17
Pruritus	1	(0.8)	1	0.85	1	(0.9)	2	1.80	3	(2.5)	3	2.56	5	(1.4)	6	1.73
Rash	2	(1.6)	2	1.70	2	(1.7)	2	1.80	0				4	(1.1)	4	1.15
Dermatitis contact	1	(0.8)	1	0.85	0				2	(1.7)	2	1.70	3	(0.8)	3	0.87
Miliaria	1	(0.8)	1	0.85	1	(0.9)	1	0.90	0				2	(0.6)	2	0.58

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Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline < 25 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Asteatosis	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Dermatitis	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Dermatitis allergic	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Drug eruption	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Dry skin	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Granuloma annulare	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Haemorrhage subcutaneous	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Hyperkeratosis	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Ingrowing nail	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Onychoclasis	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Pigmentation disorder	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Urticaria	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Respiratory, thoracic and mediastinal disorders	10	(8.2)	15	12.72	14	(12.0)	20	17.99	6	(5.1)	9	7.67	30	(8.4)	44	12.70
Upper respiratory tract inflammation	2	(1.6)	3	2.54	4	(3.4)	5	4.50	2	(1.7)	3	2.56	8	(2.2)	11	3.17
Asthma	2	(1.6)	2	1.70	3	(2.6)	3	2.70	1	(0.8)	1	0.85	6	(1.7)	6	1.73
Cough	2	(1.6)	2	1.70	4	(3.4)	6	5.40	0				6	(1.7)	8	2.31
Oropharyngeal pain	1	(0.8)	1	0.85	3	(2.6)	3	2.70	2	(1.7)	2	1.70	6	(1.7)	6	1.73
Rhinitis allergic	1	(0.8)	1	0.85	1	(0.9)	1	0.90	2	(1.7)	2	1.70	4	(1.1)	4	1.15
Emphysema	1	(0.8)	1	0.85	1	(0.9)	1	0.90	0				2	(0.6)	2	0.58
Sleep apnoea syndrome	1	(0.8)	1	0.85	1	(0.9)	1	0.90	0				2	(0.6)	2	0.58
Pleuritic pain	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Productive cough	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Pulmonary fibrosis	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Respiratory disorder	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Rhinorrhoea	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
General disorders and administration site conditions	4	(3.3)	4	3.39	10	(8.5)	12	10.79	15	(12.7)	19	16.20	29	(8.1)	35	10.10
Malaise	0				3	(2.6)	3	2.70	4	(3.4)	5	4.26	7	(2.0)	8	2.31

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline < 25 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Fatigue	0				0				3	(2.5)	3	2.56	3	(0.8)	3	0.87
Injection site bruising	0				2	(1.7)	2	1.80	1	(0.8)	1	0.85	3	(0.8)	3	0.87
Injection site reaction	1	(0.8)	1	0.85	0				2	(1.7)	2	1.70	3	(0.8)	3	0.87
Injection site induration	0				0				2	(1.7)	3	2.56	2	(0.6)	3	0.87
Oedema peripheral	0				2	(1.7)	3	2.70	0				2	(0.6)	3	0.87
Pyrexia	0				1	(0.9)	1	0.90	1	(0.8)	1	0.85	2	(0.6)	2	0.58
Asthenia	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Chest discomfort	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Feeling abnormal	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Feeling hot	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Hunger	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Injection site erythema	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Injection site pain	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Injection site pruritus	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Oedema	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Pain	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Vascular disorders	6	(4.9)	6	5.09	7	(6.0)	7	6.29	4	(3.4)	4	3.41	17	(4.8)	17	4.91
Hypertension	4	(3.3)	4	3.39	6	(5.1)	6	5.40	2	(1.7)	2	1.70	12	(3.4)	12	3.46
Arteriosclerosis	1	(0.8)	1	0.85	0				1	(0.8)	1	0.85	2	(0.6)	2	0.58
Hot flush	1	(0.8)	1	0.85	0				1	(0.8)	1	0.85	2	(0.6)	2	0.58
Varicose vein	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Hepatobiliary disorders	5	(4.1)	7	5.94	5	(4.3)	8	7.19	6	(5.1)	7	5.97	16	(4.5)	22	6.35
Hepatic steatosis	4	(3.3)	4	3.39	2	(1.7)	2	1.80	1	(0.8)	1	0.85	7	(2.0)	7	2.02
Cholelithiasis	1	(0.8)	1	0.85	1	(0.9)	1	0.90	2	(1.7)	2	1.70	4	(1.1)	4	1.15
Gallbladder polyp	1	(0.8)	1	0.85	2	(1.7)	2	1.80	1	(0.8)	1	0.85	4	(1.1)	4	1.15
Hepatic cyst	1	(0.8)	1	0.85	1	(0.9)	1	0.90	1	(0.8)	1	0.85	3	(0.8)	3	0.87
Cholecystitis acute	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Chronic hepatitis	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Hepatic function abnormal	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Hepatic mass	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29

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PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline < 25 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Metabolism and nutrition disorders	4	(3.3)	4	3.39	4	(3.4)	4	3.60	8	(6.8)	8	6.82	16	(4.5)	16	4.62
Decreased appetite	0				1	(0.9)	1	0.90	6	(5.1)	6	5.11	7	(2.0)	7	2.02
Dyslipidaemia	1	(0.8)	1	0.85	1	(0.9)	1	0.90	0				2	(0.6)	2	0.58
Hyperuricaemia	1	(0.8)	1	0.85	0				1	(0.8)	1	0.85	2	(0.6)	2	0.58
Dehydration	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Gout	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Hyperlipasaemia	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Hyperlipidaemia	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Hypertriglyceridaemia	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Cardiac disorders	5	(4.1)	5	4.24	2	(1.7)	2	1.80	5	(4.2)	5	4.26	12	(3.4)	12	3.46
Angina pectoris	2	(1.6)	2	1.70	0				0				2	(0.6)	2	0.58
Palpitations	1	(0.8)	1	0.85	0				1	(0.8)	1	0.85	2	(0.6)	2	0.58
Acute myocardial infarction	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Atrial fibrillation	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Cardiac disorder	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Coronary artery stenosis	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Sinus arrhythmia	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Supraventricular extrasystoles	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Supraventricular tachycardia	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Ventricular extrasystoles	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Psychiatric disorders	3	(2.5)	3	2.54	5	(4.3)	5	4.50	3	(2.5)	3	2.56	11	(3.1)	11	3.17
Insomnia	3	(2.5)	3	2.54	2	(1.7)	2	1.80	1	(0.8)	1	0.85	6	(1.7)	6	1.73
Depression	0				2	(1.7)	2	1.80	0				2	(0.6)	2	0.58
Sleep disorder	0				0				2	(1.7)	2	1.70	2	(0.6)	2	0.58
Neurosis	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Ear and labyrinth disorders	4	(3.3)	4	3.39	2	(1.7)	2	1.80	1	(0.8)	1	0.85	7	(2.0)	7	2.02
Vertigo	4	(3.3)	4	3.39	1	(0.9)	1	0.90	0				5	(1.4)	5	1.44
Tinnitus	0				1	(0.9)	1	0.90	1	(0.8)	1	0.85	2	(0.6)	2	0.58

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline < 25 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Renal and urinary disorders	4	(3.3)	4	3.39	1	(0.9)	1	0.90	2	(1.7)	2	1.70	7	(2.0)	7	2.02
Renal cyst	3	(2.5)	3	2.54	0				1	(0.8)	1	0.85	4	(1.1)	4	1.15
Nephrolithiasis	1	(0.8)	1	0.85	1	(0.9)	1	0.90	0				2	(0.6)	2	0.58
Calculus urinary	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Reproductive system and breast disorders	3	(2.5)	3	2.54	2	(1.7)	2	1.80	2	(1.7)	6	5.11	7	(2.0)	11	3.17
Ovarian cyst	1	(0.8)	1	0.85	0				1	(0.8)	1	0.85	2	(0.6)	2	0.58
Benign prostatic hyperplasia	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Cervical polyp	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Gynaecomastia	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Menopausal symptoms	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Menorrhagia	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Prostatic calcification	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Uterine disorder	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Uterine haemorrhage	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Uterine prolapse	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Endocrine disorders	1	(0.8)	1	0.85	4	(3.4)	5	4.50	1	(0.8)	1	0.85	6	(1.7)	7	2.02
Thyroid cyst	0				4	(3.4)	4	3.60	1	(0.8)	1	0.85	5	(1.4)	5	1.44
Thyroid mass	1	(0.8)	1	0.85	1	(0.9)	1	0.90	0				2	(0.6)	2	0.58
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.8)	1	0.85	3	(2.6)	5	4.50	1	(0.8)	1	0.85	5	(1.4)	7	2.02
Acrochordon	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Adrenal neoplasm	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Benign neoplasm of thyroid gland	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Colon adenoma	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Gastric cancer stage I	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Lung adenocarcinoma	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Metastases to lymph nodes	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline < 25 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Blood and lymphatic system disorders	1	(0.8)	1	0.85	0				2	(1.7)	2	1.70	3	(0.8)	3	0.87
Iron deficiency anaemia	1	(0.8)	1	0.85	0				2	(1.7)	2	1.70	3	(0.8)	3	0.87
Immune system disorders	0				1	(0.9)	1	0.90	2	(1.7)	2	1.70	3	(0.8)	3	0.87
Seasonal allergy	0				1	(0.9)	1	0.90	2	(1.7)	2	1.70	3	(0.8)	3	0.87
Surgical and medical procedures	1	(0.8)	1	0.85	1	(0.9)	2	1.80	1	(0.8)	1	0.85	3	(0.8)	4	1.15
Tooth extraction	1	(0.8)	1	0.85	1	(0.9)	2	1.80	0				2	(0.6)	3	0.87
Large intestinal polypectomy	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29

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MedDRA version 20.0

2.7.4.7.1-18 ベースラインの BMI（kg/m^2）が 25 以上 30 未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	112				107				109				328			
PYE (years)	110.64				105.69				109.04				325.37			
Events	89	(79.5)	394	356.09	87	(81.3)	336	317.91	93	(85.3)	370	339.33	269	(82.0)	1100	338.07
Infections and infestations	68	(60.7)	140	126.53	55	(51.4)	105	99.35	59	(54.1)	112	102.72	182	(55.5)	357	109.72
Viral upper respiratory tract infection	43	(38.4)	72	65.07	38	(35.5)	58	54.88	35	(32.1)	59	54.11	116	(35.4)	189	58.09
Influenza	11	(9.8)	11	9.94	5	(4.7)	5	4.73	3	(2.8)	3	2.75	19	(5.8)	19	5.84
Pharyngitis	6	(5.4)	7	6.33	9	(8.4)	12	11.35	3	(2.8)	3	2.75	18	(5.5)	22	6.76
Gastroenteritis	5	(4.5)	5	4.52	1	(0.9)	1	0.95	6	(5.5)	7	6.42	12	(3.7)	13	4.00
Bronchitis	4	(3.6)	4	3.62	1	(0.9)	2	1.89	3	(2.8)	3	2.75	8	(2.4)	9	2.77
Conjunctivitis	3	(2.7)	3	2.71	0				5	(4.6)	5	4.59	8	(2.4)	8	2.46
Periodontitis	2	(1.8)	2	1.81	2	(1.9)	4	3.78	4	(3.7)	4	3.67	8	(2.4)	10	3.07
Cystitis	2	(1.8)	2	1.81	3	(2.8)	5	4.73	2	(1.8)	2	1.83	7	(2.1)	9	2.77
Nasopharyngitis	3	(2.7)	7	6.33	1	(0.9)	1	0.95	2	(1.8)	2	1.83	6	(1.8)	10	3.07
Herpes zoster	3	(2.7)	3	2.71	1	(0.9)	1	0.95	1	(0.9)	1	0.92	5	(1.5)	5	1.54
Gingivitis	2	(1.8)	2	1.81	1	(0.9)	1	0.95	1	(0.9)	2	1.83	4	(1.2)	5	1.54
Gastroenteritis viral	1	(0.9)	1	0.90	1	(0.9)	1	0.95	1	(0.9)	1	0.92	3	(0.9)	3	0.92
Helicobacter infection	0				2	(1.9)	2	1.89	1	(0.9)	1	0.92	3	(0.9)	3	0.92
Tinea pedis	1	(0.9)	1	0.90	0				2	(1.8)	2	1.83	3	(0.9)	3	0.92
Urinary tract infection	0				3	(2.8)	3	2.84	0				3	(0.9)	3	0.92
Dermatitis infected	2	(1.8)	2	1.81	0				0				2	(0.6)	2	0.61
Herpes virus infection	1	(0.9)	1	0.90	0				1	(0.9)	1	0.92	2	(0.6)	2	0.61
Hordeolum	1	(0.9)	1	0.90	0				1	(0.9)	1	0.92	2	(0.6)	2	0.61
Oral herpes	1	(0.9)	1	0.90	0				1	(0.9)	1	0.92	2	(0.6)	2	0.61
Otitis externa	2	(1.8)	2	1.81	0				0				2	(0.6)	2	0.61
Pneumonia	1	(0.9)	1	0.90	0				1	(0.9)	1	0.92	2	(0.6)	2	0.61
Pulpitis dental	0				0				2	(1.8)	2	1.83	2	(0.6)	2	0.61
Sinusitis	1	(0.9)	1	0.90	0				1	(0.9)	3	2.75	2	(0.6)	4	1.23
Skin infection	2	(1.8)	2	1.81	0				0				2	(0.6)	2	0.61
Tinea infection	0				2	(1.9)	2	1.89	0				2	(0.6)	2	0.61

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Tonsillitis	0				1	(0.9)	1	0.95	1	(0.9)	1	0.92	2	(0.6)	2	0.61
Upper respiratory tract infection	1	(0.9)	1	0.90	1	(0.9)	1	0.95	0				2	(0.6)	2	0.61
Acute sinusitis	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Beta haemolytic streptococcal infection	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Cellulitis	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Conjunctivitis viral	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Dermatophytosis of nail	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Eczema infected	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Empyema	1	(0.9)	2	1.81	0				0				1	(0.3)	2	0.61
Enteritis infectious	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Furuncle	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Gastroenteritis norovirus	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Genital herpes	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Helicobacter gastritis	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Localised infection	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Mycoplasma infection	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Oesophageal candidiasis	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Paronychia	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Pharyngotonsillitis	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Purulence	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Pyelonephritis	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Gastrointestinal disorders	40	(35.7)	79	71.40	22	(20.6)	41	38.79	52	(47.7)	104	95.38	114	(34.8)	224	68.84
Constipation	11	(9.8)	11	9.94	4	(3.7)	4	3.78	17	(15.6)	21	19.26	32	(9.8)	36	11.06
Diarrhoea	6	(5.4)	8	7.23	4	(3.7)	6	5.68	12	(11.0)	18	16.51	22	(6.7)	32	9.83
Nausea	5	(4.5)	5	4.52	2	(1.9)	2	1.89	7	(6.4)	11	10.09	14	(4.3)	18	5.53
Gastrooesophageal reflux disease	5	(4.5)	5	4.52	4	(3.7)	4	3.78	4	(3.7)	4	3.67	13	(4.0)	13	4.00
Dental caries	5	(4.5)	5	4.52	3	(2.8)	3	2.84	4	(3.7)	5	4.59	12	(3.7)	13	4.00
Dyspepsia	5	(4.5)	6	5.42	0				6	(5.5)	8	7.34	11	(3.4)	14	4.30
Chronic gastritis	2	(1.8)	2	1.81	3	(2.8)	3	2.84	3	(2.8)	3	2.75	8	(2.4)	8	2.46

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Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Abdominal discomfort	2	(1.8)	3	2.71	1	(0.9)	1	0.95	4	(3.7)	4	3.67	7	(2.1)	8	2.46
Gastric polyps	2	(1.8)	2	1.81	2	(1.9)	2	1.89	2	(1.8)	2	1.83	6	(1.8)	6	1.84
Large intestine polyp	1	(0.9)	1	0.90	3	(2.8)	3	2.84	2	(1.8)	2	1.83	6	(1.8)	6	1.84
Gastritis	2	(1.8)	2	1.81	1	(0.9)	1	0.95	2	(1.8)	2	1.83	5	(1.5)	5	1.54
Periodontal disease	1	(0.9)	2	1.81	1	(0.9)	1	0.95	3	(2.8)	3	2.75	5	(1.5)	6	1.84
Vomiting	1	(0.9)	1	0.90	0				4	(3.7)	5	4.59	5	(1.5)	6	1.84
Abdominal pain	2	(1.8)	2	1.81	0				2	(1.8)	3	2.75	4	(1.2)	5	1.54
Faeces soft	1	(0.9)	1	0.90	1	(0.9)	1	0.95	2	(1.8)	3	2.75	4	(1.2)	5	1.54
Stomatitis	2	(1.8)	2	1.81	1	(0.9)	2	1.89	1	(0.9)	1	0.92	4	(1.2)	5	1.54
Abdominal distension	2	(1.8)	2	1.81	1	(0.9)	1	0.95	0				3	(0.9)	3	0.92
Abdominal pain upper	1	(0.9)	1	0.90	2	(1.9)	2	1.89	0				3	(0.9)	3	0.92
Colitis	1	(0.9)	1	0.90	2	(1.9)	2	1.89	0				3	(0.9)	3	0.92
Toothache	1	(0.9)	1	0.90	0				2	(1.8)	2	1.83	3	(0.9)	3	0.92
Food poisoning	2	(1.8)	2	1.81	0				0				2	(0.6)	2	0.61
Hiatus hernia	1	(0.9)	1	0.90	1	(0.9)	1	0.95	0				2	(0.6)	2	0.61
Parotid gland enlargement	2	(1.8)	2	1.81	0				0				2	(0.6)	2	0.61
Anal fissure	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Barrett's oesophagus	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Brunner's gland hyperplasia	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Diverticulum intestinal	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Duodenitis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Enterocolitis	1	(0.9)	2	1.81	0				0				1	(0.3)	2	0.61
Eructation	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Faecaloma	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Functional gastrointestinal disorder	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Gastric ulcer	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Gastritis erosive	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Gastroduodenitis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Haemorrhoids	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Hyperchlorhydria	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Inguinal hernia	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Oesophageal polyp	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31

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Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Pancreatic atrophy	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Pancreatic cyst	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Proctitis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Musculoskeletal and connective tissue disorders	21	(18.8)	27	24.40	22	(20.6)	27	25.55	15	(13.8)	24	22.01	58	(17.7)	78	23.97
Back pain	1	(0.9)	1	0.90	6	(5.6)	6	5.68	5	(4.6)	6	5.50	12	(3.7)	13	4.00
Arthralgia	5	(4.5)	5	4.52	2	(1.9)	2	1.89	4	(3.7)	5	4.59	11	(3.4)	12	3.69
Periarthritis	3	(2.7)	3	2.71	3	(2.8)	3	2.84	1	(0.9)	1	0.92	7	(2.1)	7	2.15
Myalgia	1	(0.9)	1	0.90	3	(2.8)	3	2.84	2	(1.8)	2	1.83	6	(1.8)	6	1.84
Spinal osteoarthritis	2	(1.8)	2	1.81	2	(1.9)	2	1.89	1	(0.9)	1	0.92	5	(1.5)	5	1.54
Musculoskeletal stiffness	2	(1.8)	2	1.81	1	(0.9)	1	0.95	1	(0.9)	2	1.83	4	(1.2)	5	1.54
Arthritis	2	(1.8)	2	1.81	0				1	(0.9)	1	0.92	3	(0.9)	3	0.92
Muscle spasms	2	(1.8)	4	3.62	1	(0.9)	1	0.95	0				3	(0.9)	5	1.54
Osteoarthritis	2	(1.8)	2	1.81	1	(0.9)	1	0.95	0				3	(0.9)	3	0.92
Pain in extremity	1	(0.9)	1	0.90	1	(0.9)	1	0.95	1	(0.9)	1	0.92	3	(0.9)	3	0.92
Neck pain	1	(0.9)	1	0.90	0				1	(0.9)	1	0.92	2	(0.6)	2	0.61
Spinal column stenosis	0				1	(0.9)	1	0.95	1	(0.9)	1	0.92	2	(0.6)	2	0.61
Groin pain	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Intervertebral disc disorder	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Intervertebral disc protrusion	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Joint contracture	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Lumbar spinal stenosis	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Musculoskeletal pain	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Nodal osteoarthritis	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Osteoporosis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Plantar fasciitis	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Rhabdomyolysis	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Tenosynovitis	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Trigger finger	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Eye disorders	25	(22.3)	27	24.40	11	(10.3)	14	13.25	14	(12.8)	17	15.59	50	(15.2)	58	17.83

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Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Diabetic retinopathy	11	(9.8)	11	9.94	5	(4.7)	7	6.62	4	(3.7)	4	3.67	20	(6.1)	22	6.76
Cataract	1	(0.9)	1	0.90	3	(2.8)	3	2.84	2	(1.8)	2	1.83	6	(1.8)	6	1.84
Dry eye	3	(2.7)	3	2.71	1	(0.9)	1	0.95	0				4	(1.2)	4	1.23
Conjunctivitis allergic	2	(1.8)	2	1.81	1	(0.9)	1	0.95	0				3	(0.9)	3	0.92
Asthenopia	1	(0.9)	1	0.90	0				1	(0.9)	1	0.92	2	(0.6)	2	0.61
Diabetic retinal oedema	2	(1.8)	2	1.81	0				0				2	(0.6)	2	0.61
Macular fibrosis	2	(1.8)	2	1.81	0				0				2	(0.6)	2	0.61
Retinal haemorrhage	0				1	(0.9)	1	0.95	1	(0.9)	1	0.92	2	(0.6)	2	0.61
Age-related macular degeneration	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Astigmatism	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Blepharitis	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Chorioretinopathy	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Erythema of eyelid	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Eye inflammation	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Glaucoma	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Keratitis	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Macular oedema	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Ocular discomfort	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Retinal degeneration	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Retinal detachment	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Retinal exudates	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Vision blurred	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Visual impairment	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Skin and subcutaneous tissue disorders	15	(13.4)	16	14.46	19	(17.8)	22	20.82	11	(10.1)	14	12.84	45	(13.7)	52	15.98
Eczema	7	(6.3)	8	7.23	4	(3.7)	4	3.78	6	(5.5)	7	6.42	17	(5.2)	19	5.84
Dermatitis atopic	1	(0.9)	1	0.90	2	(1.9)	2	1.89	0				3	(0.9)	3	0.92
Dermatitis contact	1	(0.9)	1	0.90	1	(0.9)	1	0.95	1	(0.9)	1	0.92	3	(0.9)	3	0.92
Pruritus	1	(0.9)	1	0.90	2	(1.9)	2	1.89	0				3	(0.9)	3	0.92
Hyperkeratosis	0				2	(1.9)	2	1.89	0				2	(0.6)	2	0.61
Skin mass	0				0				2	(1.8)	2	1.83	2	(0.6)	2	0.61

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	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Urticaria	0				2	(1.9)	2	1.89	0				2	(0.6)	2	0.61
Acne	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Asteatosis	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Blister	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Chronic pigmented purpura	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Dermal cyst	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Dermatitis	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Dermatitis allergic	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Dyshidrotic eczema	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Haemorrhage subcutaneous	0				1	(0.9)	3	2.84	0				1	(0.3)	3	0.92
Ingrowing nail	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Miliaria	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Nail hypertrophy	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Onycholysis	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Psoriasis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Seborrhoeic dermatitis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Solar dermatitis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Investigations	13	(11.6)	20	18.08	16	(15.0)	22	20.82	15	(13.8)	17	15.59	44	(13.4)	59	18.13
Weight increased	3	(2.7)	3	2.71	10	(9.3)	10	9.46	0				13	(4.0)	13	4.00
Lipase increased	1	(0.9)	2	1.81	0				8	(7.3)	8	7.34	9	(2.7)	10	3.07
Free fatty acids decreased	3	(2.7)	4	3.62	1	(0.9)	2	1.89	1	(0.9)	1	0.92	5	(1.5)	7	2.15
Blood proinsulin decreased	3	(2.7)	3	2.71	1	(0.9)	1	0.95	0				4	(1.2)	4	1.23
Alanine aminotransferase increased	0				1	(0.9)	1	0.95	2	(1.8)	2	1.83	3	(0.9)	3	0.92
Blood creatine phosphokinase increased	0				2	(1.9)	2	1.89	1	(0.9)	1	0.92	3	(0.9)	3	0.92
Helicobacter test positive	2	(1.8)	2	1.81	1	(0.9)	1	0.95	0				3	(0.9)	3	0.92
Insulin C-peptide decreased	2	(1.8)	2	1.81	1	(0.9)	1	0.95	0				3	(0.9)	3	0.92
Blood calcitonin increased	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Blood triglycerides increased	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
C-reactive protein increased	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31

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	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Electrocardiogram T wave amplitude decreased	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Eosinophil count increased	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Gamma-glutamyltransferase increased	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Hepatic enzyme increased	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Intraocular pressure increased	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Rheumatoid factor increased	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Urine ketone body present	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Waist circumference increased	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Weight decreased	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
White blood cell count increased	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Nervous system disorders	6	(5.4)	8	7.23	19	(17.8)	21	19.87	14	(12.8)	16	14.67	39	(11.9)	45	13.83
Headache	1	(0.9)	2	1.81	3	(2.8)	3	2.84	8	(7.3)	9	8.25	12	(3.7)	14	4.30
Hypoaesthesia	2	(1.8)	3	2.71	4	(3.7)	4	3.78	1	(0.9)	1	0.92	7	(2.1)	8	2.46
Diabetic neuropathy	1	(0.9)	1	0.90	3	(2.8)	3	2.84	1	(0.9)	1	0.92	5	(1.5)	5	1.54
Dizziness	0				3	(2.8)	3	2.84	2	(1.8)	2	1.83	5	(1.5)	5	1.54
Facial paralysis	0				2	(1.9)	2	1.89	1	(0.9)	1	0.92	3	(0.9)	3	0.92
Dysgeusia	0				0				2	(1.8)	2	1.83	2	(0.6)	2	0.61
Balance disorder	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Carotid artery stenosis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Carpal tunnel syndrome	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Head discomfort	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Migraine	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Neuralgia	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Neuropathy peripheral	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Somnolence	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31

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Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Injury, poisoning and procedural complications	11	(9.8)	11	9.94	12	(11.2)	18	17.03	9	(8.3)	14	12.84	32	(9.8)	43	13.22
Contusion	2	(1.8)	2	1.81	2	(1.9)	3	2.84	4	(3.7)	4	3.67	8	(2.4)	9	2.77
Ligament sprain	0				2	(1.9)	3	2.84	2	(1.8)	2	1.83	4	(1.2)	5	1.54
Arthropod bite	1	(0.9)	1	0.90	0				1	(0.9)	1	0.92	2	(0.6)	2	0.61
Rib fracture	1	(0.9)	1	0.90	1	(0.9)	1	0.95	0				2	(0.6)	2	0.61
Wound	0				2	(1.9)	2	1.89	0				2	(0.6)	2	0.61
Accidental overdose	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Arthropod sting	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Bone contusion	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Epicondylitis	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Excoriation	0				0				1	(0.9)	2	1.83	1	(0.3)	2	0.61
Femoral neck fracture	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Foreign body in eye	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Lip injury	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Lumbar vertebral fracture	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Median nerve injury	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Meniscus injury	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Muscle injury	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Muscle strain	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Overdose	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Scratch	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Skin abrasion	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Spinal compression fracture	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Stab wound	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Subcutaneous haematoma	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Suture related complication	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Tooth fracture	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Tooth injury	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
General disorders and administration site conditions	10	(8.9)	10	9.04	11	(10.3)	11	10.41	10	(9.2)	11	10.09	31	(9.5)	32	9.83

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Oedema peripheral	2	(1.8)	2	1.81	3	(2.8)	3	2.84	1	(0.9)	1	0.92	6	(1.8)	6	1.84
Injection site erythema	0				0				3	(2.8)	3	2.75	3	(0.9)	3	0.92
Malaise	1	(0.9)	1	0.90	0				2	(1.8)	2	1.83	3	(0.9)	3	0.92
Injection site induration	0				1	(0.9)	1	0.95	1	(0.9)	1	0.92	2	(0.6)	2	0.61
Oedema	0				1	(0.9)	1	0.95	1	(0.9)	1	0.92	2	(0.6)	2	0.61
Administration site mass	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Asthenia	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Chest discomfort	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Chills	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Fat tissue increased	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Fatigue	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Infusion site bruising	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Injection site bruising	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Injection site discolouration	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Injection site haemorrhage	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Injection site mass	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Injection site pain	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Injection site reaction	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Injection site swelling	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Peripheral swelling	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Pyrexia	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Respiratory, thoracic and mediastinal disorders	13	(11.6)	16	14.46	6	(5.6)	6	5.68	7	(6.4)	7	6.42	26	(7.9)	29	8.91
Upper respiratory tract inflammation	3	(2.7)	4	3.62	1	(0.9)	1	0.95	3	(2.8)	3	2.75	7	(2.1)	8	2.46
Sleep apnoea syndrome	1	(0.9)	1	0.90	2	(1.9)	2	1.89	1	(0.9)	1	0.92	4	(1.2)	4	1.23
Asthma	2	(1.8)	2	1.81	1	(0.9)	1	0.95	0				3	(0.9)	3	0.92
Oropharyngeal pain	1	(0.9)	1	0.90	0				2	(1.8)	2	1.83	3	(0.9)	3	0.92
Rhinitis allergic	3	(2.7)	3	2.71	0				0				3	(0.9)	3	0.92
Rhinorrhoea	1	(0.9)	1	0.90	1	(0.9)	1	0.95	0				2	(0.6)	2	0.61
Bronchitis chronic	1	(0.9)	2	1.81	0				0				1	(0.3)	2	0.61

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Chronic obstructive pulmonary disease	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Cough	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Pharyngeal oedema	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Sneezing	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Vascular disorders	8	(7.1)	8	7.23	5	(4.7)	5	4.73	3	(2.8)	4	3.67	16	(4.9)	17	5.22
Hypertension	5	(4.5)	5	4.52	3	(2.8)	3	2.84	2	(1.8)	2	1.83	10	(3.0)	10	3.07
Orthostatic hypotension	1	(0.9)	1	0.90	0				1	(0.9)	1	0.92	2	(0.6)	2	0.61
Peripheral arterial occlusive disease	0				2	(1.9)	2	1.89	0				2	(0.6)	2	0.61
Arteriosclerosis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Hypotension	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Internal haemorrhage	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Hepatobiliary disorders	4	(3.6)	5	4.52	7	(6.5)	9	8.52	4	(3.7)	5	4.59	15	(4.6)	19	5.84
Cholelithiasis	2	(1.8)	2	1.81	2	(1.9)	2	1.89	0				4	(1.2)	4	1.23
Hepatic steatosis	1	(0.9)	1	0.90	1	(0.9)	1	0.95	2	(1.8)	2	1.83	4	(1.2)	4	1.23
Gallbladder polyp	0				3	(2.8)	3	2.84	0				3	(0.9)	3	0.92
Non-alcoholic fatty liver	1	(0.9)	1	0.90	1	(0.9)	1	0.95	1	(0.9)	1	0.92	3	(0.9)	3	0.92
Cholecystitis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Hepatic calcification	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Hepatic cyst	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Hepatic function abnormal	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Liver disorder	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Metabolism and nutrition disorders	3	(2.7)	3	2.71	5	(4.7)	6	5.68	6	(5.5)	8	7.34	14	(4.3)	17	5.22
Decreased appetite	1	(0.9)	1	0.90	0				4	(3.7)	4	3.67	5	(1.5)	5	1.54
Dyslipidaemia	1	(0.9)	1	0.90	1	(0.9)	1	0.95	2	(1.8)	2	1.83	4	(1.2)	4	1.23
Hyperuricaemia	0				3	(2.8)	3	2.84	0				3	(0.9)	3	0.92
Dehydration	0				0				1	(0.9)	2	1.83	1	(0.3)	2	0.61
Gout	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31

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	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hyperlipidaemia	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Hypoglycaemia	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Renal and urinary disorders	5	(4.5)	5	4.52	5	(4.7)	7	6.62	2	(1.8)	2	1.83	12	(3.7)	14	4.30
Nephrolithiasis	0				3	(2.8)	3	2.84	1	(0.9)	1	0.92	4	(1.2)	4	1.23
Renal cyst	2	(1.8)	2	1.81	1	(0.9)	1	0.95	0				3	(0.9)	3	0.92
Chronic kidney disease	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Diabetic nephropathy	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Nephrocalcinosis	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Nephrotic syndrome	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Renal impairment	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Ureterolithiasis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Urinary retention	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Cardiac disorders	1	(0.9)	1	0.90	6	(5.6)	6	5.68	4	(3.7)	4	3.67	11	(3.4)	11	3.38
Atrial fibrillation	0				2	(1.9)	2	1.89	0				2	(0.6)	2	0.61
Myocardial ischaemia	0				2	(1.9)	2	1.89	0				2	(0.6)	2	0.61
Palpitations	0				1	(0.9)	1	0.95	1	(0.9)	1	0.92	2	(0.6)	2	0.61
Atrioventricular block complete	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Atrioventricular block first degree	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Sinus node dysfunction	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Supraventricular extrasystoles	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Ventricular extrasystoles	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Ear and labyrinth disorders	4	(3.6)	4	3.62	3	(2.8)	4	3.78	3	(2.8)	3	2.75	10	(3.0)	11	3.38
Vertigo	0				1	(0.9)	2	1.89	2	(1.8)	2	1.83	3	(0.9)	4	1.23
Vertigo positional	2	(1.8)	2	1.81	0				1	(0.9)	1	0.92	3	(0.9)	3	0.92
Tinnitus	1	(0.9)	1	0.90	1	(0.9)	1	0.95	0				2	(0.6)	2	0.61
Otorrhoea	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Sudden hearing loss	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31

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Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	(3.6)	4	3.62	2	(1.9)	2	1.89	4	(3.7)	4	3.67	10	(3.0)	10	3.07
Colon adenoma	0				0				2	(1.8)	2	1.83	2	(0.6)	2	0.61
Basal cell carcinoma	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Benign neoplasm of bladder	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Benign neoplasm of thyroid gland	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Breast cancer	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Lung neoplasm malignant	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Skin papilloma	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Thyroid neoplasm	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Uterine leiomyoma	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Psychiatric disorders	3	(2.7)	3	2.71	1	(0.9)	1	0.95	1	(0.9)	1	0.92	5	(1.5)	5	1.54
Insomnia	3	(2.7)	3	2.71	1	(0.9)	1	0.95	0				4	(1.2)	4	1.23
Anxiety	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Endocrine disorders	2	(1.8)	2	1.81	1	(0.9)	1	0.95	1	(0.9)	1	0.92	4	(1.2)	4	1.23
Thyroid cyst	1	(0.9)	1	0.90	1	(0.9)	1	0.95	0				2	(0.6)	2	0.61
Hyperthyroidism	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Silent thyroiditis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Reproductive system and breast disorders	1	(0.9)	1	0.90	2	(1.9)	4	3.78	1	(0.9)	1	0.92	4	(1.2)	6	1.84
Balanoposthitis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Cervical cyst	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Menopausal symptoms	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Menstruation irregular	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Ovarian cyst	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Pruritus genital	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31

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Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Blood and lymphatic system disorders	1	(0.9)	1	0.90	1	(0.9)	1	0.95	1	(0.9)	1	0.92	3	(0.9)	3	0.92
Anaemia	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Iron deficiency anaemia	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Polycythaemia	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Immune system disorders	2	(1.8)	3	2.71	1	(0.9)	1	0.95	0				3	(0.9)	4	1.23
Allergy to arthropod sting	1	(0.9)	2	1.81	0				0				1	(0.3)	2	0.61
Hypersensitivity	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Seasonal allergy	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Congenital, familial and genetic disorders	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Epidermolysis	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Surgical and medical procedures	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Cataract operation	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31

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2.7.4.7.1-19 ベースラインの BMI（kg/m^2）が 30 以上の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	41				47				46				134			
PYE (years)	39.42				44.91				45.48				129.82			
Events	37	(90.2)	139	352.62	42	(89.4)	141	313.93	39	(84.8)	155	340.80	118	(88.1)	435	335.09
Infections and infestations	27	(65.9)	47	119.23	25	(53.2)	53	118.00	27	(58.7)	62	136.32	79	(59.0)	162	124.79
Viral upper respiratory tract infection	20	(48.8)	29	73.57	14	(29.8)	32	71.25	20	(43.5)	37	81.35	54	(40.3)	98	75.49
Gastroenteritis	2	(4.9)	2	5.07	4	(8.5)	5	11.13	2	(4.3)	2	4.40	8	(6.0)	9	6.93
Influenza	3	(7.3)	3	7.61	1	(2.1)	1	2.23	2	(4.3)	2	4.40	6	(4.5)	6	4.62
Bronchitis	2	(4.9)	2	5.07	0				3	(6.5)	3	6.60	5	(3.7)	5	3.85
Conjunctivitis	0				2	(4.3)	2	4.45	1	(2.2)	1	2.20	3	(2.2)	3	2.31
Otitis externa	0				0				3	(6.5)	4	8.79	3	(2.2)	4	3.08
Pharyngitis	0				2	(4.3)	2	4.45	1	(2.2)	1	2.20	3	(2.2)	3	2.31
Tonsillitis	1	(2.4)	1	2.54	2	(4.3)	2	4.45	0				3	(2.2)	3	2.31
Cellulitis	0				1	(2.1)	1	2.23	1	(2.2)	1	2.20	2	(1.5)	2	1.54
Nasopharyngitis	0				2	(4.3)	4	8.91	0				2	(1.5)	4	3.08
Periodontitis	1	(2.4)	1	2.54	0				1	(2.2)	1	2.20	2	(1.5)	2	1.54
Sinusitis	2	(4.9)	2	5.07	0				0				2	(1.5)	2	1.54
Tinea pedis	0				1	(2.1)	1	2.23	1	(2.2)	1	2.20	2	(1.5)	2	1.54
Upper respiratory tract infection	0				0				2	(4.3)	3	6.60	2	(1.5)	3	2.31
Abdominal abscess	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Body tinea	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Enterocolitis bacterial	0				0				1	(2.2)	2	4.40	1	(0.7)	2	1.54
Folliculitis	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Fungal cystitis	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Gingivitis	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Helicobacter infection	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Hordeolum	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Otitis media	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Pneumonia	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline >= 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Pulpitis dental	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Purulence	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Respiratory tract infection	1	(2.4)	2	5.07	0				0				1	(0.7)	2	1.54
Sycosis barbae	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Gastrointestinal disorders	14	(34.1)	35	88.79	11	(23.4)	22	48.98	13	(28.3)	25	54.97	38	(28.4)	82	63.17
Constipation	6	(14.6)	7	17.76	4	(8.5)	4	8.91	5	(10.9)	5	10.99	15	(11.2)	16	12.33
Diarrhoea	4	(9.8)	7	17.76	2	(4.3)	2	4.45	4	(8.7)	4	8.79	10	(7.5)	13	10.01
Nausea	2	(4.9)	3	7.61	1	(2.1)	3	6.68	4	(8.7)	4	8.79	7	(5.2)	10	7.70
Vomiting	1	(2.4)	3	7.61	1	(2.1)	1	2.23	3	(6.5)	4	8.79	5	(3.7)	8	6.16
Abdominal distension	2	(4.9)	2	5.07	1	(2.1)	1	2.23	0				3	(2.2)	3	2.31
Abdominal pain	1	(2.4)	1	2.54	1	(2.1)	3	6.68	1	(2.2)	1	2.20	3	(2.2)	5	3.85
Abdominal pain upper	1	(2.4)	1	2.54	1	(2.1)	1	2.23	1	(2.2)	1	2.20	3	(2.2)	3	2.31
Dental caries	1	(2.4)	1	2.54	1	(2.1)	1	2.23	1	(2.2)	1	2.20	3	(2.2)	3	2.31
Stomatitis	2	(4.9)	3	7.61	1	(2.1)	1	2.23	0				3	(2.2)	4	3.08
Abdominal discomfort	1	(2.4)	1	2.54	1	(2.1)	1	2.23	0				2	(1.5)	2	1.54
Gastritis	1	(2.4)	1	2.54	1	(2.1)	1	2.23	0				2	(1.5)	2	1.54
Gastrooesophageal reflux disease	1	(2.4)	1	2.54	0				1	(2.2)	1	2.20	2	(1.5)	2	1.54
Chronic gastritis	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Duodenal polyp	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Dyspepsia	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Gastric polyps	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Gastric ulcer	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Gastrointestinal disorder	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Gingival swelling	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Haematochezia	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Large intestine polyp	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Proctitis	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Toothache	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Musculoskeletal and connective tissue disorders	7	(17.1)	7	17.76	11	(23.4)	16	35.62	7	(15.2)	7	15.39	25	(18.7)	30	23.11

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline >= 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Osteoarthritis	0				5	(10.6)	5	11.13	2	(4.3)	2	4.40	7	(5.2)	7	5.39
Back pain	1	(2.4)	1	2.54	2	(4.3)	2	4.45	1	(2.2)	1	2.20	4	(3.0)	4	3.08
Arthralgia	0				3	(6.4)	3	6.68	0				3	(2.2)	3	2.31
Spinal osteoarthritis	1	(2.4)	1	2.54	1	(2.1)	1	2.23	1	(2.2)	1	2.20	3	(2.2)	3	2.31
Myalgia	2	(4.9)	2	5.07	0				0				2	(1.5)	2	1.54
Tenosynovitis	0				1	(2.1)	1	2.23	1	(2.2)	1	2.20	2	(1.5)	2	1.54
Fasciitis	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Flank pain	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Joint swelling	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Musculoskeletal chest pain	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Musculoskeletal pain	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Musculoskeletal stiffness	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Periarthritis	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Tendonitis	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Trigger finger	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Eye disorders	5	(12.2)	6	15.22	5	(10.6)	9	20.04	8	(17.4)	8	17.59	18	(13.4)	23	17.72
Diabetic retinopathy	2	(4.9)	2	5.07	0				2	(4.3)	2	4.40	4	(3.0)	4	3.08
Asthenopia	0				1	(2.1)	1	2.23	2	(4.3)	2	4.40	3	(2.2)	3	2.31
Conjunctivitis allergic	0				1	(2.1)	1	2.23	2	(4.3)	2	4.40	3	(2.2)	3	2.31
Conjunctival haemorrhage	1	(2.4)	1	2.54	1	(2.1)	2	4.45	0				2	(1.5)	3	2.31
Vision blurred	0				1	(2.1)	1	2.23	1	(2.2)	1	2.20	2	(1.5)	2	1.54
Blepharitis	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Blepharospasm	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Cataract	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Cystoid macular oedema	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Dry eye	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Exposure keratitis	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Posterior capsule opacification	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Retinal haemorrhage	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline >= 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Injury, poisoning and procedural complications	2	(4.9)	3	7.61	5	(10.6)	5	11.13	7	(15.2)	8	17.59	14	(10.4)	16	12.33
Contusion	0				3	(6.4)	3	6.68	1	(2.2)	1	2.20	4	(3.0)	4	3.08
Accidental overdose	1	(2.4)	1	2.54	0				1	(2.2)	1	2.20	2	(1.5)	2	1.54
Ligament sprain	1	(2.4)	2	5.07	0				1	(2.2)	1	2.20	2	(1.5)	3	2.31
Arthropod sting	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Chest injury	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Hand fracture	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Pubis fracture	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Spinal compression fracture	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Thermal burn	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Wrong drug administered	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Nervous system disorders	5	(12.2)	8	20.29	3	(6.4)	3	6.68	6	(13.0)	7	15.39	14	(10.4)	18	13.87
Headache	3	(7.3)	6	15.22	1	(2.1)	1	2.23	1	(2.2)	1	2.20	5	(3.7)	8	6.16
Dizziness	0				1	(2.1)	1	2.23	1	(2.2)	1	2.20	2	(1.5)	2	1.54
Cervicobrachial syndrome	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Diabetic neuropathy	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Facial paralysis	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Head discomfort	0				0				1	(2.2)	2	4.40	1	(0.7)	2	1.54
Hypoaesthesia	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Hypoglycaemic unconsciousness	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Lumbar radiculopathy	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Skin and subcutaneous tissue disorders	3	(7.3)	3	7.61	3	(6.4)	5	11.13	8	(17.4)	10	21.99	14	(10.4)	18	13.87
Eczema	2	(4.9)	2	5.07	0				2	(4.3)	2	4.40	4	(3.0)	4	3.08
Dermatitis contact	0				0				3	(6.5)	4	8.79	3	(2.2)	4	3.08
Asteatosis	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Dermal cyst	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Dermatitis allergic	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Hand dermatitis	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77

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Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline >= 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Pruritus	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Rash	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Scab	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Swelling face	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Urticaria	0				1	(2.1)	2	4.45	0				1	(0.7)	2	1.54
General disorders and administration site conditions	4	(9.8)	5	12.68	4	(8.5)	4	8.91	4	(8.7)	4	8.79	12	(9.0)	13	10.01
Oedema peripheral	2	(4.9)	2	5.07	2	(4.3)	2	4.45	0				4	(3.0)	4	3.08
Injection site pruritus	1	(2.4)	1	2.54	0				1	(2.2)	1	2.20	2	(1.5)	2	1.54
Oedema	0				1	(2.1)	1	2.23	1	(2.2)	1	2.20	2	(1.5)	2	1.54
Inflammation	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Injection site swelling	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Malaise	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Sense of oppression	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Thirst	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Investigations	4	(9.8)	6	15.22	2	(4.3)	2	4.45	6	(13.0)	6	13.19	12	(9.0)	14	10.78
Weight increased	1	(2.4)	1	2.54	2	(4.3)	2	4.45	0				3	(2.2)	3	2.31
Blood calcitonin increased	0				0				2	(4.3)	2	4.40	2	(1.5)	2	1.54
Lipase increased	1	(2.4)	1	2.54	0				1	(2.2)	1	2.20	2	(1.5)	2	1.54
Alanine aminotransferase increased	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Aspartate aminotransferase increased	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Blood triglycerides increased	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Carbohydrate antigen 125 increased	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Free fatty acids decreased	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Gamma-glutamyltransferase increased	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77

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Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline >= 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Occult blood positive	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Respiratory, thoracic and mediastinal disorders	5	(12.2)	5	12.68	4	(8.5)	4	8.91	3	(6.5)	4	8.79	12	(9.0)	13	10.01
Rhinitis allergic	3	(7.3)	3	7.61	1	(2.1)	1	2.23	0				4	(3.0)	4	3.08
Asthma	0				1	(2.1)	1	2.23	2	(4.3)	2	4.40	3	(2.2)	3	2.31
Upper respiratory tract inflammation	1	(2.4)	1	2.54	1	(2.1)	1	2.23	1	(2.2)	1	2.20	3	(2.2)	3	2.31
Cough	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Dysphonia	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Sleep apnoea syndrome	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Metabolism and nutrition disorders	3	(7.3)	3	7.61	4	(8.5)	4	8.91	1	(2.2)	1	2.20	8	(6.0)	8	6.16
Decreased appetite	0				2	(4.3)	2	4.45	1	(2.2)	1	2.20	3	(2.2)	3	2.31
Overweight	2	(4.9)	2	5.07	1	(2.1)	1	2.23	0				3	(2.2)	3	2.31
Hypokalaemia	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Obesity	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Psychiatric disorders	0				3	(6.4)	3	6.68	2	(4.3)	2	4.40	5	(3.7)	5	3.85
Insomnia	0				3	(6.4)	3	6.68	1	(2.2)	1	2.20	4	(3.0)	4	3.08
Suicide attempt	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Vascular disorders	1	(2.4)	1	2.54	4	(8.5)	4	8.91	0				5	(3.7)	5	3.85
Hypertension	1	(2.4)	1	2.54	3	(6.4)	3	6.68	0				4	(3.0)	4	3.08
Arteriosclerosis	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Cardiac disorders	1	(2.4)	1	2.54	1	(2.1)	1	2.23	2	(4.3)	2	4.40	4	(3.0)	4	3.08
Atrial fibrillation	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Cardiomegaly	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Palpitations	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Tachycardia	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline >= 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Renal and urinary disorders	1	(2.4)	1	2.54	1	(2.1)	1	2.23	2	(4.3)	3	6.60	4	(3.0)	5	3.85
Renal cyst	0				1	(2.1)	1	2.23	1	(2.2)	1	2.20	2	(1.5)	2	1.54
Calculus urinary	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Hydronephrosis	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Ureterolithiasis	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Reproductive system and breast disorders	1	(2.4)	1	2.54	3	(6.4)	3	6.68	0				4	(3.0)	4	3.08
Pruritus genital	1	(2.4)	1	2.54	2	(4.3)	2	4.45	0				3	(2.2)	3	2.31
Endometrial hyperplasia	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Hepatobiliary disorders	1	(2.4)	1	2.54	0				2	(4.3)	3	6.60	3	(2.2)	4	3.08
Cholelithiasis	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Drug-induced liver injury	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Gallbladder polyp	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Hepatic steatosis	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Ear and labyrinth disorders	1	(2.4)	3	7.61	0				1	(2.2)	1	2.20	2	(1.5)	4	3.08
Vertigo	1	(2.4)	3	7.61	0				1	(2.2)	1	2.20	2	(1.5)	4	3.08
Endocrine disorders	1	(2.4)	1	2.54	1	(2.1)	1	2.23	0				2	(1.5)	2	1.54
Thyroid cyst	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Thyroid mass	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(2.4)	1	2.54	1	(2.1)	1	2.23	0				2	(1.5)	2	1.54
Oligodendroglioma	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Skin papilloma	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Blood and lymphatic system disorders	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Splenomegaly	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline >= 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Immune system disorders	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Seasonal allergy	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Surgical and medical procedures	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Cardiac ablation	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

2.7.4.7.1-20 ベースラインの BMI（kg/m^2）が 25 未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	26				28				54			
PYE (years)	13.42				13.74				27.16			
Events	21	(80.8)	64	476.77	19	(67.9)	40	291.21	40	(74.1)	104	382.92
Infections and infestations	9	(34.6)	13	96.84	11	(39.3)	14	101.92	20	(37.0)	27	99.41
Viral upper respiratory tract infection	4	(15.4)	4	29.80	10	(35.7)	10	72.80	14	(25.9)	14	51.55
Pharyngitis	4	(15.4)	5	37.25	0				4	(7.4)	5	18.41
Bronchitis	0				2	(7.1)	2	14.56	2	(3.7)	2	7.36
Periodontitis	2	(7.7)	2	14.90	0				2	(3.7)	2	7.36
Hordeolum	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Infected dermal cyst	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Influenza	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Sinusitis	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Gastrointestinal disorders	11	(42.3)	28	208.59	3	(10.7)	7	50.96	14	(25.9)	35	128.87
Nausea	4	(15.4)	4	29.80	2	(7.1)	2	14.56	6	(11.1)	6	22.09
Abdominal discomfort	3	(11.5)	3	22.35	1	(3.6)	1	7.28	4	(7.4)	4	14.73
Constipation	3	(11.5)	4	29.80	1	(3.6)	1	7.28	4	(7.4)	5	18.41
Chronic gastritis	3	(11.5)	4	29.80	0				3	(5.6)	4	14.73
Diarrhoea	3	(11.5)	4	29.80	0				3	(5.6)	4	14.73
Hiatus hernia	2	(7.7)	2	14.90	0				2	(3.7)	2	7.36
Abdominal distension	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Dental caries	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Epigastric discomfort	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Gastritis erosive	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Gastrointestinal motility disorder	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Gastrooesophageal reflux disease	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Hyperchlorhydria	1	(3.8)	2	14.90	0				1	(1.9)	2	7.36
Oesophageal disorder	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Vomiting	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
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PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline < 25 kg/m^2 - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Eye disorders	6	(23.1)	7	52.15	3	(10.7)	4	29.12	9	(16.7)	11	40.50
Diabetic retinopathy	5	(19.2)	6	44.70	3	(10.7)	3	21.84	8	(14.8)	9	33.14
Dry eye	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Pingueculitis	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Musculoskeletal and connective tissue disorders	4	(15.4)	4	29.80	3	(10.7)	3	21.84	7	(13.0)	7	25.77
Muscle spasms	1	(3.8)	1	7.45	1	(3.6)	1	7.28	2	(3.7)	2	7.36
Arthralgia	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Back pain	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Intervertebral disc protrusion	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Myalgia	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Periarthritis	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
General disorders and administration site conditions	2	(7.7)	2	14.90	3	(10.7)	3	21.84	5	(9.3)	5	18.41
Administration site induration	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Induration	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Inflammation	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Injection site induration	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Pyrexia	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Injury, poisoning and procedural complications	3	(11.5)	3	22.35	1	(3.6)	1	7.28	4	(7.4)	4	14.73
Arthropod bite	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Heat stroke	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Laceration	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Wrong drug administered	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Metabolism and nutrition disorders	3	(11.5)	3	22.35	0				3	(5.6)	3	11.05
Decreased appetite	2	(7.7)	2	14.90	0				2	(3.7)	2	7.36
Hyperuricaemia	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(3.8)	1	7.45	1	(3.6)	1	7.28	2	(3.7)	2	7.36

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline < 25 kg/m^2 - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Adenocarcinoma	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Renal cell carcinoma	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Nervous system disorders	0				2	(7.1)	3	21.84	2	(3.7)	3	11.05
Carpal tunnel syndrome	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Diabetic neuropathy	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Dizziness	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Vascular disorders	0				2	(7.1)	2	14.56	2	(3.7)	2	7.36
Hypertension	0				2	(7.1)	2	14.56	2	(3.7)	2	7.36
Cardiac disorders	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Supraventricular extrasystoles	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Endocrine disorders	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Thyroid mass	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Hepatobiliary disorders	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Hepatic steatosis	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Investigations	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Helicobacter test positive	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
Skin and subcutaneous tissue disorders	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Skin swelling	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68

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R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

2.7.4.7.1-21 ベースラインの BMI（kg/m^2）が 25 以上 30 未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	64				53				117			
PYE (years)	33.06				26.07				59.13			
Events	50	(78.1)	175	529.35	40	(75.5)	93	356.70	90	(76.9)	268	453.22
Infections and infestations	21	(32.8)	36	108.89	19	(35.8)	29	111.23	40	(34.2)	65	109.92
Viral upper respiratory tract infection	14	(21.9)	19	57.47	9	(17.0)	14	53.70	23	(19.7)	33	55.81
Gastroenteritis	4	(6.3)	6	18.15	1	(1.9)	1	3.84	5	(4.3)	7	11.84
Upper respiratory tract infection	1	(1.6)	1	3.02	2	(3.8)	3	11.51	3	(2.6)	4	6.76
Cystitis	1	(1.6)	1	3.02	1	(1.9)	1	3.84	2	(1.7)	2	3.38
Herpes zoster	1	(1.6)	1	3.02	1	(1.9)	1	3.84	2	(1.7)	2	3.38
Influenza	1	(1.6)	1	3.02	1	(1.9)	1	3.84	2	(1.7)	2	3.38
Sinusitis	2	(3.1)	2	6.05	0				2	(1.7)	2	3.38
Abscess	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Adenoviral conjunctivitis	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Bronchitis	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Cellulitis	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Gingivitis	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Herpes simplex	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Otitis externa	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Pharyngitis	0				1	(1.9)	2	7.67	1	(0.9)	2	3.38
Tonsillitis	1	(1.6)	2	6.05	0				1	(0.9)	2	3.38
Upper respiratory tract infection bacterial	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Urinary tract infection	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Gastrointestinal disorders	26	(40.6)	45	136.12	12	(22.6)	17	65.20	38	(32.5)	62	104.85
Diarrhoea	9	(14.1)	12	36.30	2	(3.8)	2	7.67	11	(9.4)	14	23.68
Vomiting	7	(10.9)	9	27.22	1	(1.9)	1	3.84	8	(6.8)	10	16.91
Constipation	5	(7.8)	5	15.12	2	(3.8)	2	7.67	7	(6.0)	7	11.84
Nausea	4	(6.3)	5	15.12	2	(3.8)	3	11.51	6	(5.1)	8	13.53
Abdominal discomfort	3	(4.7)	3	9.07	2	(3.8)	2	7.67	5	(4.3)	5	8.46
Dyspepsia	3	(4.7)	4	12.10	0				3	(2.6)	4	6.76

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R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Faeces soft	1	(1.6)	1	3.02	1	(1.9)	1	3.84	2	(1.7)	2	3.38
Gastritis	1	(1.6)	1	3.02	1	(1.9)	1	3.84	2	(1.7)	2	3.38
Gastrooesophageal reflux disease	1	(1.6)	1	3.02	1	(1.9)	1	3.84	2	(1.7)	2	3.38
Abdominal pain	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Chronic gastritis	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Dental caries	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Duodenal ulcer	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Hiatus hernia	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Large intestine polyp	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Periodontal disease	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Varices oesophageal	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Eye disorders	12	(18.8)	13	39.32	10	(18.9)	11	42.19	22	(18.8)	24	40.59
Diabetic retinopathy	9	(14.1)	9	27.22	9	(17.0)	10	38.35	18	(15.4)	19	32.13
Blepharospasm	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Cataract	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Conjunctival haemorrhage	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Posterior capsule opacification	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Retinal haemorrhage	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Musculoskeletal and connective tissue disorders	10	(15.6)	14	42.35	7	(13.2)	8	30.68	17	(14.5)	22	37.20
Back pain	4	(6.3)	5	15.12	2	(3.8)	2	7.67	6	(5.1)	7	11.84
Arthralgia	2	(3.1)	2	6.05	1	(1.9)	1	3.84	3	(2.6)	3	5.07
Musculoskeletal pain	2	(3.1)	2	6.05	0				2	(1.7)	2	3.38
Tenosynovitis	1	(1.6)	1	3.02	1	(1.9)	1	3.84	2	(1.7)	2	3.38
Arthritis	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Flank pain	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Musculoskeletal stiffness	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Neck pain	1	(1.6)	2	6.05	0				1	(0.9)	2	3.38
Osteoarthritis	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Periarthritis	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Trigger finger	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Metabolism and nutrition disorders	11	(17.2)	11	33.27	3	(5.7)	3	11.51	14	(12.0)	14	23.68
Decreased appetite	5	(7.8)	5	15.12	0				5	(4.3)	5	8.46
Dyslipidaemia	2	(3.1)	2	6.05	1	(1.9)	1	3.84	3	(2.6)	3	5.07
Gout	2	(3.1)	2	6.05	1	(1.9)	1	3.84	3	(2.6)	3	5.07
Hyperuricaemia	2	(3.1)	2	6.05	0				2	(1.7)	2	3.38
Dehydration	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Injury, poisoning and procedural complications	6	(9.4)	10	30.25	3	(5.7)	3	11.51	9	(7.7)	13	21.98
Fall	3	(4.7)	3	9.07	0				3	(2.6)	3	5.07
Contusion	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Excoriation	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Foot fracture	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Fractured coccyx	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Heat illness	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Hip fracture	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Laceration	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Ligament sprain	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Postoperative fever	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Tooth injury	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Investigations	6	(9.4)	6	18.15	2	(3.8)	2	7.67	8	(6.8)	8	13.53
Lipase increased	2	(3.1)	2	6.05	0				2	(1.7)	2	3.38
Electrocardiogram ST-T segment depression	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Electrocardiogram T wave inversion	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Free fatty acids decreased	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Gamma-glutamyltransferase increased	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Oxygen saturation decreased	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Weight decreased	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Respiratory, thoracic and mediastinal disorders	5	(7.8)	8	24.20	3	(5.7)	3	11.51	8	(6.8)	11	18.60
Upper respiratory tract inflammation	1	(1.6)	2	6.05	2	(3.8)	2	7.67	3	(2.6)	4	6.76
Atelectasis	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Cough	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Oropharyngeal pain	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Pleural effusion	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Respiratory tract inflammation	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Sputum increased	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Sputum retention	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
General disorders and administration site conditions	5	(7.8)	6	18.15	2	(3.8)	2	7.67	7	(6.0)	8	13.53
Malaise	2	(3.1)	3	9.07	0				2	(1.7)	3	5.07
Administration site induration	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Generalised oedema	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Inflammation	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Injection site discomfort	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Pyrexia	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Nervous system disorders	5	(7.8)	7	21.17	2	(3.8)	2	7.67	7	(6.0)	9	15.22
Dizziness	2	(3.1)	2	6.05	1	(1.9)	1	3.84	3	(2.6)	3	5.07
Headache	2	(3.1)	2	6.05	0				2	(1.7)	2	3.38
Hypoaesthesia	2	(3.1)	2	6.05	0				2	(1.7)	2	3.38
Lacunar infarction	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Sciatica	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Skin and subcutaneous tissue disorders	3	(4.7)	4	12.10	4	(7.5)	4	15.34	7	(6.0)	8	13.53
Eczema	2	(3.1)	2	6.05	1	(1.9)	1	3.84	3	(2.6)	3	5.07
Dermatitis	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Miliaria	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Penile ulceration	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Pustular psoriasis	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Rash	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Renal and urinary disorders	4	(6.3)	7	21.17	2	(3.8)	2	7.67	6	(5.1)	9	15.22
Nephrolithiasis	2	(3.1)	2	6.05	1	(1.9)	1	3.84	3	(2.6)	3	5.07
Renal cyst	2	(3.1)	2	6.05	1	(1.9)	1	3.84	3	(2.6)	3	5.07

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Acute kidney injury	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Haematuria	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Ureterolithiasis	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Ear and labyrinth disorders	0				2	(3.8)	3	11.51	2	(1.7)	3	5.07
Vertigo	0				2	(3.8)	3	11.51	2	(1.7)	3	5.07
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(1.6)	1	3.02	1	(1.9)	1	3.84	2	(1.7)	2	3.38
Pancreatic carcinoma	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Uterine leiomyoma	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Vascular disorders	2	(3.1)	2	6.05	0				2	(1.7)	2	3.38
Arteriosclerosis	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Hypertension	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Blood and lymphatic system disorders	0				1	(1.9)	3	11.51	1	(0.9)	3	5.07
Leukopenia	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Lymphopenia	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Neutropenia	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Cardiac disorders	1	(1.6)	2	6.05	0				1	(0.9)	2	3.38
Acute myocardial infarction	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Cardiac failure congestive	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Hepatobiliary disorders	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Hepatic cirrhosis	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Immune system disorders	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Seasonal allergy	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Psychiatric disorders	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Insomnia	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

2.7.4.7.1-22 ベースラインの BMI（kg/m^2）が 30 以上の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	15				24				39			
PYE (years)	7.79				12.46				20.25			
Events	11	(73.3)	41	526.00	21	(87.5)	77	618.12	32	(82.1)	118	582.66
Gastrointestinal disorders	8	(53.3)	15	192.44	9	(37.5)	16	128.44	17	(43.6)	31	153.07
Diarrhoea	3	(20.0)	4	51.32	3	(12.5)	4	32.11	6	(15.4)	8	39.50
Abdominal discomfort	2	(13.3)	2	25.66	2	(8.3)	2	16.05	4	(10.3)	4	19.75
Constipation	1	(6.7)	1	12.83	1	(4.2)	1	8.03	2	(5.1)	2	9.88
Enteritis	1	(6.7)	2	25.66	1	(4.2)	1	8.03	2	(5.1)	3	14.81
Gastrooesophageal reflux disease	1	(6.7)	1	12.83	1	(4.2)	1	8.03	2	(5.1)	2	9.88
Nausea	2	(13.3)	3	38.49	0				2	(5.1)	3	14.81
Vomiting	1	(6.7)	1	12.83	1	(4.2)	1	8.03	2	(5.1)	2	9.88
Abdominal pain	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Dyspepsia	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Food poisoning	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Gastritis	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94
Gastritis erosive	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Glossitis	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Stomatitis	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Infections and infestations	5	(33.3)	8	102.63	8	(33.3)	9	72.25	13	(33.3)	17	83.94
Viral upper respiratory tract infection	3	(20.0)	4	51.32	5	(20.8)	6	48.16	8	(20.5)	10	49.38
Bronchitis	1	(6.7)	1	12.83	2	(8.3)	2	16.05	3	(7.7)	3	14.81
Gastroenteritis	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Herpes zoster	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94
Pharyngitis	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94
Tinea pedis	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94
Eye disorders	4	(26.7)	4	51.32	7	(29.2)	8	64.22	11	(28.2)	12	59.25
Diabetic retinopathy	3	(20.0)	3	38.49	5	(20.8)	5	40.14	8	(20.5)	8	39.50
Cataract	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
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PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline >= 30 kg/m^2 - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Cataract nuclear	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Retinal detachment	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Retinopathy	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94
Nervous system disorders	4	(26.7)	4	51.32	7	(29.2)	9	72.25	11	(28.2)	13	64.19
Dizziness	0				2	(8.3)	3	24.08	2	(5.1)	3	14.81
Headache	1	(6.7)	1	12.83	1	(4.2)	1	8.03	2	(5.1)	2	9.88
Carpal tunnel syndrome	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94
Diabetic neuropathy	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94
Dysgeusia	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Hypoaesthesia	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Loss of consciousness	0				1	(4.2)	2	16.05	1	(2.6)	2	9.88
Migraine	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94
Neuropathy peripheral	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
General disorders and administration site conditions	2	(13.3)	2	25.66	5	(20.8)	5	40.14	7	(17.9)	7	34.56
Oedema peripheral	2	(13.3)	2	25.66	1	(4.2)	1	8.03	3	(7.7)	3	14.81
Pyrexia	0				2	(8.3)	2	16.05	2	(5.1)	2	9.88
Inflammation	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Malaise	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Injury, poisoning and procedural complications	1	(6.7)	1	12.83	6	(25.0)	7	56.19	7	(17.9)	8	39.50
Contusion	1	(6.7)	1	12.83	3	(12.5)	3	24.08	4	(10.3)	4	19.75
Laceration	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Thermal burn	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Tibia fracture	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Tooth fracture	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Skin and subcutaneous tissue disorders	1	(6.7)	1	12.83	5	(20.8)	5	40.14	6	(15.4)	6	29.63
Eczema	0				3	(12.5)	3	24.08	3	(7.7)	3	14.81
Acne	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Hyperkeratosis	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94

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PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline >= 30 kg/m^2 - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Skin irritation	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Musculoskeletal and connective tissue disorders	0				4	(16.7)	4	32.11	4	(10.3)	4	19.75
Back pain	0				3	(12.5)	3	24.08	3	(7.7)	3	14.81
Intervertebral disc protrusion	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Respiratory, thoracic and mediastinal disorders	1	(6.7)	1	12.83	3	(12.5)	3	24.08	4	(10.3)	4	19.75
Bronchitis chronic	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Cough	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Oropharyngeal pain	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94
Upper respiratory tract inflammation	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Investigations	0				3	(12.5)	3	24.08	3	(7.7)	3	14.81
Helicobacter test positive	0				2	(8.3)	2	16.05	2	(5.1)	2	9.88
Glomerular filtration rate decreased	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Vascular disorders	3	(20.0)	3	38.49	0				3	(7.7)	3	14.81
Hypertension	2	(13.3)	2	25.66	0				2	(5.1)	2	9.88
Orthostatic hypotension	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94
Hepatobiliary disorders	0				2	(8.3)	2	16.05	2	(5.1)	2	9.88
Cholecystitis acute	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Cholelithiasis	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Psychiatric disorders	0				2	(8.3)	2	16.05	2	(5.1)	2	9.88
Insomnia	0				2	(8.3)	2	16.05	2	(5.1)	2	9.88
Ear and labyrinth disorders	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94
Vertigo	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94
Metabolism and nutrition disorders	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94
Decreased appetite	1	(6.7)	1	12.83	0				1	(2.6)	1	4.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline >= 30 kg/m^2 - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Renal and urinary disorders	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Nephrolithiasis	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Reproductive system and breast disorders	0				1	(4.2)	3	24.08	1	(2.6)	3	14.81
Uterine cyst	0				1	(4.2)	2	16.05	1	(2.6)	2	9.88
Uterine mass	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

2.7.4.7.1-23 ベースラインの年齢が 65 歳未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	197				183				202				582			
PYE (years)	193.01				179.38				202.03				574.43			
Events	161	(81.7)	625	323.82	142	(77.6)	558	311.07	167	(82.7)	660	326.68	470	(80.8)	1843	320.84
Infections and infestations	115	(58.4)	216	111.91	93	(50.8)	191	106.48	108	(53.5)	210	103.94	316	(54.3)	617	107.41
Viral upper respiratory tract infection	79	(40.1)	126	65.28	64	(35.0)	115	64.11	72	(35.6)	119	58.90	215	(36.9)	360	62.67
Influenza	12	(6.1)	12	6.22	8	(4.4)	8	4.46	7	(3.5)	7	3.46	27	(4.6)	27	4.70
Gastroenteritis	10	(5.1)	10	5.18	6	(3.3)	7	3.90	8	(4.0)	8	3.96	24	(4.1)	25	4.35
Pharyngitis	6	(3.0)	6	3.11	11	(6.0)	14	7.80	5	(2.5)	5	2.47	22	(3.8)	25	4.35
Bronchitis	5	(2.5)	7	3.63	3	(1.6)	4	2.23	8	(4.0)	8	3.96	16	(2.7)	19	3.31
Periodontitis	4	(2.0)	4	2.07	5	(2.7)	8	4.46	5	(2.5)	5	2.47	14	(2.4)	17	2.96
Conjunctivitis	3	(1.5)	3	1.55	3	(1.6)	3	1.67	4	(2.0)	4	1.98	10	(1.7)	10	1.74
Cystitis	1	(0.5)	1	0.52	3	(1.6)	5	2.79	3	(1.5)	3	1.48	7	(1.2)	9	1.57
Helicobacter infection	1	(0.5)	1	0.52	3	(1.6)	3	1.67	3	(1.5)	3	1.48	7	(1.2)	7	1.22
Otitis externa	4	(2.0)	4	2.07	0				3	(1.5)	4	1.98	7	(1.2)	8	1.39
Tonsillitis	2	(1.0)	2	1.04	3	(1.6)	3	1.67	2	(1.0)	2	0.99	7	(1.2)	7	1.22
Herpes zoster	2	(1.0)	2	1.04	4	(2.2)	4	2.23	0				6	(1.0)	6	1.04
Nasopharyngitis	3	(1.5)	7	3.63	1	(0.5)	2	1.11	2	(1.0)	2	0.99	6	(1.0)	11	1.91
Sinusitis	4	(2.0)	4	2.07	0				2	(1.0)	4	1.98	6	(1.0)	8	1.39
Tinea pedis	0				1	(0.5)	1	0.56	5	(2.5)	5	2.47	6	(1.0)	6	1.04
Gingivitis	0				2	(1.1)	2	1.11	2	(1.0)	3	1.48	4	(0.7)	5	0.87
Upper respiratory tract infection	1	(0.5)	1	0.52	1	(0.5)	2	1.11	2	(1.0)	3	1.48	4	(0.7)	6	1.04
Cellulitis	0				1	(0.5)	1	0.56	2	(1.0)	2	0.99	3	(0.5)	3	0.52
Gastroenteritis viral	1	(0.5)	1	0.52	1	(0.5)	1	0.56	1	(0.5)	1	0.49	3	(0.5)	3	0.52
Hordeolum	1	(0.5)	1	0.52	0				2	(1.0)	2	0.99	3	(0.5)	3	0.52
Pneumonia	1	(0.5)	1	0.52	0				2	(1.0)	2	0.99	3	(0.5)	3	0.52
Pulpitis dental	1	(0.5)	1	0.52	0				2	(1.0)	2	0.99	3	(0.5)	3	0.52
Dermatitis infected	2	(1.0)	2	1.04	0				0				2	(0.3)	2	0.35
Helicobacter gastritis	0				0				2	(1.0)	2	0.99	2	(0.3)	2	0.35

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PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Herpes virus infection	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35
Oral herpes	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35
Otitis media	0				1	(0.5)	1	0.56	1	(0.5)	1	0.49	2	(0.3)	2	0.35
Rhinitis	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35
Abdominal abscess	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Acute sinusitis	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Beta haemolytic streptococcal infection	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Body tinea	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Conjunctivitis viral	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Eczema impetiginous	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Eczema infected	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Empyema	1	(0.5)	2	1.04	0				0				1	(0.2)	2	0.35
Enteritis infectious	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Enterocolitis bacterial	0				0				1	(0.5)	2	0.99	1	(0.2)	2	0.35
Folliculitis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Fungal cystitis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Furuncle	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Gastroenteritis norovirus	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Genital herpes	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Infected dermal cyst	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Infectious colitis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Mycoplasma infection	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Oesophageal candidiasis	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Paronychia	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Peritonsillitis	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Pharyngotonsillitis	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Pneumonia haemophilus	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Purulence	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Pyelonephritis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Respiratory tract infection	1	(0.5)	2	1.04	0				0				1	(0.2)	2	0.35
Skin infection	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Sycosis barbae	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Tinea capitis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Tinea infection	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Urinary tract infection	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Gastrointestinal disorders	70	(35.5)	133	68.91	43	(23.5)	77	42.93	84	(41.6)	170	84.14	197	(33.8)	380	66.15
Constipation	18	(9.1)	19	9.84	8	(4.4)	8	4.46	30	(14.9)	33	16.33	56	(9.6)	60	10.45
Diarrhoea	12	(6.1)	17	8.81	8	(4.4)	10	5.57	21	(10.4)	28	13.86	41	(7.0)	55	9.57
Nausea	6	(3.0)	10	5.18	4	(2.2)	6	3.34	15	(7.4)	21	10.39	25	(4.3)	37	6.44
Gastrooesophageal reflux disease	9	(4.6)	9	4.66	4	(2.2)	4	2.23	7	(3.5)	7	3.46	20	(3.4)	20	3.48
Dental caries	7	(3.6)	7	3.63	5	(2.7)	5	2.79	5	(2.5)	6	2.97	17	(2.9)	18	3.13
Abdominal discomfort	3	(1.5)	4	2.07	5	(2.7)	6	3.34	7	(3.5)	7	3.46	15	(2.6)	17	2.96
Chronic gastritis	4	(2.0)	4	2.07	5	(2.7)	5	2.79	5	(2.5)	5	2.47	14	(2.4)	14	2.44
Dyspepsia	5	(2.5)	6	3.11	0				9	(4.5)	11	5.44	14	(2.4)	17	2.96
Abdominal pain upper	4	(2.0)	5	2.59	4	(2.2)	4	2.23	3	(1.5)	3	1.48	11	(1.9)	12	2.09
Vomiting	1	(0.5)	3	1.55	2	(1.1)	2	1.11	8	(4.0)	9	4.45	11	(1.9)	14	2.44
Gastritis	4	(2.0)	4	2.07	2	(1.1)	2	1.11	4	(2.0)	4	1.98	10	(1.7)	10	1.74
Stomatitis	6	(3.0)	7	3.63	3	(1.6)	4	2.23	1	(0.5)	1	0.49	10	(1.7)	12	2.09
Abdominal distension	5	(2.5)	5	2.59	3	(1.6)	3	1.67	1	(0.5)	1	0.49	9	(1.5)	9	1.57
Abdominal pain	3	(1.5)	3	1.55	3	(1.6)	5	2.79	3	(1.5)	4	1.98	9	(1.5)	12	2.09
Gastric polyps	1	(0.5)	1	0.52	2	(1.1)	2	1.11	5	(2.5)	5	2.47	8	(1.4)	8	1.39
Large intestine polyp	4	(2.0)	4	2.07	1	(0.5)	1	0.56	3	(1.5)	3	1.48	8	(1.4)	8	1.39
Periodontal disease	1	(0.5)	1	0.52	2	(1.1)	2	1.11	4	(2.0)	4	1.98	7	(1.2)	7	1.22
Colitis	3	(1.5)	3	1.55	1	(0.5)	1	0.56	1	(0.5)	1	0.49	5	(0.9)	5	0.87
Hiatus hernia	2	(1.0)	2	1.04	2	(1.1)	2	1.11	0				4	(0.7)	4	0.70
Toothache	1	(0.5)	1	0.52	1	(0.5)	1	0.56	2	(1.0)	2	0.99	4	(0.7)	4	0.70
Faeces soft	1	(0.5)	1	0.52	0				2	(1.0)	3	1.48	3	(0.5)	4	0.70
Enterocolitis	2	(1.0)	3	1.55	0				0				2	(0.3)	3	0.52
Eructation	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35
Gastric ulcer	2	(1.0)	2	1.04	0				0				2	(0.3)	2	0.35
Gastritis erosive	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35
Parotid gland enlargement	2	(1.0)	2	1.04	0				0				2	(0.3)	2	0.35
Abdominal pain lower	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Anal fissure	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Barrett's oesophagus	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Brunner's gland hyperplasia	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Dry mouth	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Duodenal polyp	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Duodenitis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Faecaloma	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Food poisoning	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Functional gastrointestinal disorder	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Gastrointestinal disorder	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Gingival swelling	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Haematochezia	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Haemorrhoids	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Hyperchlorhydria	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Melaena	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Mouth ulceration	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Oral discomfort	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Pancreatic atrophy	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Pancreatic cyst	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Periodontal inflammation	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Proctitis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Musculoskeletal and connective tissue disorders	37	(18.8)	42	21.76	31	(16.9)	44	24.53	26	(12.9)	38	18.81	94	(16.2)	124	21.59
Back pain	6	(3.0)	6	3.11	10	(5.5)	10	5.57	8	(4.0)	11	5.44	24	(4.1)	27	4.70
Arthralgia	5	(2.5)	5	2.59	5	(2.7)	6	3.34	2	(1.0)	2	0.99	12	(2.1)	13	2.26
Periarthritis	3	(1.5)	3	1.55	4	(2.2)	4	2.23	2	(1.0)	2	0.99	9	(1.5)	9	1.57
Musculoskeletal stiffness	3	(1.5)	3	1.55	1	(0.5)	1	0.56	4	(2.0)	5	2.47	8	(1.4)	9	1.57
Myalgia	3	(1.5)	3	1.55	3	(1.6)	3	1.67	1	(0.5)	1	0.49	7	(1.2)	7	1.22
Osteoarthritis	1	(0.5)	1	0.52	4	(2.2)	4	2.23	2	(1.0)	2	0.99	7	(1.2)	7	1.22
Arthritis	2	(1.0)	2	1.04	1	(0.5)	1	0.56	1	(0.5)	1	0.49	4	(0.7)	4	0.70

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Intervertebral disc protrusion	3	(1.5)	3	1.55	0				1	(0.5)	1	0.49	4	(0.7)	4	0.70
Muscle spasms	1	(0.5)	3	1.55	1	(0.5)	1	0.56	2	(1.0)	3	1.48	4	(0.7)	7	1.22
Pain in extremity	2	(1.0)	2	1.04	1	(0.5)	1	0.56	1	(0.5)	1	0.49	4	(0.7)	4	0.70
Tenosynovitis	2	(1.0)	2	1.04	0				2	(1.0)	2	0.99	4	(0.7)	4	0.70
Joint swelling	1	(0.5)	1	0.52	1	(0.5)	1	0.56	1	(0.5)	1	0.49	3	(0.5)	3	0.52
Musculoskeletal pain	2	(1.0)	2	1.04	1	(0.5)	1	0.56	0				3	(0.5)	3	0.52
Spinal osteoarthritis	2	(1.0)	2	1.04	1	(0.5)	1	0.56	0				3	(0.5)	3	0.52
Flank pain	1	(0.5)	1	0.52	1	(0.5)	1	0.56	0				2	(0.3)	2	0.35
Intervertebral disc disorder	0				1	(0.5)	1	0.56	1	(0.5)	1	0.49	2	(0.3)	2	0.35
Osteoporosis	1	(0.5)	1	0.52	1	(0.5)	1	0.56	0				2	(0.3)	2	0.35
Fasciitis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Groin pain	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Joint contracture	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Lumbar spinal stenosis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Myalgia intercostal	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Neck pain	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Nodal osteoarthritis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Osteitis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Plantar fasciitis	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Rhabdomyolysis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Synovial cyst	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Tendonitis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Trigger finger	0				1	(0.5)	2	1.11	0				1	(0.2)	2	0.35
Eye disorders	31	(15.7)	36	18.65	19	(10.4)	27	15.05	26	(12.9)	30	14.85	76	(13.1)	93	16.19
Diabetic retinopathy	15	(7.6)	15	7.77	7	(3.8)	9	5.02	7	(3.5)	7	3.46	29	(5.0)	31	5.40
Conjunctivitis allergic	3	(1.5)	3	1.55	2	(1.1)	2	1.11	2	(1.0)	2	0.99	7	(1.2)	7	1.22
Asthenopia	1	(0.5)	1	0.52	3	(1.6)	3	1.67	2	(1.0)	2	0.99	6	(1.0)	6	1.04
Cataract	2	(1.0)	2	1.04	1	(0.5)	1	0.56	3	(1.5)	3	1.48	6	(1.0)	6	1.04
Vitreous floaters	2	(1.0)	2	1.04	1	(0.5)	1	0.56	2	(1.0)	2	0.99	5	(0.9)	5	0.87
Dry eye	2	(1.0)	2	1.04	2	(1.1)	2	1.11	0				4	(0.7)	4	0.70
Retinal haemorrhage	2	(1.0)	2	1.04	1	(0.5)	1	0.56	1	(0.5)	1	0.49	4	(0.7)	4	0.70

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Conjunctival haemorrhage	1	(0.5)	1	0.52	1	(0.5)	2	1.11	0				2	(0.3)	3	0.52
Diabetic retinal oedema	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35
Glaucoma	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35
Retinopathy	0				0				2	(1.0)	2	0.99	2	(0.3)	2	0.35
Vision blurred	0				2	(1.1)	2	1.11	0				2	(0.3)	2	0.35
Age-related macular degeneration	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Blepharitis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Blepharospasm	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Chorioretinopathy	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Conjunctivochalasis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Erythema of eyelid	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Exposure keratitis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Eye inflammation	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Keratitis	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Macular oedema	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Ocular discomfort	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Posterior capsule opacification	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Retinal degeneration	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Retinal detachment	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Retinal exudates	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Retinal tear	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Retinopathy proliferative	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Visual impairment	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Vitreous haemorrhage	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Investigations	24	(12.2)	35	18.13	21	(11.5)	37	20.63	25	(12.4)	27	13.36	70	(12.0)	99	17.23
Weight increased	4	(2.0)	4	2.07	16	(8.7)	16	8.92	1	(0.5)	1	0.49	21	(3.6)	21	3.66
Lipase increased	4	(2.0)	6	3.11	0				13	(6.4)	13	6.43	17	(2.9)	19	3.31
Free fatty acids decreased	4	(2.0)	5	2.59	4	(2.2)	5	2.79	1	(0.5)	1	0.49	9	(1.5)	11	1.91
Blood proinsulin decreased	4	(2.0)	4	2.07	3	(1.6)	3	1.67	0				7	(1.2)	7	1.22
Insulin C-peptide decreased	2	(1.0)	2	1.04	4	(2.2)	4	2.23	0				6	(1.0)	6	1.04

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Alanine aminotransferase increased	1	(0.5)	1	0.52	1	(0.5)	1	0.56	2	(1.0)	2	0.99	4	(0.7)	4	0.70
Blood creatine phosphokinase increased	0				3	(1.6)	4	2.23	1	(0.5)	1	0.49	4	(0.7)	5	0.87
Blood calcitonin increased	1	(0.5)	1	0.52	0				2	(1.0)	2	0.99	3	(0.5)	3	0.52
Blood triglycerides increased	1	(0.5)	1	0.52	0				2	(1.0)	2	0.99	3	(0.5)	3	0.52
Helicobacter test positive	1	(0.5)	1	0.52	1	(0.5)	1	0.56	1	(0.5)	1	0.49	3	(0.5)	3	0.52
Electrocardiogram T wave amplitude decreased	2	(1.0)	2	1.04	0				0				2	(0.3)	2	0.35
Gamma-glutamyltransferase increased	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35
Amylase increased	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Aspartate aminotransferase increased	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Blood creatine phosphokinase MM increased	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Blood potassium increased	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Blood pressure increased	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
C-reactive protein increased	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Carbohydrate antigen 125 increased	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Electrocardiogram QT prolonged	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Occult blood positive	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Rheumatoid factor increased	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Urine ketone body present	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Weight decreased	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
White blood cell count increased	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Skin and subcutaneous tissue disorders	21	(10.7)	23	11.92	23	(12.6)	28	15.61	22	(10.9)	26	12.87	66	(11.3)	77	13.40

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Eczema	10	(5.1)	12	6.22	3	(1.6)	3	1.67	7	(3.5)	8	3.96	20	(3.4)	23	4.00
Dermatitis contact	1	(0.5)	1	0.52	1	(0.5)	1	0.56	5	(2.5)	6	2.97	7	(1.2)	8	1.39
Pruritus	2	(1.0)	2	1.04	2	(1.1)	2	1.11	2	(1.0)	2	0.99	6	(1.0)	6	1.04
Asteatosis	0				0				3	(1.5)	3	1.48	3	(0.5)	3	0.52
Dermatitis allergic	1	(0.5)	1	0.52	2	(1.1)	2	1.11	0				3	(0.5)	3	0.52
Dermatitis atopic	1	(0.5)	1	0.52	2	(1.1)	2	1.11	0				3	(0.5)	3	0.52
Hyperkeratosis	0				3	(1.6)	3	1.67	0				3	(0.5)	3	0.52
Rash	1	(0.5)	1	0.52	2	(1.1)	2	1.11	0				3	(0.5)	3	0.52
Dermal cyst	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35
Miliaria	0				2	(1.1)	2	1.11	0				2	(0.3)	2	0.35
Urticaria	0				2	(1.1)	3	1.67	0				2	(0.3)	3	0.52
Acne	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Blister	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Dermatitis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Dry skin	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Dyshidrotic eczema	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Granuloma annulare	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Haemorrhage subcutaneous	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Hand dermatitis	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Ingrowing nail	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Nail hypertrophy	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Onychoclasis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Onycholysis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Psoriasis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Scab	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Seborrhoeic dermatitis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Skin mass	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Solar dermatitis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Swelling face	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Nervous system disorders	16	(8.1)	23	11.92	20	(10.9)	30	16.72	22	(10.9)	25	12.37	58	(10.0)	78	13.58
Headache	6	(3.0)	10	5.18	6	(3.3)	11	6.13	12	(5.9)	14	6.93	24	(4.1)	35	6.09
Dizziness	2	(1.0)	5	2.59	3	(1.6)	3	1.67	2	(1.0)	2	0.99	7	(1.2)	10	1.74

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hypoaesthesia	0				4	(2.2)	4	2.23	2	(1.0)	2	0.99	6	(1.0)	6	1.04
Diabetic neuropathy	2	(1.0)	2	1.04	2	(1.1)	2	1.11	1	(0.5)	1	0.49	5	(0.9)	5	0.87
Dysgeusia	0				0				3	(1.5)	3	1.48	3	(0.5)	3	0.52
Migraine	0				1	(0.5)	1	0.56	1	(0.5)	1	0.49	2	(0.3)	2	0.35
Somnolence	1	(0.5)	1	0.52	1	(0.5)	2	1.11	0				2	(0.3)	3	0.52
Balance disorder	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Carotid arteriosclerosis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Carotid artery stenosis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Cerebral infarction	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Cervicobrachial syndrome	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Facial paralysis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Head discomfort	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Hypoglycaemic unconsciousness	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Loss of consciousness	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Lumbar radiculopathy	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Neuralgia	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Sciatica	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Thalamic infarction	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Thrombotic cerebral infarction	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
General disorders and administration site conditions	15	(7.6)	16	8.29	15	(8.2)	17	9.48	22	(10.9)	26	12.87	52	(8.9)	59	10.27
Oedema peripheral	3	(1.5)	3	1.55	6	(3.3)	7	3.90	1	(0.5)	1	0.49	10	(1.7)	11	1.91
Malaise	2	(1.0)	2	1.04	2	(1.1)	2	1.11	5	(2.5)	5	2.47	9	(1.5)	9	1.57
Injection site induration	0				1	(0.5)	1	0.56	3	(1.5)	4	1.98	4	(0.7)	5	0.87
Fatigue	0				1	(0.5)	1	0.56	2	(1.0)	2	0.99	3	(0.5)	3	0.52
Injection site bruising	0				1	(0.5)	1	0.56	2	(1.0)	2	0.99	3	(0.5)	3	0.52
Injection site erythema	1	(0.5)	1	0.52	0				2	(1.0)	2	0.99	3	(0.5)	3	0.52
Oedema	0				1	(0.5)	1	0.56	2	(1.0)	2	0.99	3	(0.5)	3	0.52
Injection site pain	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Injection site pruritus	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35
Injection site reaction	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35
Pyrexia	0				1	(0.5)	1	0.56	1	(0.5)	1	0.49	2	(0.3)	2	0.35
Administration site mass	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Chest discomfort	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Chills	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Fat tissue increased	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Feeling abnormal	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Feeling hot	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Hunger	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Inflammation	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Injection site discolouration	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Injection site haemorrhage	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Injection site mass	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Injection site swelling	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Peripheral swelling	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Sense of oppression	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Injury, poisoning and procedural complications	14	(7.1)	15	7.77	17	(9.3)	23	12.82	19	(9.4)	24	11.88	50	(8.6)	62	10.79
Contusion	3	(1.5)	3	1.55	4	(2.2)	5	2.79	6	(3.0)	6	2.97	13	(2.2)	14	2.44
Ligament sprain	1	(0.5)	2	1.04	4	(2.2)	5	2.79	3	(1.5)	3	1.48	8	(1.4)	10	1.74
Arthropod bite	2	(1.0)	2	1.04	0				1	(0.5)	1	0.49	3	(0.5)	3	0.52
Arthropod sting	1	(0.5)	1	0.52	0				2	(1.0)	2	0.99	3	(0.5)	3	0.52
Rib fracture	1	(0.5)	1	0.52	1	(0.5)	1	0.56	1	(0.5)	1	0.49	3	(0.5)	3	0.52
Accidental overdose	1	(0.5)	1	0.52	1	(0.5)	1	0.56	0				2	(0.3)	2	0.35
Skin abrasion	0				0				2	(1.0)	2	0.99	2	(0.3)	2	0.35
Tooth injury	1	(0.5)	1	0.52	1	(0.5)	1	0.56	0				2	(0.3)	2	0.35
Avulsion fracture	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Chest injury	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Clavicle fracture	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Epicondylitis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Excoriation	0				0				1	(0.5)	2	0.99	1	(0.2)	2	0.35
Femoral neck fracture	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Foreign body in eye	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Heat illness	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Laceration	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Limb injury	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Lip injury	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Median nerve injury	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Muscle injury	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Muscle strain	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Scratch	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Spinal compression fracture	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Stab wound	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Subcutaneous haematoma	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Suture related complication	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Tooth fracture	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Wound	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Wrong drug administered	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Respiratory, thoracic and mediastinal disorders	20	(10.2)	26	13.47	16	(8.7)	19	10.59	14	(6.9)	18	8.91	50	(8.6)	63	10.97
Upper respiratory tract inflammation	5	(2.5)	7	3.63	4	(2.2)	4	2.23	5	(2.5)	6	2.97	14	(2.4)	17	2.96
Rhinitis allergic	6	(3.0)	6	3.11	2	(1.1)	2	1.11	2	(1.0)	2	0.99	10	(1.7)	10	1.74
Asthma	2	(1.0)	2	1.04	5	(2.7)	5	2.79	2	(1.0)	2	0.99	9	(1.5)	9	1.57
Oropharyngeal pain	1	(0.5)	1	0.52	2	(1.1)	2	1.11	4	(2.0)	4	1.98	7	(1.2)	7	1.22
Sleep apnoea syndrome	1	(0.5)	1	0.52	4	(2.2)	4	2.23	1	(0.5)	1	0.49	6	(1.0)	6	1.04
Cough	3	(1.5)	3	1.55	1	(0.5)	2	1.11	1	(0.5)	1	0.49	5	(0.9)	6	1.04
Rhinorrhoea	2	(1.0)	2	1.04	0				0				2	(0.3)	2	0.35
Emphysema	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Pharyngeal oedema	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Pleuritic pain	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Productive cough	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17

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PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Pulmonary fibrosis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Sneezing	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Metabolism and nutrition disorders	8	(4.1)	8	4.14	11	(6.0)	12	6.69	10	(5.0)	12	5.94	29	(5.0)	32	5.57
Decreased appetite	1	(0.5)	1	0.52	2	(1.1)	2	1.11	6	(3.0)	6	2.97	9	(1.5)	9	1.57
Dyslipidaemia	2	(1.0)	2	1.04	2	(1.1)	2	1.11	2	(1.0)	2	0.99	6	(1.0)	6	1.04
Hyperuricaemia	0				3	(1.6)	3	1.67	1	(0.5)	1	0.49	4	(0.7)	4	0.70
Overweight	2	(1.0)	2	1.04	1	(0.5)	1	0.56	0				3	(0.5)	3	0.52
Gout	0				2	(1.1)	2	1.11	0				2	(0.3)	2	0.35
Hyperlipidaemia	1	(0.5)	1	0.52	1	(0.5)	1	0.56	0				2	(0.3)	2	0.35
Dehydration	0				0				1	(0.5)	2	0.99	1	(0.2)	2	0.35
Hypertriglyceridaemia	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Hypoglycaemia	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Hypokalaemia	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Obesity	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Hepatobiliary disorders	7	(3.6)	9	4.66	7	(3.8)	8	4.46	10	(5.0)	13	6.43	24	(4.1)	30	5.22
Hepatic steatosis	4	(2.0)	4	2.07	1	(0.5)	1	0.56	3	(1.5)	3	1.48	8	(1.4)	8	1.39
Gallbladder polyp	1	(0.5)	1	0.52	4	(2.2)	4	2.23	2	(1.0)	2	0.99	7	(1.2)	7	1.22
Cholelithiasis	2	(1.0)	2	1.04	1	(0.5)	1	0.56	2	(1.0)	2	0.99	5	(0.9)	5	0.87
Hepatic cyst	1	(0.5)	1	0.52	0				2	(1.0)	2	0.99	3	(0.5)	3	0.52
Hepatic function abnormal	0				1	(0.5)	1	0.56	1	(0.5)	1	0.49	2	(0.3)	2	0.35
Non-alcoholic fatty liver	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35
Cholecystitis acute	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Drug-induced liver injury	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Liver disorder	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Vascular disorders	9	(4.6)	9	4.66	7	(3.8)	7	3.90	4	(2.0)	4	1.98	20	(3.4)	20	3.48
Hypertension	6	(3.0)	6	3.11	6	(3.3)	6	3.34	3	(1.5)	3	1.48	15	(2.6)	15	2.61
Arteriosclerosis	1	(0.5)	1	0.52	1	(0.5)	1	0.56	0				2	(0.3)	2	0.35
Orthostatic hypotension	1	(0.5)	1	0.52	0				1	(0.5)	1	0.49	2	(0.3)	2	0.35
Internal haemorrhage	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Psychiatric disorders	4	(2.0)	4	2.07	5	(2.7)	5	2.79	5	(2.5)	5	2.47	14	(2.4)	14	2.44
Insomnia	4	(2.0)	4	2.07	4	(2.2)	4	2.23	1	(0.5)	1	0.49	9	(1.5)	9	1.57
Sleep disorder	0				0				2	(1.0)	2	0.99	2	(0.3)	2	0.35
Anxiety	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Depression	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Suicide attempt	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Renal and urinary disorders	3	(1.5)	3	1.55	5	(2.7)	7	3.90	5	(2.5)	6	2.97	13	(2.2)	16	2.79
Renal cyst	1	(0.5)	1	0.52	2	(1.1)	2	1.11	1	(0.5)	1	0.49	4	(0.7)	4	0.70
Nephrolithiasis	0				2	(1.1)	2	1.11	1	(0.5)	1	0.49	3	(0.5)	3	0.52
Calculus urinary	0				0				2	(1.0)	2	0.99	2	(0.3)	2	0.35
Ureterolithiasis	2	(1.0)	2	1.04	0				0				2	(0.3)	2	0.35
Chronic kidney disease	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Hydronephrosis	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Nephrocalcinosis	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Nephrotic syndrome	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Renal impairment	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Ear and labyrinth disorders	6	(3.0)	8	4.14	2	(1.1)	3	1.67	4	(2.0)	4	1.98	12	(2.1)	15	2.61
Vertigo	3	(1.5)	5	2.59	1	(0.5)	2	1.11	2	(1.0)	2	0.99	6	(1.0)	9	1.57
Vertigo positional	2	(1.0)	2	1.04	0				1	(0.5)	1	0.49	3	(0.5)	3	0.52
Tinnitus	0				1	(0.5)	1	0.56	1	(0.5)	1	0.49	2	(0.3)	2	0.35
Sudden hearing loss	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Reproductive system and breast disorders	4	(2.0)	4	2.07	5	(2.7)	7	3.90	3	(1.5)	7	3.46	12	(2.1)	18	3.13
Ovarian cyst	1	(0.5)	1	0.52	1	(0.5)	1	0.56	1	(0.5)	1	0.49	3	(0.5)	3	0.52
Pruritus genital	1	(0.5)	1	0.52	2	(1.1)	2	1.11	0				3	(0.5)	3	0.52
Menopausal symptoms	0				1	(0.5)	1	0.56	1	(0.5)	1	0.49	2	(0.3)	2	0.35
Balanoposthitis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Benign prostatic hyperplasia	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Cervical cyst	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Cervical polyp	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Endometrial hyperplasia	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Menorrhagia	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Menstruation irregular	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Uterine disorder	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Uterine haemorrhage	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Uterine prolapse	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Cardiac disorders	2	(1.0)	2	1.04	3	(1.6)	3	1.67	5	(2.5)	5	2.47	10	(1.7)	10	1.74
Palpitations	1	(0.5)	1	0.52	1	(0.5)	1	0.56	2	(1.0)	2	0.99	4	(0.7)	4	0.70
Atrial fibrillation	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Coronary artery stenosis	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Myocardial ischaemia	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Sinus node dysfunction	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Supraventricular extrasystoles	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Tachycardia	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	(2.0)	4	2.07	3	(1.6)	3	1.67	3	(1.5)	3	1.48	10	(1.7)	10	1.74
Colon adenoma	0				0				2	(1.0)	2	0.99	2	(0.3)	2	0.35
Skin papilloma	2	(1.0)	2	1.04	0				0				2	(0.3)	2	0.35
Acrochordon	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Benign neoplasm of thyroid gland	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Breast cancer	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Oligodendroglioma	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Thyroid neoplasm	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Uterine leiomyoma	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Endocrine disorders	3	(1.5)	3	1.55	3	(1.6)	3	1.67	1	(0.5)	1	0.49	7	(1.2)	7	1.22
Thyroid cyst	2	(1.0)	2	1.04	2	(1.1)	2	1.11	0				4	(0.7)	4	0.70
Hyperthyroidism	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Silent thyroiditis	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Thyroid mass	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Blood and lymphatic system disorders	1	(0.5)	1	0.52	1	(0.5)	1	0.56	4	(2.0)	4	1.98	6	(1.0)	6	1.04
Iron deficiency anaemia	0				1	(0.5)	1	0.56	2	(1.0)	2	0.99	3	(0.5)	3	0.52
Anaemia	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Polycythaemia	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Splenomegaly	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Immune system disorders	3	(1.5)	4	2.07	2	(1.1)	2	1.11	1	(0.5)	1	0.49	6	(1.0)	7	1.22
Seasonal allergy	2	(1.0)	2	1.04	1	(0.5)	1	0.56	1	(0.5)	1	0.49	4	(0.7)	4	0.70
Allergy to arthropod sting	1	(0.5)	2	1.04	0				0				1	(0.2)	2	0.35
Hypersensitivity	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Surgical and medical procedures	1	(0.5)	1	0.52	2	(1.1)	3	1.67	1	(0.5)	1	0.49	4	(0.7)	5	0.87
Tooth extraction	1	(0.5)	1	0.52	1	(0.5)	2	1.11	0				2	(0.3)	3	0.52
Cataract operation	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Large intestinal polypectomy	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Congenital, familial and genetic disorders	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Epidermolysis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17

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2.7.4.7.1-24 ベースラインの年齢が 65 歳以上の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira			IDeg			Lira			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	78			88			71			237		
PYE (years)	74.99			82.43			69.80			227.22		
Events	68	(87.2)	248	330.71	74	(84.1)	271	328.78	62	(87.3)	225	322.33	204	(86.1)	744	327.44
Infections and infestations	40	(51.3)	75	100.01	46	(52.3)	83	100.70	39	(54.9)	61	87.39	125	(52.7)	219	96.38
Viral upper respiratory tract infection	27	(34.6)	40	53.34	27	(30.7)	46	55.81	22	(31.0)	36	51.57	76	(32.1)	122	53.69
Pharyngitis	5	(6.4)	7	9.33	4	(4.5)	4	4.85	4	(5.6)	4	5.73	13	(5.5)	15	6.60
Cystitis	3	(3.8)	5	6.67	5	(5.7)	5	6.07	0				8	(3.4)	10	4.40
Gastroenteritis	2	(2.6)	2	2.67	1	(1.1)	1	1.21	3	(4.2)	4	5.73	6	(2.5)	7	3.08
Influenza	3	(3.8)	3	4.00	1	(1.1)	1	1.21	2	(2.8)	2	2.87	6	(2.5)	6	2.64
Bronchitis	2	(2.6)	2	2.67	3	(3.4)	3	3.64	0				5	(2.1)	5	2.20
Herpes zoster	2	(2.6)	2	2.67	1	(1.1)	1	1.21	1	(1.4)	1	1.43	4	(1.7)	4	1.76
Conjunctivitis	0				1	(1.1)	1	1.21	2	(2.8)	2	2.87	3	(1.3)	3	1.32
Nasopharyngitis	0				2	(2.3)	3	3.64	1	(1.4)	1	1.43	3	(1.3)	4	1.76
Periodontitis	2	(2.6)	2	2.67	1	(1.1)	2	2.43	0				3	(1.3)	4	1.76
Upper respiratory tract infection	0				1	(1.1)	1	1.21	2	(2.8)	2	2.87	3	(1.3)	3	1.32
Gingival abscess	2	(2.6)	2	2.67	0				0				2	(0.8)	2	0.88
Gingivitis	2	(2.6)	2	2.67	0				0				2	(0.8)	2	0.88
Helicobacter infection	0				1	(1.1)	1	1.21	1	(1.4)	1	1.43	2	(0.8)	2	0.88
Oral herpes	1	(1.3)	1	1.33	0				1	(1.4)	1	1.43	2	(0.8)	2	0.88
Pneumonia	0				1	(1.1)	1	1.21	1	(1.4)	1	1.43	2	(0.8)	2	0.88
Urinary tract infection	0				2	(2.3)	2	2.43	0				2	(0.8)	2	0.88
Acute sinusitis	0				1	(1.1)	2	2.43	0				1	(0.4)	2	0.88
Bronchitis bacterial	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Cellulitis	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Dermatophytosis of nail	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Folliculitis	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Gastroenteritis bacterial	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Helicobacter gastritis	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Herpes virus infection	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Herpes zoster meningitis	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Hordeolum	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Localised infection	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Paronychia	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Pneumonia mycoplasmal	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Purulence	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Sinusitis	1	(1.3)	2	2.67	0				0				1	(0.4)	2	0.88
Skin infection	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Tinea infection	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Tinea pedis	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Tonsillitis	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Ureteritis	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Urethritis	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Vaginal infection	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Gastrointestinal disorders	26	(33.3)	54	72.01	19	(21.6)	33	40.04	30	(42.3)	48	68.76	75	(31.6)	135	59.41
Constipation	9	(11.5)	9	12.00	4	(4.5)	4	4.85	8	(11.3)	9	12.89	21	(8.9)	22	9.68
Nausea	3	(3.8)	3	4.00	1	(1.1)	1	1.21	8	(11.3)	9	12.89	12	(5.1)	13	5.72
Diarrhoea	3	(3.8)	3	4.00	4	(4.5)	4	4.85	3	(4.2)	3	4.30	10	(4.2)	10	4.40
Chronic gastritis	4	(5.1)	4	5.33	3	(3.4)	3	3.64	2	(2.8)	3	4.30	9	(3.8)	10	4.40
Gastrooesophageal reflux disease	4	(5.1)	4	5.33	3	(3.4)	3	3.64	1	(1.4)	1	1.43	8	(3.4)	8	3.52
Dental caries	2	(2.6)	2	2.67	2	(2.3)	2	2.43	2	(2.8)	2	2.87	6	(2.5)	6	2.64
Abdominal distension	3	(3.8)	3	4.00	0				2	(2.8)	2	2.87	5	(2.1)	5	2.20
Large intestine polyp	2	(2.6)	2	2.67	2	(2.3)	2	2.43	1	(1.4)	1	1.43	5	(2.1)	5	2.20
Periodontal disease	3	(3.8)	4	5.33	1	(1.1)	1	1.21	1	(1.4)	1	1.43	5	(2.1)	6	2.64
Abdominal pain upper	3	(3.8)	3	4.00	1	(1.1)	1	1.21	0				4	(1.7)	4	1.76
Stomatitis	4	(5.1)	4	5.33	0				0				4	(1.7)	4	1.76
Vomiting	1	(1.3)	1	1.33	1	(1.1)	1	1.21	2	(2.8)	3	4.30	4	(1.7)	5	2.20
Abdominal discomfort	0				1	(1.1)	1	1.21	2	(2.8)	2	2.87	3	(1.3)	3	1.32
Dyspepsia	1	(1.3)	1	1.33	1	(1.1)	1	1.21	1	(1.4)	1	1.43	3	(1.3)	3	1.32
Colitis	0				1	(1.1)	1	1.21	1	(1.4)	1	1.43	2	(0.8)	2	0.88

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Enteritis	1	(1.3)	2	2.67	1	(1.1)	1	1.21	0				2	(0.8)	3	1.32
Faeces soft	0				1	(1.1)	1	1.21	1	(1.4)	1	1.43	2	(0.8)	2	0.88
Gastric polyps	1	(1.3)	1	1.33	1	(1.1)	1	1.21	0				2	(0.8)	2	0.88
Hyperchlorhydria	0				1	(1.1)	1	1.21	1	(1.4)	1	1.43	2	(0.8)	2	0.88
Anal fissure	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Autoimmune pancreatitis	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Barrett's oesophagus	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Diverticulum intestinal	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Eructation	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Flatulence	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Food poisoning	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Gastric ulcer	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Gastritis	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Gastroduodenitis	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Gastrointestinal disorder	0				0				1	(1.4)	2	2.87	1	(0.4)	2	0.88
Haemorrhoidal haemorrhage	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Hypoaesthesia oral	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Inguinal hernia	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Oesophageal polyp	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Pancreatic cyst	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Pancreatitis acute	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Proctitis	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Toothache	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Musculoskeletal and connective tissue disorders	16	(20.5)	21	28.00	20	(22.7)	27	32.76	15	(21.1)	22	31.52	51	(21.5)	70	30.81
Back pain	6	(7.7)	6	8.00	2	(2.3)	2	2.43	5	(7.0)	5	7.16	13	(5.5)	13	5.72
Spinal osteoarthritis	2	(2.6)	2	2.67	3	(3.4)	3	3.64	2	(2.8)	2	2.87	7	(3.0)	7	3.08
Arthralgia	2	(2.6)	2	2.67	1	(1.1)	1	1.21	3	(4.2)	4	5.73	6	(2.5)	7	3.08
Muscle spasms	3	(3.8)	3	4.00	1	(1.1)	1	1.21	2	(2.8)	3	4.30	6	(2.5)	7	3.08
Myalgia	3	(3.8)	3	4.00	0				1	(1.4)	1	1.43	4	(1.7)	4	1.76
Osteoarthritis	2	(2.6)	2	2.67	2	(2.3)	2	2.43	0				4	(1.7)	4	1.76
Trigger finger	0				3	(3.4)	3	3.64	1	(1.4)	1	1.43	4	(1.7)	4	1.76

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Intervertebral disc protrusion	0				2	(2.3)	2	2.43	1	(1.4)	1	1.43	3	(1.3)	3	1.32
Tenosynovitis	0				2	(2.3)	2	2.43	1	(1.4)	1	1.43	3	(1.3)	3	1.32
Musculoskeletal pain	0				1	(1.1)	2	2.43	1	(1.4)	1	1.43	2	(0.8)	3	1.32
Neck pain	1	(1.3)	1	1.33	1	(1.1)	1	1.21	0				2	(0.8)	2	0.88
Spinal column stenosis	0				1	(1.1)	1	1.21	1	(1.4)	1	1.43	2	(0.8)	2	0.88
Bone pain	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Cervical spinal stenosis	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Flank pain	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Lumbar spinal stenosis	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Musculoskeletal chest pain	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Osteoporosis	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Pain in extremity	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Periarthritis	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Rheumatoid arthritis	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Spondylolisthesis	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Tendon pain	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Eye disorders	14	(17.9)	16	21.34	9	(10.2)	10	12.13	13	(18.3)	18	25.79	36	(15.2)	44	19.36
Diabetic retinopathy	2	(2.6)	2	2.67	5	(5.7)	5	6.07	4	(5.6)	4	5.73	11	(4.6)	11	4.84
Cataract	2	(2.6)	2	2.67	3	(3.4)	3	3.64	2	(2.8)	2	2.87	7	(3.0)	7	3.08
Glaucoma	1	(1.3)	1	1.33	0				2	(2.8)	2	2.87	3	(1.3)	3	1.32
Macular fibrosis	2	(2.6)	2	2.67	0				1	(1.4)	1	1.43	3	(1.3)	3	1.32
Asthenopia	0				0				2	(2.8)	2	2.87	2	(0.8)	2	0.88
Dry eye	1	(1.3)	1	1.33	0				1	(1.4)	1	1.43	2	(0.8)	2	0.88
Vision blurred	1	(1.3)	1	1.33	0				1	(1.4)	1	1.43	2	(0.8)	2	0.88
Astigmatism	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Blepharitis	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Blepharitis allergic	0				1	(1.1)	2	2.43	0				1	(0.4)	2	0.88
Conjunctivitis allergic	1	(1.3)	2	2.67	0				0				1	(0.4)	2	0.88
Cystoid macular oedema	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Diabetic retinal oedema	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Eye haemorrhage	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Keratitis	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Macular degeneration	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Macular hole	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Posterior capsule opacification	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Retinal detachment	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Nervous system disorders	5	(6.4)	6	8.00	16	(18.2)	19	23.05	9	(12.7)	10	14.33	30	(12.7)	35	15.40
Dizziness	1	(1.3)	1	1.33	5	(5.7)	6	7.28	1	(1.4)	1	1.43	7	(3.0)	8	3.52
Headache	1	(1.3)	1	1.33	1	(1.1)	1	1.21	3	(4.2)	3	4.30	5	(2.1)	5	2.20
Hypoaesthesia	2	(2.6)	3	4.00	2	(2.3)	2	2.43	1	(1.4)	1	1.43	5	(2.1)	6	2.64
Diabetic neuropathy	0				2	(2.3)	2	2.43	1	(1.4)	1	1.43	3	(1.3)	3	1.32
Facial paralysis	0				2	(2.3)	2	2.43	1	(1.4)	1	1.43	3	(1.3)	3	1.32
Carotid arteriosclerosis	0				2	(2.3)	2	2.43	0				2	(0.8)	2	0.88
Carpal tunnel syndrome	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Head discomfort	0				0				1	(1.4)	2	2.87	1	(0.4)	2	0.88
Intercostal neuralgia	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Migraine	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Neuropathy peripheral	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Presyncope	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Tongue biting	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Injury, poisoning and procedural complications	8	(10.3)	9	12.00	12	(13.6)	14	16.98	9	(12.7)	12	17.19	29	(12.2)	35	15.40
Contusion	2	(2.6)	2	2.67	2	(2.3)	2	2.43	3	(4.2)	4	5.73	7	(3.0)	8	3.52
Arthropod bite	0				2	(2.3)	2	2.43	0				2	(0.8)	2	0.88
Arthropod sting	0				1	(1.1)	2	2.43	1	(1.4)	1	1.43	2	(0.8)	3	1.32
Heat illness	1	(1.3)	1	1.33	0				1	(1.4)	1	1.43	2	(0.8)	2	0.88
Spinal compression fracture	1	(1.3)	1	1.33	0				1	(1.4)	1	1.43	2	(0.8)	2	0.88
Accidental overdose	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Bone contusion	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Foreign body in eye	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Hand fracture	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Head injury	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Heat stroke	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Incorrect dose administered	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Laceration	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Ligament sprain	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Lower limb fracture	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Lumbar vertebral fracture	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Meniscus injury	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Overdose	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Pubis fracture	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Rib fracture	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Thermal burn	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Thoracic vertebral fracture	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Wound	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Skin and subcutaneous tissue disorders	11	(14.1)	12	16.00	9	(10.2)	12	14.56	6	(8.5)	7	10.03	26	(11.0)	31	13.64
Eczema	6	(7.7)	6	8.00	3	(3.4)	3	3.64	2	(2.8)	2	2.87	11	(4.6)	11	4.84
Pruritus	1	(1.3)	1	1.33	1	(1.1)	2	2.43	1	(1.4)	1	1.43	3	(1.3)	4	1.76
Dermatitis contact	1	(1.3)	1	1.33	0				1	(1.4)	1	1.43	2	(0.8)	2	0.88
Rash	1	(1.3)	1	1.33	1	(1.1)	1	1.21	0				2	(0.8)	2	0.88
Urticaria	1	(1.3)	1	1.33	1	(1.1)	1	1.21	0				2	(0.8)	2	0.88
Chronic pigmented purpura	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Dermatitis	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Drug eruption	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Haemorrhage subcutaneous	0				1	(1.1)	3	3.64	0				1	(0.4)	3	1.32
Ingrowing nail	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Miliaria	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Pigmentation disorder	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Skin mass	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Investigations	6	(7.7)	8	10.67	6	(6.8)	6	7.28	9	(12.7)	12	17.19	21	(8.9)	26	11.44
Amylase increased	1	(1.3)	1	1.33	0				3	(4.2)	3	4.30	4	(1.7)	4	1.76

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Lipase increased	2	(2.6)	2	2.67	0				2	(2.8)	2	2.87	4	(1.7)	4	1.76
Helicobacter test positive	2	(2.6)	2	2.67	0				1	(1.4)	1	1.43	3	(1.3)	3	1.32
Weight increased	0				3	(3.4)	3	3.64	0				3	(1.3)	3	1.32
Blood proinsulin decreased	1	(1.3)	1	1.33	0				1	(1.4)	1	1.43	2	(0.8)	2	0.88
Pancreatic enzymes increased	0				0				2	(2.8)	2	2.87	2	(0.8)	2	0.88
Cardiac murmur	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Carotid intima-media thickness increased	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Eosinophil count increased	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Glomerular filtration rate decreased	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Hepatic enzyme increased	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Insulin C-peptide decreased	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Intraocular pressure increased	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Waist circumference increased	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
General disorders and administration site conditions	3	(3.8)	3	4.00	10	(11.4)	10	12.13	7	(9.9)	8	11.46	20	(8.4)	21	9.24
Asthenia	0				2	(2.3)	2	2.43	0				2	(0.8)	2	0.88
Injection site reaction	1	(1.3)	1	1.33	0				1	(1.4)	1	1.43	2	(0.8)	2	0.88
Malaise	0				1	(1.1)	1	1.21	1	(1.4)	2	2.87	2	(0.8)	3	1.32
Oedema	0				2	(2.3)	2	2.43	0				2	(0.8)	2	0.88
Oedema peripheral	1	(1.3)	1	1.33	1	(1.1)	1	1.21	0				2	(0.8)	2	0.88
Chest discomfort	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Fatigue	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Infusion site bruising	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Injection site bruising	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Injection site erythema	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Injection site pruritus	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Injection site swelling	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44

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PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Pain	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Pyrexia	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Thirst	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Respiratory, thoracic and mediastinal disorders	8	(10.3)	10	13.34	8	(9.1)	11	13.35	2	(2.8)	2	2.87	18	(7.6)	23	10.12
Upper respiratory tract inflammation	1	(1.3)	1	1.33	2	(2.3)	3	3.64	1	(1.4)	1	1.43	4	(1.7)	5	2.20
Asthma	2	(2.6)	2	2.67	0				1	(1.4)	1	1.43	3	(1.3)	3	1.32
Cough	0				3	(3.4)	4	4.85	0				3	(1.3)	4	1.76
Oropharyngeal pain	1	(1.3)	1	1.33	1	(1.1)	1	1.21	0				2	(0.8)	2	0.88
Bronchitis chronic	1	(1.3)	2	2.67	0				0				1	(0.4)	2	0.88
Chronic obstructive pulmonary disease	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Dysphonia	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Emphysema	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Respiratory disorder	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Rhinitis allergic	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Rhinorrhoea	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Sleep apnoea syndrome	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Vascular disorders	6	(7.7)	6	8.00	9	(10.2)	9	10.92	3	(4.2)	4	5.73	18	(7.6)	19	8.36
Hypertension	4	(5.1)	4	5.33	6	(6.8)	6	7.28	1	(1.4)	1	1.43	11	(4.6)	11	4.84
Arteriosclerosis	1	(1.3)	1	1.33	0				1	(1.4)	1	1.43	2	(0.8)	2	0.88
Hot flush	1	(1.3)	1	1.33	0				1	(1.4)	1	1.43	2	(0.8)	2	0.88
Peripheral arterial occlusive disease	0				2	(2.3)	2	2.43	0				2	(0.8)	2	0.88
Hypotension	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Varicose vein	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Cardiac disorders	5	(6.4)	5	6.67	6	(6.8)	6	7.28	6	(8.5)	6	8.60	17	(7.2)	17	7.48
Atrial fibrillation	0				1	(1.1)	1	1.21	2	(2.8)	2	2.87	3	(1.3)	3	1.32
Angina pectoris	2	(2.6)	2	2.67	0				0				2	(0.8)	2	0.88

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Ventricular extrasystoles	2	(2.6)	2	2.67	0				0				2	(0.8)	2	0.88
Acute myocardial infarction	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Atrioventricular block complete	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Atrioventricular block first degree	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Cardiac disorder	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Cardiomegaly	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Myocardial ischaemia	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Palpitations	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Sinus arrhythmia	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Supraventricular extrasystoles	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Supraventricular tachycardia	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Hepatobiliary disorders	3	(3.8)	4	5.33	5	(5.7)	9	10.92	2	(2.8)	2	2.87	10	(4.2)	15	6.60
Cholelithiasis	1	(1.3)	1	1.33	2	(2.3)	2	2.43	1	(1.4)	1	1.43	4	(1.7)	4	1.76
Hepatic steatosis	2	(2.6)	2	2.67	2	(2.3)	2	2.43	0				4	(1.7)	4	1.76
Cholecystitis	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Chronic hepatitis	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Gallbladder polyp	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Hepatic calcification	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Hepatic cyst	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Hepatic mass	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Non-alcoholic fatty liver	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Renal and urinary disorders	7	(9.0)	7	9.33	2	(2.3)	2	2.43	1	(1.4)	1	1.43	10	(4.2)	10	4.40
Renal cyst	4	(5.1)	4	5.33	0				1	(1.4)	1	1.43	5	(2.1)	5	2.20
Nephrolithiasis	1	(1.3)	1	1.33	2	(2.3)	2	2.43	0				3	(1.3)	3	1.32
Diabetic nephropathy	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Urinary retention	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Metabolism and nutrition disorders	2	(2.6)	2	2.67	2	(2.3)	2	2.43	5	(7.0)	5	7.16	9	(3.8)	9	3.96
Decreased appetite	0				1	(1.1)	1	1.21	5	(7.0)	5	7.16	6	(2.5)	6	2.64
Dehydration	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Hyperlipasaemia	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Hyperuricaemia	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Ear and labyrinth disorders	3	(3.8)	3	4.00	3	(3.4)	3	3.64	1	(1.4)	1	1.43	7	(3.0)	7	3.08
Vertigo	2	(2.6)	2	2.67	1	(1.1)	1	1.21	1	(1.4)	1	1.43	4	(1.7)	4	1.76
Tinnitus	1	(1.3)	1	1.33	1	(1.1)	1	1.21	0				2	(0.8)	2	0.88
Otorrhoea	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(2.6)	2	2.67	3	(3.4)	5	6.07	2	(2.8)	2	2.87	7	(3.0)	9	3.96
Adrenal neoplasm	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Basal cell carcinoma	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Benign neoplasm of bladder	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Benign neoplasm of thyroid gland	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Colon adenoma	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Gastric cancer stage I	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Lung adenocarcinoma	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Lung neoplasm malignant	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Metastases to lymph nodes	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Psychiatric disorders	2	(2.6)	2	2.67	4	(4.5)	4	4.85	1	(1.4)	1	1.43	7	(3.0)	7	3.08
Insomnia	2	(2.6)	2	2.67	2	(2.3)	2	2.43	1	(1.4)	1	1.43	5	(2.1)	5	2.20
Depression	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Neurosis	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Endocrine disorders	1	(1.3)	1	1.33	3	(3.4)	4	4.85	1	(1.4)	1	1.43	5	(2.1)	6	2.64
Thyroid cyst	0				3	(3.4)	3	3.64	1	(1.4)	1	1.43	4	(1.7)	4	1.76

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Thyroid mass	1	(1.3)	1	1.33	1	(1.1)	1	1.21	0				2	(0.8)	2	0.88
Reproductive system and breast disorders	1	(1.3)	1	1.33	2	(2.3)	2	2.43	0				3	(1.3)	3	1.32
Gynaecomastia	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Prostatic calcification	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Pruritus genital	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Blood and lymphatic system disorders	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Iron deficiency anaemia	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Immune system disorders	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Seasonal allergy	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Surgical and medical procedures	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Cardiac ablation	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44

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2.7.4.7.1-25 ベースラインの年齢が 65 歳以上 75 歳未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	76				84				66				226			
PYE (years)	73.16				79.21				64.70				217.07			
Events	66	(86.8)	237	323.93	71	(84.5)	263	332.05	57	(86.4)	199	307.57	194	(85.8)	699	322.02
Infections and infestations	39	(51.3)	74	101.14	45	(53.6)	80	101.00	37	(56.1)	54	83.46	121	(53.5)	208	95.82
Viral upper respiratory tract infection	27	(35.5)	40	54.67	26	(31.0)	45	56.81	21	(31.8)	33	51.00	74	(32.7)	118	54.36
Pharyngitis	5	(6.6)	7	9.57	4	(4.8)	4	5.05	4	(6.1)	4	6.18	13	(5.8)	15	6.91
Cystitis	3	(3.9)	5	6.83	5	(6.0)	5	6.31	0				8	(3.5)	10	4.61
Influenza	3	(3.9)	3	4.10	1	(1.2)	1	1.26	2	(3.0)	2	3.09	6	(2.7)	6	2.76
Gastroenteritis	2	(2.6)	2	2.73	1	(1.2)	1	1.26	2	(3.0)	2	3.09	5	(2.2)	5	2.30
Bronchitis	1	(1.3)	1	1.37	3	(3.6)	3	3.79	0				4	(1.8)	4	1.84
Herpes zoster	2	(2.6)	2	2.73	1	(1.2)	1	1.26	1	(1.5)	1	1.55	4	(1.8)	4	1.84
Conjunctivitis	0				1	(1.2)	1	1.26	2	(3.0)	2	3.09	3	(1.3)	3	1.38
Periodontitis	2	(2.6)	2	2.73	1	(1.2)	2	2.53	0				3	(1.3)	4	1.84
Upper respiratory tract infection	0				1	(1.2)	1	1.26	2	(3.0)	2	3.09	3	(1.3)	3	1.38
Gingival abscess	2	(2.6)	2	2.73	0				0				2	(0.9)	2	0.92
Gingivitis	2	(2.6)	2	2.73	0				0				2	(0.9)	2	0.92
Helicobacter infection	0				1	(1.2)	1	1.26	1	(1.5)	1	1.55	2	(0.9)	2	0.92
Nasopharyngitis	0				2	(2.4)	3	3.79	0				2	(0.9)	3	1.38
Oral herpes	1	(1.3)	1	1.37	0				1	(1.5)	1	1.55	2	(0.9)	2	0.92
Pneumonia	0				1	(1.2)	1	1.26	1	(1.5)	1	1.55	2	(0.9)	2	0.92
Acute sinusitis	0				1	(1.2)	2	2.53	0				1	(0.4)	2	0.92
Bronchitis bacterial	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Cellulitis	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Dermatophytosis of nail	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Folliculitis	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Gastroenteritis bacterial	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Helicobacter gastritis	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Herpes zoster meningitis	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65 <= < 75 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hordeolum	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Paronychia	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Pneumonia mycoplasmal	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Purulence	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Sinusitis	1	(1.3)	2	2.73	0				0				1	(0.4)	2	0.92
Skin infection	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Tinea infection	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Tinea pedis	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Tonsillitis	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Ureteritis	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Urethritis	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Urinary tract infection	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Vaginal infection	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Gastrointestinal disorders	25	(32.9)	47	64.24	18	(21.4)	32	40.40	26	(39.4)	43	66.46	69	(30.5)	122	56.20
Constipation	8	(10.5)	8	10.93	4	(4.8)	4	5.05	7	(10.6)	8	12.36	19	(8.4)	20	9.21
Nausea	3	(3.9)	3	4.10	1	(1.2)	1	1.26	6	(9.1)	7	10.82	10	(4.4)	11	5.07
Diarrhoea	3	(3.9)	3	4.10	3	(3.6)	3	3.79	3	(4.5)	3	4.64	9	(4.0)	9	4.15
Chronic gastritis	3	(3.9)	3	4.10	3	(3.6)	3	3.79	1	(1.5)	1	1.55	7	(3.1)	7	3.22
Gastrooesophageal reflux disease	3	(3.9)	3	4.10	3	(3.6)	3	3.79	1	(1.5)	1	1.55	7	(3.1)	7	3.22
Dental caries	2	(2.6)	2	2.73	2	(2.4)	2	2.53	2	(3.0)	2	3.09	6	(2.7)	6	2.76
Abdominal distension	3	(3.9)	3	4.10	0				2	(3.0)	2	3.09	5	(2.2)	5	2.30
Large intestine polyp	2	(2.6)	2	2.73	2	(2.4)	2	2.53	1	(1.5)	1	1.55	5	(2.2)	5	2.30
Periodontal disease	3	(3.9)	4	5.47	1	(1.2)	1	1.26	1	(1.5)	1	1.55	5	(2.2)	6	2.76
Abdominal pain upper	3	(3.9)	3	4.10	1	(1.2)	1	1.26	0				4	(1.8)	4	1.84
Stomatitis	4	(5.3)	4	5.47	0				0				4	(1.8)	4	1.84
Vomiting	1	(1.3)	1	1.37	1	(1.2)	1	1.26	2	(3.0)	3	4.64	4	(1.8)	5	2.30
Abdominal discomfort	0				1	(1.2)	1	1.26	2	(3.0)	2	3.09	3	(1.3)	3	1.38
Dyspepsia	1	(1.3)	1	1.37	1	(1.2)	1	1.26	1	(1.5)	1	1.55	3	(1.3)	3	1.38
Colitis	0				1	(1.2)	1	1.26	1	(1.5)	1	1.55	2	(0.9)	2	0.92
Enteritis	1	(1.3)	2	2.73	1	(1.2)	1	1.26	0				2	(0.9)	3	1.38
Faeces soft	0				1	(1.2)	1	1.26	1	(1.5)	1	1.55	2	(0.9)	2	0.92

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65 <= < 75 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hyperchlorhydria	0				1	(1.2)	1	1.26	1	(1.5)	1	1.55	2	(0.9)	2	0.92
Anal fissure	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Autoimmune pancreatitis	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Barrett's oesophagus	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Diverticulum intestinal	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Eructation	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Flatulence	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Gastric polyps	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Gastric ulcer	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Gastritis	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Gastrointestinal disorder	0				0				1	(1.5)	2	3.09	1	(0.4)	2	0.92
Haemorrhoidal haemorrhage	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Hypoaesthesia oral	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Inguinal hernia	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Oesophageal polyp	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Pancreatic cyst	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Pancreatitis acute	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Toothache	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Musculoskeletal and connective tissue disorders	16	(21.1)	21	28.70	20	(23.8)	27	34.09	13	(19.7)	17	26.27	49	(21.7)	65	29.94
Back pain	6	(7.9)	6	8.20	2	(2.4)	2	2.53	4	(6.1)	4	6.18	12	(5.3)	12	5.53
Spinal osteoarthritis	2	(2.6)	2	2.73	3	(3.6)	3	3.79	2	(3.0)	2	3.09	7	(3.1)	7	3.22
Arthralgia	2	(2.6)	2	2.73	1	(1.2)	1	1.26	2	(3.0)	3	4.64	5	(2.2)	6	2.76
Muscle spasms	3	(3.9)	3	4.10	1	(1.2)	1	1.26	1	(1.5)	1	1.55	5	(2.2)	5	2.30
Osteoarthritis	2	(2.6)	2	2.73	2	(2.4)	2	2.53	0				4	(1.8)	4	1.84
Trigger finger	0				3	(3.6)	3	3.79	1	(1.5)	1	1.55	4	(1.8)	4	1.84
Intervertebral disc protrusion	0				2	(2.4)	2	2.53	1	(1.5)	1	1.55	3	(1.3)	3	1.38
Myalgia	3	(3.9)	3	4.10	0				0				3	(1.3)	3	1.38
Tenosynovitis	0				2	(2.4)	2	2.53	1	(1.5)	1	1.55	3	(1.3)	3	1.38
Musculoskeletal pain	0				1	(1.2)	2	2.53	1	(1.5)	1	1.55	2	(0.9)	3	1.38
Neck pain	1	(1.3)	1	1.37	1	(1.2)	1	1.26	0				2	(0.9)	2	0.92

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65 <= < 75 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Spinal column stenosis	0				1	(1.2)	1	1.26	1	(1.5)	1	1.55	2	(0.9)	2	0.92
Bone pain	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Cervical spinal stenosis	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Flank pain	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Lumbar spinal stenosis	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Musculoskeletal chest pain	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Osteoporosis	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Pain in extremity	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Periarthritis	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Rheumatoid arthritis	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Spondylolisthesis	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Tendon pain	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Eye disorders	14	(18.4)	16	21.87	8	(9.5)	9	11.36	10	(15.2)	13	20.09	32	(14.2)	38	17.51
Diabetic retinopathy	2	(2.6)	2	2.73	5	(6.0)	5	6.31	4	(6.1)	4	6.18	11	(4.9)	11	5.07
Cataract	2	(2.6)	2	2.73	2	(2.4)	2	2.53	0				4	(1.8)	4	1.84
Glaucoma	1	(1.3)	1	1.37	0				2	(3.0)	2	3.09	3	(1.3)	3	1.38
Macular fibrosis	2	(2.6)	2	2.73	0				1	(1.5)	1	1.55	3	(1.3)	3	1.38
Asthenopia	0				0				2	(3.0)	2	3.09	2	(0.9)	2	0.92
Dry eye	1	(1.3)	1	1.37	0				1	(1.5)	1	1.55	2	(0.9)	2	0.92
Vision blurred	1	(1.3)	1	1.37	0				1	(1.5)	1	1.55	2	(0.9)	2	0.92
Blepharitis allergic	0				1	(1.2)	2	2.53	0				1	(0.4)	2	0.92
Conjunctivitis allergic	1	(1.3)	2	2.73	0				0				1	(0.4)	2	0.92
Cystoid macular oedema	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Diabetic retinal oedema	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Eye haemorrhage	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Keratitis	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Macular hole	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Posterior capsule opacification	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Retinal detachment	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65 <= < 75 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Injury, poisoning and procedural complications	8	(10.5)	9	12.30	12	(14.3)	14	17.68	9	(13.6)	12	18.55	29	(12.8)	35	16.12
Contusion	2	(2.6)	2	2.73	2	(2.4)	2	2.53	3	(4.5)	4	6.18	7	(3.1)	8	3.69
Arthropod bite	0				2	(2.4)	2	2.53	0				2	(0.9)	2	0.92
Arthropod sting	0				1	(1.2)	2	2.53	1	(1.5)	1	1.55	2	(0.9)	3	1.38
Heat illness	1	(1.3)	1	1.37	0				1	(1.5)	1	1.55	2	(0.9)	2	0.92
Spinal compression fracture	1	(1.3)	1	1.37	0				1	(1.5)	1	1.55	2	(0.9)	2	0.92
Accidental overdose	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Bone contusion	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Foreign body in eye	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Hand fracture	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Head injury	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Heat stroke	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Incorrect dose administered	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Laceration	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Ligament sprain	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Lower limb fracture	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Lumbar vertebral fracture	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Meniscus injury	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Overdose	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Pubis fracture	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Rib fracture	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Thermal burn	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Thoracic vertebral fracture	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Wound	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Nervous system disorders	5	(6.6)	6	8.20	14	(16.7)	17	21.46	8	(12.1)	9	13.91	27	(11.9)	32	14.74
Dizziness	1	(1.3)	1	1.37	4	(4.8)	5	6.31	1	(1.5)	1	1.55	6	(2.7)	7	3.22
Hypoaesthesia	2	(2.6)	3	4.10	2	(2.4)	2	2.53	1	(1.5)	1	1.55	5	(2.2)	6	2.76
Headache	1	(1.3)	1	1.37	1	(1.2)	1	1.26	2	(3.0)	2	3.09	4	(1.8)	4	1.84
Facial paralysis	0				2	(2.4)	2	2.53	1	(1.5)	1	1.55	3	(1.3)	3	1.38
Carotid arteriosclerosis	0				2	(2.4)	2	2.53	0				2	(0.9)	2	0.92
Diabetic neuropathy	0				1	(1.2)	1	1.26	1	(1.5)	1	1.55	2	(0.9)	2	0.92

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65 <= < 75 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Carpal tunnel syndrome	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Head discomfort	0				0				1	(1.5)	2	3.09	1	(0.4)	2	0.92
Intercostal neuralgia	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Migraine	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Neuropathy peripheral	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Presyncope	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Tongue biting	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Skin and subcutaneous tissue disorders	11	(14.5)	12	16.40	9	(10.7)	12	15.15	6	(9.1)	7	10.82	26	(11.5)	31	14.28
Eczema	6	(7.9)	6	8.20	3	(3.6)	3	3.79	2	(3.0)	2	3.09	11	(4.9)	11	5.07
Pruritus	1	(1.3)	1	1.37	1	(1.2)	2	2.53	1	(1.5)	1	1.55	3	(1.3)	4	1.84
Dermatitis contact	1	(1.3)	1	1.37	0				1	(1.5)	1	1.55	2	(0.9)	2	0.92
Rash	1	(1.3)	1	1.37	1	(1.2)	1	1.26	0				2	(0.9)	2	0.92
Urticaria	1	(1.3)	1	1.37	1	(1.2)	1	1.26	0				2	(0.9)	2	0.92
Chronic pigmented purpura	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Dermatitis	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Drug eruption	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Haemorrhage subcutaneous	0				1	(1.2)	3	3.79	0				1	(0.4)	3	1.38
Ingrowing nail	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Miliaria	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Pigmentation disorder	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Skin mass	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Investigations	6	(7.9)	8	10.93	6	(7.1)	6	7.58	9	(13.6)	12	18.55	21	(9.3)	26	11.98
Amylase increased	1	(1.3)	1	1.37	0				3	(4.5)	3	4.64	4	(1.8)	4	1.84
Lipase increased	2	(2.6)	2	2.73	0				2	(3.0)	2	3.09	4	(1.8)	4	1.84
Helicobacter test positive	2	(2.6)	2	2.73	0				1	(1.5)	1	1.55	3	(1.3)	3	1.38
Weight increased	0				3	(3.6)	3	3.79	0				3	(1.3)	3	1.38
Blood proinsulin decreased	1	(1.3)	1	1.37	0				1	(1.5)	1	1.55	2	(0.9)	2	0.92
Pancreatic enzymes increased	0				0				2	(3.0)	2	3.09	2	(0.9)	2	0.92
Cardiac murmur	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65 <= < 75 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Carotid intima-media thickness increased	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Eosinophil count increased	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Glomerular filtration rate decreased	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Hepatic enzyme increased	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Insulin C-peptide decreased	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Intraocular pressure increased	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Waist circumference increased	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
General disorders and administration site conditions	3	(3.9)	3	4.10	9	(10.7)	9	11.36	6	(9.1)	7	10.82	18	(8.0)	19	8.75
Asthenia	0				2	(2.4)	2	2.53	0				2	(0.9)	2	0.92
Injection site reaction	1	(1.3)	1	1.37	0				1	(1.5)	1	1.55	2	(0.9)	2	0.92
Malaise	0				1	(1.2)	1	1.26	1	(1.5)	2	3.09	2	(0.9)	3	1.38
Oedema peripheral	1	(1.3)	1	1.37	1	(1.2)	1	1.26	0				2	(0.9)	2	0.92
Fatigue	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Infusion site bruising	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Injection site bruising	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Injection site erythema	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Injection site pruritus	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Injection site swelling	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Oedema	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Pain	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Pyrexia	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Thirst	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Respiratory, thoracic and mediastinal disorders	8	(10.5)	10	13.67	8	(9.5)	11	13.89	2	(3.0)	2	3.09	18	(8.0)	23	10.60

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65 <= < 75 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Upper respiratory tract inflammation	1	(1.3)	1	1.37	2	(2.4)	3	3.79	1	(1.5)	1	1.55	4	(1.8)	5	2.30
Asthma	2	(2.6)	2	2.73	0				1	(1.5)	1	1.55	3	(1.3)	3	1.38
Cough	0				3	(3.6)	4	5.05	0				3	(1.3)	4	1.84
Oropharyngeal pain	1	(1.3)	1	1.37	1	(1.2)	1	1.26	0				2	(0.9)	2	0.92
Bronchitis chronic	1	(1.3)	2	2.73	0				0				1	(0.4)	2	0.92
Chronic obstructive pulmonary disease	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Dysphonia	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Emphysema	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Respiratory disorder	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Rhinitis allergic	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Rhinorrhoea	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Sleep apnoea syndrome	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Vascular disorders	6	(7.9)	6	8.20	9	(10.7)	9	11.36	3	(4.5)	4	6.18	18	(8.0)	19	8.75
Hypertension	4	(5.3)	4	5.47	6	(7.1)	6	7.58	1	(1.5)	1	1.55	11	(4.9)	11	5.07
Arteriosclerosis	1	(1.3)	1	1.37	0				1	(1.5)	1	1.55	2	(0.9)	2	0.92
Hot flush	1	(1.3)	1	1.37	0				1	(1.5)	1	1.55	2	(0.9)	2	0.92
Peripheral arterial occlusive disease	0				2	(2.4)	2	2.53	0				2	(0.9)	2	0.92
Hypotension	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Varicose vein	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Cardiac disorders	4	(5.3)	4	5.47	6	(7.1)	6	7.58	4	(6.1)	4	6.18	14	(6.2)	14	6.45
Angina pectoris	2	(2.6)	2	2.73	0				0				2	(0.9)	2	0.92
Atrial fibrillation	0				1	(1.2)	1	1.26	1	(1.5)	1	1.55	2	(0.9)	2	0.92
Ventricular extrasystoles	2	(2.6)	2	2.73	0				0				2	(0.9)	2	0.92
Acute myocardial infarction	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Atrioventricular block complete	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Atrioventricular block first degree	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46

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R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65 <= < 75 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Cardiomegaly	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Myocardial ischaemia	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Palpitations	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Supraventricular extrasystoles	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Supraventricular tachycardia	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Hepatobiliary disorders	3	(3.9)	4	5.47	5	(6.0)	9	11.36	2	(3.0)	2	3.09	10	(4.4)	15	6.91
Cholelithiasis	1	(1.3)	1	1.37	2	(2.4)	2	2.53	1	(1.5)	1	1.55	4	(1.8)	4	1.84
Hepatic steatosis	2	(2.6)	2	2.73	2	(2.4)	2	2.53	0				4	(1.8)	4	1.84
Cholecystitis	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Chronic hepatitis	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Gallbladder polyp	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Hepatic calcification	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Hepatic cyst	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Hepatic mass	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Non-alcoholic fatty liver	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Renal and urinary disorders	7	(9.2)	7	9.57	2	(2.4)	2	2.53	1	(1.5)	1	1.55	10	(4.4)	10	4.61
Renal cyst	4	(5.3)	4	5.47	0				1	(1.5)	1	1.55	5	(2.2)	5	2.30
Nephrolithiasis	1	(1.3)	1	1.37	2	(2.4)	2	2.53	0				3	(1.3)	3	1.38
Diabetic nephropathy	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Urinary retention	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Metabolism and nutrition disorders	2	(2.6)	2	2.73	2	(2.4)	2	2.53	5	(7.6)	5	7.73	9	(4.0)	9	4.15
Decreased appetite	0				1	(1.2)	1	1.26	5	(7.6)	5	7.73	6	(2.7)	6	2.76
Dehydration	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Hyperlipasaemia	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Hyperuricaemia	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Ear and labyrinth disorders	3	(3.9)	3	4.10	3	(3.6)	3	3.79	1	(1.5)	1	1.55	7	(3.1)	7	3.22
Vertigo	2	(2.6)	2	2.73	1	(1.2)	1	1.26	1	(1.5)	1	1.55	4	(1.8)	4	1.84

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65 <= < 75 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Tinnitus	1	(1.3)	1	1.37	1	(1.2)	1	1.26	0				2	(0.9)	2	0.92
Otorrhoea	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(1.3)	1	1.37	3	(3.6)	5	6.31	2	(3.0)	2	3.09	6	(2.7)	8	3.69
Adrenal neoplasm	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Basal cell carcinoma	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Benign neoplasm of thyroid gland	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Colon adenoma	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Gastric cancer stage I	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Lung adenocarcinoma	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Lung neoplasm malignant	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Metastases to lymph nodes	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Psychiatric disorders	1	(1.3)	1	1.37	4	(4.8)	4	5.05	1	(1.5)	1	1.55	6	(2.7)	6	2.76
Insomnia	1	(1.3)	1	1.37	2	(2.4)	2	2.53	1	(1.5)	1	1.55	4	(1.8)	4	1.84
Depression	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Neurosis	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Endocrine disorders	1	(1.3)	1	1.37	3	(3.6)	4	5.05	1	(1.5)	1	1.55	5	(2.2)	6	2.76
Thyroid cyst	0				3	(3.6)	3	3.79	1	(1.5)	1	1.55	4	(1.8)	4	1.84
Thyroid mass	1	(1.3)	1	1.37	1	(1.2)	1	1.26	0				2	(0.9)	2	0.92
Reproductive system and breast disorders	1	(1.3)	1	1.37	2	(2.4)	2	2.53	0				3	(1.3)	3	1.38
Gynaecomastia	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Prostatic calcification	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Pruritus genital	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Blood and lymphatic system disorders	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65 <= < 75 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Iron deficiency anaemia	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Immune system disorders	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Seasonal allergy	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Surgical and medical procedures	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Cardiac ablation	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-26 ベースラインの年齢が 75 歳以上の被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	2				4				5				11			
PYE (years)	1.83				3.22				5.10				10.15			
Events	2	(100.0)	11	602.36	3	(75.0)	8	248.47	5	(100.0)	26	509.47	10	(90.9)	45	443.38
Gastrointestinal disorders	1	(50.0)	7	383.32	1	(25.0)	1	31.06	4	(80.0)	5	97.97	6	(54.5)	13	128.09
Chronic gastritis	1	(50.0)	1	54.76	0				1	(20.0)	2	39.19	2	(18.2)	3	29.56
Constipation	1	(50.0)	1	54.76	0				1	(20.0)	1	19.59	2	(18.2)	2	19.71
Nausea	0				0				2	(40.0)	2	39.19	2	(18.2)	2	19.71
Diarrhoea	0				1	(25.0)	1	31.06	0				1	(9.1)	1	9.85
Food poisoning	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85
Gastric polyps	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85
Gastroduodenitis	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85
Gastrooesophageal reflux disease	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85
Proctitis	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85
Eye disorders	0				1	(25.0)	1	31.06	3	(60.0)	5	97.97	4	(36.4)	6	59.12
Cataract	0				1	(25.0)	1	31.06	2	(40.0)	2	39.19	3	(27.3)	3	29.56
Astigmatism	0				0				1	(20.0)	1	19.59	1	(9.1)	1	9.85
Blepharitis	0				0				1	(20.0)	1	19.59	1	(9.1)	1	9.85
Macular degeneration	0				0				1	(20.0)	1	19.59	1	(9.1)	1	9.85
Infections and infestations	1	(50.0)	1	54.76	1	(25.0)	3	93.18	2	(40.0)	7	137.16	4	(36.4)	11	108.38
Viral upper respiratory tract infection	0				1	(25.0)	1	31.06	1	(20.0)	3	58.78	2	(18.2)	4	39.41
Bronchitis	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85
Gastroenteritis	0				0				1	(20.0)	2	39.19	1	(9.1)	2	19.71
Herpes virus infection	0				0				1	(20.0)	1	19.59	1	(9.1)	1	9.85
Localised infection	0				1	(25.0)	1	31.06	0				1	(9.1)	1	9.85
Nasopharyngitis	0				0				1	(20.0)	1	19.59	1	(9.1)	1	9.85
Urinary tract infection	0				1	(25.0)	1	31.06	0				1	(9.1)	1	9.85

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PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 75 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Cardiac disorders	1	(50.0)	1	54.76	0				2	(40.0)	2	39.19	3	(27.3)	3	29.56
Atrial fibrillation	0				0				1	(20.0)	1	19.59	1	(9.1)	1	9.85
Cardiac disorder	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85
Sinus arrhythmia	0				0				1	(20.0)	1	19.59	1	(9.1)	1	9.85
Nervous system disorders	0				2	(50.0)	2	62.12	1	(20.0)	1	19.59	3	(27.3)	3	29.56
Diabetic neuropathy	0				1	(25.0)	1	31.06	0				1	(9.1)	1	9.85
Dizziness	0				1	(25.0)	1	31.06	0				1	(9.1)	1	9.85
Headache	0				0				1	(20.0)	1	19.59	1	(9.1)	1	9.85
General disorders and administration site conditions	0				1	(25.0)	1	31.06	1	(20.0)	1	19.59	2	(18.2)	2	19.71
Chest discomfort	0				0				1	(20.0)	1	19.59	1	(9.1)	1	9.85
Oedema	0				1	(25.0)	1	31.06	0				1	(9.1)	1	9.85
Musculoskeletal and connective tissue disorders	0				0				2	(40.0)	5	97.97	2	(18.2)	5	49.26
Arthralgia	0				0				1	(20.0)	1	19.59	1	(9.1)	1	9.85
Back pain	0				0				1	(20.0)	1	19.59	1	(9.1)	1	9.85
Muscle spasms	0				0				1	(20.0)	2	39.19	1	(9.1)	2	19.71
Myalgia	0				0				1	(20.0)	1	19.59	1	(9.1)	1	9.85
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85
Benign neoplasm of bladder	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85
Psychiatric disorders	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85
Insomnia	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85

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MedDRA version 20.0

2.7.4.7.1-27 ベースラインの年齢が 65 歳未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	75				85				160			
PYE (years)	38.80				43.35				82.16			
Events	58	(77.3)	187	481.91	65	(76.5)	169	389.82	123	(76.9)	356	433.31
Infections and infestations	27	(36.0)	44	113.39	30	(35.3)	40	92.26	57	(35.6)	84	102.24
Viral upper respiratory tract infection	16	(21.3)	20	51.54	20	(23.5)	25	57.66	36	(22.5)	45	54.77
Bronchitis	1	(1.3)	1	2.58	4	(4.7)	4	9.23	5	(3.1)	5	6.09
Gastroenteritis	4	(5.3)	6	15.46	1	(1.2)	1	2.31	5	(3.1)	7	8.52
Pharyngitis	4	(5.3)	5	12.89	1	(1.2)	2	4.61	5	(3.1)	7	8.52
Influenza	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43
Periodontitis	2	(2.7)	2	5.15	0				2	(1.3)	2	2.43
Sinusitis	2	(2.7)	2	5.15	0				2	(1.3)	2	2.43
Upper respiratory tract infection	1	(1.3)	1	2.58	1	(1.2)	2	4.61	2	(1.3)	3	3.65
Abscess	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Adenoviral conjunctivitis	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Cystitis	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Gingivitis	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Herpes zoster	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Hordeolum	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Infected dermal cyst	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Tinea pedis	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Tonsillitis	1	(1.3)	2	5.15	0				1	(0.6)	2	2.43
Upper respiratory tract infection bacterial	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Gastrointestinal disorders	31	(41.3)	56	144.32	17	(20.0)	28	64.58	48	(30.0)	84	102.24
Diarrhoea	12	(16.0)	16	41.23	4	(4.7)	5	11.53	16	(10.0)	21	25.56
Abdominal discomfort	5	(6.7)	5	12.89	4	(4.7)	4	9.23	9	(5.6)	9	10.95
Nausea	6	(8.0)	6	15.46	3	(3.5)	4	9.23	9	(5.6)	10	12.17
Constipation	6	(8.0)	7	18.04	1	(1.2)	1	2.31	7	(4.4)	8	9.74
Vomiting	3	(4.0)	4	10.31	2	(2.4)	2	4.61	5	(3.1)	6	7.30
Chronic gastritis	2	(2.7)	2	5.15	1	(1.2)	1	2.31	3	(1.9)	3	3.65

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Gastritis	2	(2.7)	2	5.15	1	(1.2)	1	2.31	3	(1.9)	3	3.65
Gastrooesophageal reflux disease	2	(2.7)	2	5.15	1	(1.2)	1	2.31	3	(1.9)	3	3.65
Abdominal pain	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43
Dental caries	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43
Enteritis	1	(1.3)	2	5.15	1	(1.2)	1	2.31	2	(1.3)	3	3.65
Faeces soft	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43
Hiatus hernia	2	(2.7)	2	5.15	0				2	(1.3)	2	2.43
Abdominal distension	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Duodenal ulcer	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Dyspepsia	1	(1.3)	2	5.15	0				1	(0.6)	2	2.43
Gastritis erosive	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Gastrointestinal motility disorder	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Glossitis	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Large intestine polyp	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Oesophageal disorder	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Stomatitis	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Eye disorders	18	(24.0)	20	51.54	19	(22.4)	22	50.75	37	(23.1)	42	51.12
Diabetic retinopathy	14	(18.7)	15	38.66	16	(18.8)	17	39.21	30	(18.8)	32	38.95
Cataract	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43
Blepharospasm	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Cataract nuclear	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Conjunctival haemorrhage	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Dry eye	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Pingueculitis	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Posterior capsule opacification	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Retinal detachment	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Retinal haemorrhage	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Musculoskeletal and connective tissue disorders	7	(9.3)	10	25.77	11	(12.9)	11	25.37	18	(11.3)	21	25.56
Back pain	3	(4.0)	3	7.73	4	(4.7)	4	9.23	7	(4.4)	7	8.52
Arthralgia	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43
Intervertebral disc protrusion	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Musculoskeletal pain	2	(2.7)	2	5.15	0				2	(1.3)	2	2.43
Periarthritis	0				2	(2.4)	2	4.61	2	(1.3)	2	2.43
Arthritis	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Flank pain	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Muscle spasms	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Neck pain	1	(1.3)	2	5.15	0				1	(0.6)	2	2.43
Tenosynovitis	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
General disorders and administration site conditions	5	(6.7)	5	12.89	10	(11.8)	10	23.07	15	(9.4)	15	18.26
Inflammation	1	(1.3)	1	2.58	2	(2.4)	2	4.61	3	(1.9)	3	3.65
Pyrexia	1	(1.3)	1	2.58	2	(2.4)	2	4.61	3	(1.9)	3	3.65
Administration site induration	0				2	(2.4)	2	4.61	2	(1.3)	2	2.43
Malaise	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43
Oedema peripheral	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43
Induration	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Injection site discomfort	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Injection site induration	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Metabolism and nutrition disorders	13	(17.3)	13	33.50	2	(2.4)	2	4.61	15	(9.4)	15	18.26
Decreased appetite	6	(8.0)	6	15.46	0				6	(3.8)	6	7.30
Dyslipidaemia	2	(2.7)	2	5.15	1	(1.2)	1	2.31	3	(1.9)	3	3.65
Hyperuricaemia	3	(4.0)	3	7.73	0				3	(1.9)	3	3.65
Gout	2	(2.7)	2	5.15	0				2	(1.3)	2	2.43
Dehydration	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Nervous system disorders	6	(8.0)	6	15.46	8	(9.4)	11	25.37	14	(8.8)	17	20.69
Headache	3	(4.0)	3	7.73	1	(1.2)	1	2.31	4	(2.5)	4	4.87
Dizziness	0				3	(3.5)	4	9.23	3	(1.9)	4	4.87
Diabetic neuropathy	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43
Carpal tunnel syndrome	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Dysgeusia	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Hypoaesthesia	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Loss of consciousness	0				1	(1.2)	2	4.61	1	(0.6)	2	2.43
Migraine	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Sciatica	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Injury, poisoning and procedural complications	6	(8.0)	8	20.62	7	(8.2)	8	18.45	13	(8.1)	16	19.47
Contusion	1	(1.3)	1	2.58	2	(2.4)	2	4.61	3	(1.9)	3	3.65
Laceration	2	(2.7)	2	5.15	1	(1.2)	1	2.31	3	(1.9)	3	3.65
Arthropod bite	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Excoriation	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Fall	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Foot fracture	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Fractured coccyx	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Hip fracture	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Thermal burn	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Tibia fracture	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Tooth fracture	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Tooth injury	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Skin and subcutaneous tissue disorders	3	(4.0)	4	10.31	9	(10.6)	9	20.76	12	(7.5)	13	15.82
Eczema	2	(2.7)	2	5.15	4	(4.7)	4	9.23	6	(3.8)	6	7.30
Acne	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Hyperkeratosis	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Miliaria	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Penile ulceration	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Rash	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Skin irritation	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Skin swelling	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Investigations	5	(6.7)	5	12.89	3	(3.5)	3	6.92	8	(5.0)	8	9.74
Lipase increased	2	(2.7)	2	5.15	0				2	(1.3)	2	2.43
Electrocardiogram T wave inversion	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Free fatty acids decreased	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Gamma-glutamyltransferase increased	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Glomerular filtration rate decreased	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Helicobacter test positive	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Weight decreased	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Respiratory, thoracic and mediastinal disorders	3	(4.0)	4	10.31	5	(5.9)	5	11.53	8	(5.0)	9	10.95
Upper respiratory tract inflammation	1	(1.3)	2	5.15	2	(2.4)	2	4.61	3	(1.9)	4	4.87
Cough	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43
Bronchitis chronic	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Oropharyngeal pain	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Respiratory tract inflammation	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Vascular disorders	4	(5.3)	4	10.31	2	(2.4)	2	4.61	6	(3.8)	6	7.30
Hypertension	2	(2.7)	2	5.15	2	(2.4)	2	4.61	4	(2.5)	4	4.87
Arteriosclerosis	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Orthostatic hypotension	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Renal and urinary disorders	2	(2.7)	4	10.31	3	(3.5)	3	6.92	5	(3.1)	7	8.52
Nephrolithiasis	1	(1.3)	1	2.58	2	(2.4)	2	4.61	3	(1.9)	3	3.65
Renal cyst	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43
Haematuria	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Ureterolithiasis	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Ear and labyrinth disorders	1	(1.3)	1	2.58	2	(2.4)	3	6.92	3	(1.9)	4	4.87
Vertigo	1	(1.3)	1	2.58	2	(2.4)	3	6.92	3	(1.9)	4	4.87
Hepatobiliary disorders	0				3	(3.5)	3	6.92	3	(1.9)	3	3.65
Cholecystitis acute	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Cholelithiasis	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Hepatic steatosis	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Psychiatric disorders	1	(1.3)	1	2.58	2	(2.4)	2	4.61	3	(1.9)	3	3.65
Insomnia	1	(1.3)	1	2.58	2	(2.4)	2	4.61	3	(1.9)	3	3.65

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43
Adenocarcinoma	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Pancreatic carcinoma	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Blood and lymphatic system disorders	0				1	(1.2)	3	6.92	1	(0.6)	3	3.65
Leukopenia	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Lymphopenia	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Neutropenia	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Immune system disorders	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Seasonal allergy	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Reproductive system and breast disorders	0				1	(1.2)	3	6.92	1	(0.6)	3	3.65
Uterine cyst	0				1	(1.2)	2	4.61	1	(0.6)	2	2.43
Uterine mass	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22

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2.7.4.7.1-28 ベースラインの年齢が 65 歳以上の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	30				20				50			
PYE (years)	15.47				8.91				24.39			
Events	24	(80.0)	93	601.00	15	(75.0)	41	460.07	39	(78.0)	134	549.49
Gastrointestinal disorders	14	(46.7)	32	206.79	7	(35.0)	12	134.65	21	(42.0)	44	180.43
Constipation	3	(10.0)	3	19.39	3	(15.0)	3	33.66	6	(12.0)	6	24.60
Vomiting	6	(20.0)	7	45.24	0				6	(12.0)	7	28.70
Nausea	4	(13.3)	6	38.77	1	(5.0)	1	11.22	5	(10.0)	7	28.70
Abdominal discomfort	3	(10.0)	3	19.39	1	(5.0)	1	11.22	4	(8.0)	4	16.40
Diarrhoea	3	(10.0)	4	25.85	1	(5.0)	1	11.22	4	(8.0)	5	20.50
Dyspepsia	2	(6.7)	2	12.92	1	(5.0)	1	11.22	3	(6.0)	3	12.30
Gastrooesophageal reflux disease	1	(3.3)	1	6.46	1	(5.0)	1	11.22	2	(4.0)	2	8.20
Chronic gastritis	1	(3.3)	2	12.92	0				1	(2.0)	2	8.20
Epigastric discomfort	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Food poisoning	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Gastritis erosive	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Hiatus hernia	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Hyperchlorhydria	1	(3.3)	2	12.92	0				1	(2.0)	2	8.20
Periodontal disease	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Varices oesophageal	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Infections and infestations	8	(26.7)	13	84.01	8	(40.0)	12	134.65	16	(32.0)	25	102.52
Viral upper respiratory tract infection	5	(16.7)	7	45.24	4	(20.0)	5	56.11	9	(18.0)	12	49.21
Herpes zoster	1	(3.3)	1	6.46	1	(5.0)	1	11.22	2	(4.0)	2	8.20
Bronchitis	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Cellulitis	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Cystitis	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Gastroenteritis	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Herpes simplex	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Influenza	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Otitis externa	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10

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Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Pharyngitis	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Sinusitis	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Upper respiratory tract infection	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Urinary tract infection	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Musculoskeletal and connective tissue disorders	7	(23.3)	8	51.70	3	(15.0)	4	44.88	10	(20.0)	12	49.21
Back pain	2	(6.7)	3	19.39	1	(5.0)	1	11.22	3	(6.0)	4	16.40
Arthralgia	2	(6.7)	2	12.92	0				2	(4.0)	2	8.20
Muscle spasms	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Musculoskeletal stiffness	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Myalgia	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Osteoarthritis	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Tenosynovitis	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Trigger finger	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Injury, poisoning and procedural complications	4	(13.3)	6	38.77	3	(15.0)	3	33.66	7	(14.0)	9	36.91
Contusion	1	(3.3)	1	6.46	1	(5.0)	1	11.22	2	(4.0)	2	8.20
Fall	2	(6.7)	2	12.92	0				2	(4.0)	2	8.20
Heat illness	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Heat stroke	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Ligament sprain	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Postoperative fever	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Wrong drug administered	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Nervous system disorders	3	(10.0)	5	32.31	3	(15.0)	3	33.66	6	(12.0)	8	32.81
Dizziness	2	(6.7)	2	12.92	1	(5.0)	1	11.22	3	(6.0)	3	12.30
Hypoaesthesia	1	(3.3)	1	6.46	1	(5.0)	1	11.22	2	(4.0)	2	8.20
Carpal tunnel syndrome	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Lacunar infarction	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Neuropathy peripheral	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Eye disorders	4	(13.3)	4	25.85	1	(5.0)	1	11.22	5	(10.0)	5	20.50
Diabetic retinopathy	3	(10.0)	3	19.39	1	(5.0)	1	11.22	4	(8.0)	4	16.40

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Retinopathy	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
General disorders and administration site conditions	4	(13.3)	5	32.31	0				4	(8.0)	5	20.50
Generalised oedema	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Malaise	1	(3.3)	2	12.92	0				1	(2.0)	2	8.20
Oedema peripheral	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Pyrexia	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Investigations	2	(6.7)	2	12.92	2	(10.0)	2	22.44	4	(8.0)	4	16.40
Helicobacter test positive	0				2	(10.0)	2	22.44	2	(4.0)	2	8.20
Electrocardiogram ST-T segment depression	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Oxygen saturation decreased	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Respiratory, thoracic and mediastinal disorders	3	(10.0)	5	32.31	1	(5.0)	1	11.22	4	(8.0)	6	24.60
Atelectasis	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Oropharyngeal pain	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Pleural effusion	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Sputum increased	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Sputum retention	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Upper respiratory tract inflammation	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Metabolism and nutrition disorders	2	(6.7)	2	12.92	1	(5.0)	1	11.22	3	(6.0)	3	12.30
Decreased appetite	2	(6.7)	2	12.92	0				2	(4.0)	2	8.20
Gout	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Cardiac disorders	2	(6.7)	3	19.39	0				2	(4.0)	3	12.30
Acute myocardial infarction	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Cardiac failure congestive	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Supraventricular extrasystoles	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(3.3)	1	6.46	1	(5.0)	1	11.22	2	(4.0)	2	8.20

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Renal cell carcinoma	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Uterine leiomyoma	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Renal and urinary disorders	2	(6.7)	3	19.39	0				2	(4.0)	3	12.30
Acute kidney injury	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Nephrolithiasis	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Renal cyst	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Skin and subcutaneous tissue disorders	1	(3.3)	1	6.46	1	(5.0)	1	11.22	2	(4.0)	2	8.20
Dermatitis	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Pustular psoriasis	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Endocrine disorders	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Thyroid mass	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Hepatobiliary disorders	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Hepatic cirrhosis	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Vascular disorders	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Hypertension	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-29 ベースラインの年齢が 65 歳以上 75 歳未満の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	28				19				47			
PYE (years)	14.44				8.66				23.10			
Events	22	(78.6)	69	477.86	14	(73.7)	40	461.76	36	(76.6)	109	471.82
Gastrointestinal disorders	12	(42.9)	27	186.99	7	(36.8)	12	138.53	19	(40.4)	39	168.82
Constipation	2	(7.1)	2	13.85	3	(15.8)	3	34.63	5	(10.6)	5	21.64
Vomiting	5	(17.9)	6	41.55	0				5	(10.6)	6	25.97
Abdominal discomfort	3	(10.7)	3	20.78	1	(5.3)	1	11.54	4	(8.5)	4	17.31
Diarrhoea	3	(10.7)	4	27.70	1	(5.3)	1	11.54	4	(8.5)	5	21.64
Nausea	3	(10.7)	4	27.70	1	(5.3)	1	11.54	4	(8.5)	5	21.64
Dyspepsia	1	(3.6)	1	6.93	1	(5.3)	1	11.54	2	(4.3)	2	8.66
Gastrooesophageal reflux disease	1	(3.6)	1	6.93	1	(5.3)	1	11.54	2	(4.3)	2	8.66
Chronic gastritis	1	(3.6)	2	13.85	0				1	(2.1)	2	8.66
Epigastric discomfort	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Food poisoning	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Gastritis erosive	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Hiatus hernia	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Hyperchlorhydria	1	(3.6)	2	13.85	0				1	(2.1)	2	8.66
Periodontal disease	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Varices oesophageal	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Infections and infestations	8	(28.6)	13	90.03	7	(36.8)	11	126.98	15	(31.9)	24	103.89
Viral upper respiratory tract infection	5	(17.9)	7	48.48	3	(15.8)	4	46.18	8	(17.0)	11	47.61
Herpes zoster	1	(3.6)	1	6.93	1	(5.3)	1	11.54	2	(4.3)	2	8.66
Bronchitis	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Cellulitis	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Cystitis	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Gastroenteritis	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Herpes simplex	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Influenza	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Otitis externa	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65<= <75 years - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Pharyngitis	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Sinusitis	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Upper respiratory tract infection	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Urinary tract infection	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Musculoskeletal and connective tissue disorders	6	(21.4)	6	41.55	3	(15.8)	4	46.18	9	(19.1)	10	43.29
Arthralgia	2	(7.1)	2	13.85	0				2	(4.3)	2	8.66
Back pain	1	(3.6)	1	6.93	1	(5.3)	1	11.54	2	(4.3)	2	8.66
Muscle spasms	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Musculoskeletal stiffness	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Myalgia	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Osteoarthritis	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Tenosynovitis	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Trigger finger	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Injury, poisoning and procedural complications	3	(10.7)	4	27.70	3	(15.8)	3	34.63	6	(12.8)	7	30.30
Contusion	1	(3.6)	1	6.93	1	(5.3)	1	11.54	2	(4.3)	2	8.66
Fall	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Heat illness	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Heat stroke	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Ligament sprain	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Wrong drug administered	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Eye disorders	4	(14.3)	4	27.70	1	(5.3)	1	11.54	5	(10.6)	5	21.64
Diabetic retinopathy	3	(10.7)	3	20.78	1	(5.3)	1	11.54	4	(8.5)	4	17.31
Retinopathy	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Nervous system disorders	2	(7.1)	2	13.85	3	(15.8)	3	34.63	5	(10.6)	5	21.64
Dizziness	1	(3.6)	1	6.93	1	(5.3)	1	11.54	2	(4.3)	2	8.66
Carpal tunnel syndrome	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Hypoaesthesia	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Neuropathy peripheral	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65<= <75 years - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
General disorders and administration site conditions	3	(10.7)	4	27.70	0				3	(6.4)	4	17.31
Malaise	1	(3.6)	2	13.85	0				1	(2.1)	2	8.66
Oedema peripheral	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Pyrexia	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Investigations	1	(3.6)	1	6.93	2	(10.5)	2	23.09	3	(6.4)	3	12.99
Helicobacter test positive	0				2	(10.5)	2	23.09	2	(4.3)	2	8.66
Electrocardiogram ST-T segment depression	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Respiratory, thoracic and mediastinal disorders	2	(7.1)	2	13.85	1	(5.3)	1	11.54	3	(6.4)	3	12.99
Oropharyngeal pain	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Sputum retention	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Upper respiratory tract inflammation	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Metabolism and nutrition disorders	1	(3.6)	1	6.93	1	(5.3)	1	11.54	2	(4.3)	2	8.66
Decreased appetite	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Gout	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Skin and subcutaneous tissue disorders	1	(3.6)	1	6.93	1	(5.3)	1	11.54	2	(4.3)	2	8.66
Dermatitis	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Pustular psoriasis	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Cardiac disorders	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Supraventricular extrasystoles	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Endocrine disorders	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Thyroid mass	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Hepatobiliary disorders	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Hepatic cirrhosis	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65<= <75 years - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Renal cell carcinoma	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Renal and urinary disorders	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
Acute kidney injury	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-30 ベースラインの年齢が 75 歳以上の被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	2				1				3			
PYE (years)	1.03				0.25				1.28			
Events	2	(100.0)	24	2319.05	1	(100.0)	1	401.37	3	(100.0)	25	1946.96
Gastrointestinal disorders	2	(100.0)	5	483.13	0				2	(66.7)	5	389.39
Constipation	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Dyspepsia	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Nausea	1	(50.0)	2	193.25	0				1	(33.3)	2	155.76
Vomiting	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Cardiac disorders	1	(50.0)	2	193.25	0				1	(33.3)	2	155.76
Acute myocardial infarction	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Cardiac failure congestive	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
General disorders and administration site conditions	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Generalised oedema	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Infections and infestations	0				1	(100.0)	1	401.37	1	(33.3)	1	77.88
Viral upper respiratory tract infection	0				1	(100.0)	1	401.37	1	(33.3)	1	77.88
Injury, poisoning and procedural complications	1	(50.0)	2	193.25	0				1	(33.3)	2	155.76
Fall	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Postoperative fever	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Investigations	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Oxygen saturation decreased	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Metabolism and nutrition disorders	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Decreased appetite	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 75 years - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Musculoskeletal and connective tissue disorders	1	(50.0)	2	193.25	0				1	(33.3)	2	155.76
Back pain	1	(50.0)	2	193.25	0				1	(33.3)	2	155.76
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Uterine leiomyoma	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Nervous system disorders	1	(50.0)	3	289.88	0				1	(33.3)	3	233.64
Dizziness	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Hypoaesthesia	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Lacunar infarction	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Renal and urinary disorders	1	(50.0)	2	193.25	0				1	(33.3)	2	155.76
Nephrolithiasis	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Renal cyst	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Respiratory, thoracic and mediastinal disorders	1	(50.0)	3	289.88	0				1	(33.3)	3	233.64
Atelectasis	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Pleural effusion	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Sputum increased	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Vascular disorders	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Hypertension	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-31 ベースライン時に正常腎機能を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	24				20				23				67			
PYE (years)	23.25				18.69				21.69				63.62			
Events	20	(83.3)	85	365.59	16	(80.0)	73	390.67	19	(82.6)	81	373.50	55	(82.1)	239	375.66
Infections and infestations	15	(62.5)	30	129.03	12	(60.0)	28	149.85	14	(60.9)	26	119.89	41	(61.2)	84	132.03
Viral upper respiratory tract infection	11	(45.8)	19	81.72	8	(40.0)	21	112.38	11	(47.8)	20	92.22	30	(44.8)	60	94.31
Influenza	3	(12.5)	3	12.90	0				2	(8.7)	2	9.22	5	(7.5)	5	7.86
Gastroenteritis	2	(8.3)	2	8.60	2	(10.0)	2	10.70	0				4	(6.0)	4	6.29
Helicobacter infection	0				2	(10.0)	2	10.70	0				2	(3.0)	2	3.14
Pharyngitis	1	(4.2)	1	4.30	1	(5.0)	1	5.35	0				2	(3.0)	2	3.14
Beta haemolytic streptococcal infection	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Bronchitis	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Conjunctivitis viral	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Gastroenteritis norovirus	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Gingivitis	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Helicobacter gastritis	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Herpes zoster	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Hordeolum	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Nasopharyngitis	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Periodontitis	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Pharyngotonsillitis	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Gastrointestinal disorders	6	(25.0)	17	73.12	6	(30.0)	20	107.03	11	(47.8)	23	106.06	23	(34.3)	60	94.31
Diarrhoea	2	(8.3)	3	12.90	2	(10.0)	2	10.70	4	(17.4)	4	18.44	8	(11.9)	9	14.15
Constipation	2	(8.3)	3	12.90	1	(5.0)	1	5.35	4	(17.4)	4	18.44	7	(10.4)	8	12.57
Dental caries	2	(8.3)	2	8.60	2	(10.0)	2	10.70	2	(8.7)	2	9.22	6	(9.0)	6	9.43
Nausea	1	(4.2)	2	8.60	2	(10.0)	4	21.41	3	(13.0)	7	32.28	6	(9.0)	13	20.43
Vomiting	1	(4.2)	3	12.90	1	(5.0)	1	5.35	4	(17.4)	4	18.44	6	(9.0)	8	12.57

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PYE: Patient years of exposure (1 PYE = 365.25 days),
Normal renal function: eGFR >= 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal renal function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Abdominal discomfort	2	(8.3)	2	8.60	0				2	(8.7)	2	9.22	4	(6.0)	4	6.29
Abdominal pain upper	1	(4.2)	2	8.60	1	(5.0)	1	5.35	0				2	(3.0)	3	4.72
Abdominal distension	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Abdominal pain	0				1	(5.0)	3	16.05	0				1	(1.5)	3	4.72
Chronic gastritis	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Gastrooesophageal reflux disease	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Gingival swelling	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Stomatitis	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Toothache	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
General disorders and administration site conditions	5	(20.8)	6	25.81	1	(5.0)	1	5.35	3	(13.0)	3	13.83	9	(13.4)	10	15.72
Administration site mass	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Chills	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Fat tissue increased	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Injection site discolouration	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Injection site pruritus	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Injection site reaction	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Injection site swelling	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Malaise	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Oedema	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Pyrexia	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Musculoskeletal and connective tissue disorders	2	(8.3)	2	8.60	4	(20.0)	6	32.11	2	(8.7)	3	13.83	8	(11.9)	11	17.29
Back pain	0				3	(15.0)	3	16.05	0				3	(4.5)	3	4.72
Musculoskeletal stiffness	1	(4.2)	1	4.30	0				1	(4.3)	1	4.61	2	(3.0)	2	3.14
Myalgia	1	(4.2)	1	4.30	1	(5.0)	1	5.35	0				2	(3.0)	2	3.14
Joint swelling	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57

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Normal renal function: eGFR >= 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal renal function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Myalgia intercostal	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Osteoarthritis	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Tendonitis	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Nervous system disorders	2	(8.3)	2	8.60	2	(10.0)	2	10.70	4	(17.4)	6	27.67	8	(11.9)	10	15.72
Headache	1	(4.2)	1	4.30	0				4	(17.4)	5	23.06	5	(7.5)	6	9.43
Dysgeusia	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Head discomfort	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Hypoaesthesia	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Lumbar radiculopathy	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Eye disorders	4	(16.7)	5	21.51	2	(10.0)	2	10.70	1	(4.3)	1	4.61	7	(10.4)	8	12.57
Diabetic retinopathy	2	(8.3)	2	8.60	1	(5.0)	1	5.35	0				3	(4.5)	3	4.72
Asthenopia	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Conjunctivitis allergic	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Dry eye	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Retinal haemorrhage	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Vision blurred	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Respiratory, thoracic and mediastinal disorders	4	(16.7)	4	17.20	1	(5.0)	1	5.35	2	(8.7)	3	13.83	7	(10.4)	8	12.57
Rhinitis allergic	2	(8.3)	2	8.60	1	(5.0)	1	5.35	0				3	(4.5)	3	4.72
Asthma	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Cough	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Oropharyngeal pain	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Pleuritic pain	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Sleep apnoea syndrome	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Investigations	4	(16.7)	4	17.20	0				2	(8.7)	2	9.22	6	(9.0)	6	9.43
Blood calcitonin increased	1	(4.2)	1	4.30	0				1	(4.3)	1	4.61	2	(3.0)	2	3.14
Blood creatine phosphokinase MM increased	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal renal function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Blood triglycerides increased	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Carbohydrate antigen 125 increased	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Electrocardiogram T wave amplitude decreased	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Metabolism and nutrition disorders	3	(12.5)	3	12.90	3	(15.0)	3	16.05	0				6	(9.0)	6	9.43
Overweight	1	(4.2)	1	4.30	1	(5.0)	1	5.35	0				2	(3.0)	2	3.14
Decreased appetite	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Dyslipidaemia	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Hyperuricaemia	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Hypoglycaemia	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Injury, poisoning and procedural complications	1	(4.2)	1	4.30	3	(15.0)	5	26.76	1	(4.3)	1	4.61	5	(7.5)	7	11.00
Accidental overdose	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Arthropod sting	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Contusion	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Ligament sprain	0				1	(5.0)	2	10.70	0				1	(1.5)	2	3.14
Muscle strain	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Subcutaneous haematoma	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Skin and subcutaneous tissue disorders	3	(12.5)	3	12.90	0				2	(8.7)	3	13.83	5	(7.5)	6	9.43
Eczema	1	(4.2)	1	4.30	0				1	(4.3)	2	9.22	2	(3.0)	3	4.72
Dermal cyst	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Dermatitis atopic	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Pruritus	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Psychiatric disorders	0				1	(5.0)	1	5.35	2	(8.7)	2	9.22	3	(4.5)	3	4.72

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Adverse events by system organ class and preferred term - treatment emergent - subjects with normal renal function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Insomnia	0				1	(5.0)	1	5.35	1	(4.3)	1	4.61	2	(3.0)	2	3.14
Suicide attempt	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Renal and urinary disorders	2	(8.3)	2	8.60	0				1	(4.3)	1	4.61	3	(4.5)	3	4.72
Ureterolithiasis	2	(8.3)	2	8.60	0				0				2	(3.0)	2	3.14
Nephrocalcinosis	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Reproductive system and breast disorders	1	(4.2)	1	4.30	1	(5.0)	3	16.05	1	(4.3)	5	23.06	3	(4.5)	9	14.15
Ovarian cyst	0				1	(5.0)	1	5.35	1	(4.3)	1	4.61	2	(3.0)	2	3.14
Balanoposthitis	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Cervical cyst	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Cervical polyp	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Menorrhagia	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Pruritus genital	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Uterine haemorrhage	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Uterine prolapse	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Vascular disorders	2	(8.3)	2	8.60	1	(5.0)	1	5.35	0				3	(4.5)	3	4.72
Hypertension	2	(8.3)	2	8.60	0				0				2	(3.0)	2	3.14
Arteriosclerosis	0				1	(5.0)	1	5.35	0				1	(1.5)	1	1.57
Blood and lymphatic system disorders	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Iron deficiency anaemia	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Cardiac disorders	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Palpitations	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Endocrine disorders	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Silent thyroiditis	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57

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Adverse events by system organ class and preferred term - treatment emergent - subjects with normal renal function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hepatobiliary disorders	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Hepatic steatosis	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Skin papilloma	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57

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R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Normal renal function: eGFR >= 90 mL/min/1.73 m2,
MedDRA version 20.0

2.7.4.7.1-32 ベースライン時に軽度腎機能障害を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	251				251				250				752			
PYE (years)	244.75				243.12				250.15				738.02			
Events	209	(83.3)	788	321.96	200	(79.7)	756	310.96	210	(84.0)	804	321.40	619	(82.3)	2348	318.15
Infections and infestations	140	(55.8)	261	106.64	127	(50.6)	246	101.18	133	(53.2)	245	97.94	400	(53.2)	752	101.89
Viral upper respiratory tract infection	95	(37.8)	147	60.06	83	(33.1)	140	57.58	83	(33.2)	135	53.97	261	(34.7)	422	57.18
Pharyngitis	10	(4.0)	12	4.90	14	(5.6)	17	6.99	9	(3.6)	9	3.60	33	(4.4)	38	5.15
Influenza	12	(4.8)	12	4.90	9	(3.6)	9	3.70	7	(2.8)	7	2.80	28	(3.7)	28	3.79
Gastroenteritis	10	(4.0)	10	4.09	5	(2.0)	6	2.47	11	(4.4)	12	4.80	26	(3.5)	28	3.79
Bronchitis	6	(2.4)	8	3.27	6	(2.4)	7	2.88	8	(3.2)	8	3.20	20	(2.7)	23	3.12
Periodontitis	5	(2.0)	5	2.04	6	(2.4)	10	4.11	5	(2.0)	5	2.00	16	(2.1)	20	2.71
Cystitis	4	(1.6)	6	2.45	8	(3.2)	10	4.11	3	(1.2)	3	1.20	15	(2.0)	19	2.57
Conjunctivitis	3	(1.2)	3	1.23	4	(1.6)	4	1.65	6	(2.4)	6	2.40	13	(1.7)	13	1.76
Herpes zoster	3	(1.2)	3	1.23	5	(2.0)	5	2.06	1	(0.4)	1	0.40	9	(1.2)	9	1.22
Nasopharyngitis	3	(1.2)	7	2.86	3	(1.2)	5	2.06	2	(0.8)	2	0.80	8	(1.1)	14	1.90
Tonsillitis	2	(0.8)	2	0.82	4	(1.6)	4	1.65	2	(0.8)	2	0.80	8	(1.1)	8	1.08
Helicobacter infection	1	(0.4)	1	0.41	2	(0.8)	2	0.82	4	(1.6)	4	1.60	7	(0.9)	7	0.95
Otitis externa	4	(1.6)	4	1.63	0				3	(1.2)	4	1.60	7	(0.9)	8	1.08
Sinusitis	5	(2.0)	6	2.45	0				2	(0.8)	4	1.60	7	(0.9)	10	1.35
Tinea pedis	1	(0.4)	1	0.41	1	(0.4)	1	0.41	5	(2.0)	5	2.00	7	(0.9)	7	0.95
Upper respiratory tract infection	1	(0.4)	1	0.41	2	(0.8)	3	1.23	4	(1.6)	5	2.00	7	(0.9)	9	1.22
Gingivitis	2	(0.8)	2	0.82	1	(0.4)	1	0.41	2	(0.8)	3	1.20	5	(0.7)	6	0.81
Pneumonia	1	(0.4)	1	0.41	1	(0.4)	1	0.41	3	(1.2)	3	1.20	5	(0.7)	5	0.68
Cellulitis	0				1	(0.4)	1	0.41	3	(1.2)	3	1.20	4	(0.5)	4	0.54
Oral herpes	2	(0.8)	2	0.82	0				2	(0.8)	2	0.80	4	(0.5)	4	0.54
Gastroenteritis viral	1	(0.4)	1	0.41	1	(0.4)	1	0.41	1	(0.4)	1	0.40	3	(0.4)	3	0.41
Herpes virus infection	1	(0.4)	1	0.41	0				2	(0.8)	2	0.80	3	(0.4)	3	0.41
Hordeolum	1	(0.4)	1	0.41	0				2	(0.8)	2	0.80	3	(0.4)	3	0.41

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PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Pulpitis dental	1	(0.4)	1	0.41	0				2	(0.8)	2	0.80	3	(0.4)	3	0.41
Urinary tract infection	0				3	(1.2)	3	1.23	0				3	(0.4)	3	0.41
Acute sinusitis	0				1	(0.4)	2	0.82	1	(0.4)	1	0.40	2	(0.3)	3	0.41
Dermatitis infected	2	(0.8)	2	0.82	0				0				2	(0.3)	2	0.27
Folliculitis	1	(0.4)	1	0.41	1	(0.4)	1	0.41	0				2	(0.3)	2	0.27
Gingival abscess	2	(0.8)	2	0.82	0				0				2	(0.3)	2	0.27
Helicobacter gastritis	0				1	(0.4)	1	0.41	1	(0.4)	1	0.40	2	(0.3)	2	0.27
Otitis media	0				1	(0.4)	1	0.41	1	(0.4)	1	0.40	2	(0.3)	2	0.27
Paronychia	1	(0.4)	1	0.41	0				1	(0.4)	1	0.40	2	(0.3)	2	0.27
Purulence	2	(0.8)	2	0.82	0				0				2	(0.3)	2	0.27
Rhinitis	1	(0.4)	1	0.41	0				1	(0.4)	1	0.40	2	(0.3)	2	0.27
Skin infection	2	(0.8)	2	0.82	0				0				2	(0.3)	2	0.27
Tinea infection	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Abdominal abscess	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Body tinea	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Bronchitis bacterial	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Dermatophytosis of nail	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Eczema impetiginous	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Eczema infected	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Empyema	1	(0.4)	2	0.82	0				0				1	(0.1)	2	0.27
Enteritis infectious	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Enterocolitis bacterial	0				0				1	(0.4)	2	0.80	1	(0.1)	2	0.27
Fungal cystitis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Furuncle	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Gastroenteritis bacterial	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Genital herpes	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Herpes zoster meningitis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Infected dermal cyst	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Infectious colitis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Localised infection	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Mycoplasma infection	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Oesophageal candidiasis	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14

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Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Peritonsillitis	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Pneumonia haemophilus	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Pneumonia mycoplasmal	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Pyelonephritis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Respiratory tract infection	1	(0.4)	2	0.82	0				0				1	(0.1)	2	0.27
Sycosis barbae	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Tinea capitis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Ureteritis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Urethritis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Vaginal infection	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Gastrointestinal disorders	90	(35.9)	170	69.46	56	(22.3)	90	37.02	103	(41.2)	195	77.95	249	(33.1)	455	61.65
Constipation	25	(10.0)	25	10.21	11	(4.4)	11	4.52	34	(13.6)	38	15.19	70	(9.3)	74	10.03
Diarrhoea	13	(5.2)	17	6.95	10	(4.0)	12	4.94	20	(8.0)	27	10.79	43	(5.7)	56	7.59
Nausea	8	(3.2)	11	4.49	3	(1.2)	3	1.23	20	(8.0)	23	9.19	31	(4.1)	37	5.01
Gastrooesophageal reflux disease	13	(5.2)	13	5.31	6	(2.4)	6	2.47	8	(3.2)	8	3.20	27	(3.6)	27	3.66
Chronic gastritis	8	(3.2)	8	3.27	7	(2.8)	7	2.88	7	(2.8)	8	3.20	22	(2.9)	23	3.12
Dental caries	7	(2.8)	7	2.86	5	(2.0)	5	2.06	5	(2.0)	6	2.40	17	(2.3)	18	2.44
Dyspepsia	6	(2.4)	7	2.86	1	(0.4)	1	0.41	10	(4.0)	12	4.80	17	(2.3)	20	2.71
Abdominal discomfort	1	(0.4)	2	0.82	6	(2.4)	7	2.88	7	(2.8)	7	2.80	14	(1.9)	16	2.17
Abdominal distension	8	(3.2)	8	3.27	2	(0.8)	2	0.82	3	(1.2)	3	1.20	13	(1.7)	13	1.76
Abdominal pain upper	6	(2.4)	6	2.45	4	(1.6)	4	1.65	3	(1.2)	3	1.20	13	(1.7)	13	1.76
Large intestine polyp	6	(2.4)	6	2.45	3	(1.2)	3	1.23	4	(1.6)	4	1.60	13	(1.7)	13	1.76
Stomatitis	10	(4.0)	11	4.49	2	(0.8)	3	1.23	1	(0.4)	1	0.40	13	(1.7)	15	2.03
Periodontal disease	4	(1.6)	5	2.04	3	(1.2)	3	1.23	5	(2.0)	5	2.00	12	(1.6)	13	1.76
Gastritis	5	(2.0)	5	2.04	2	(0.8)	2	0.82	4	(1.6)	4	1.60	11	(1.5)	11	1.49
Gastric polyps	2	(0.8)	2	0.82	3	(1.2)	3	1.23	5	(2.0)	5	2.00	10	(1.3)	10	1.35
Vomiting	1	(0.4)	1	0.41	2	(0.8)	2	0.82	6	(2.4)	8	3.20	9	(1.2)	11	1.49
Abdominal pain	3	(1.2)	3	1.23	2	(0.8)	2	0.82	3	(1.2)	4	1.60	8	(1.1)	9	1.22
Colitis	3	(1.2)	3	1.23	2	(0.8)	2	0.82	2	(0.8)	2	0.80	7	(0.9)	7	0.95
Faeces soft	1	(0.4)	1	0.41	1	(0.4)	1	0.41	3	(1.2)	4	1.60	5	(0.7)	6	0.81

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hiatus hernia	2	(0.8)	2	0.82	2	(0.8)	2	0.82	0				4	(0.5)	4	0.54
Toothache	1	(0.4)	1	0.41	0				3	(1.2)	3	1.20	4	(0.5)	4	0.54
Eructation	1	(0.4)	1	0.41	0				2	(0.8)	2	0.80	3	(0.4)	3	0.41
Gastric ulcer	2	(0.8)	2	0.82	1	(0.4)	1	0.41	0				3	(0.4)	3	0.41
Hyperchlorhydria	1	(0.4)	1	0.41	1	(0.4)	1	0.41	1	(0.4)	1	0.40	3	(0.4)	3	0.41
Anal fissure	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Barrett's oesophagus	2	(0.8)	2	0.82	0				0				2	(0.3)	2	0.27
Enteritis	1	(0.4)	2	0.82	1	(0.4)	1	0.41	0				2	(0.3)	3	0.41
Enterocolitis	2	(0.8)	3	1.23	0				0				2	(0.3)	3	0.41
Food poisoning	2	(0.8)	2	0.82	0				0				2	(0.3)	2	0.27
Gastritis erosive	1	(0.4)	1	0.41	0				1	(0.4)	1	0.40	2	(0.3)	2	0.27
Gastrointestinal disorder	0				0				2	(0.8)	3	1.20	2	(0.3)	3	0.41
Pancreatic cyst	0				1	(0.4)	1	0.41	1	(0.4)	1	0.40	2	(0.3)	2	0.27
Parotid gland enlargement	2	(0.8)	2	0.82	0				0				2	(0.3)	2	0.27
Proctitis	2	(0.8)	2	0.82	0				0				2	(0.3)	2	0.27
Abdominal pain lower	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Autoimmune pancreatitis	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Brunner's gland hyperplasia	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Diverticulum intestinal	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Dry mouth	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Duodenal polyp	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Duodenitis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Faecaloma	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Flatulence	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Functional gastrointestinal disorder	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Gastroduodenitis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Haematochezia	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Haemorrhoidal haemorrhage	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Haemorrhoids	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Hypoaesthesia oral	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Inguinal hernia	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14

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Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Melaena	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Mouth ulceration	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Oesophageal polyp	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Oral discomfort	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Pancreatic atrophy	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Pancreatitis acute	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Periodontal inflammation	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Musculoskeletal and connective tissue disorders	51	(20.3)	61	24.92	47	(18.7)	65	26.74	39	(15.6)	57	22.79	137	(18.2)	183	24.80
Back pain	12	(4.8)	12	4.90	9	(3.6)	9	3.70	13	(5.2)	16	6.40	34	(4.5)	37	5.01
Arthralgia	7	(2.8)	7	2.86	6	(2.4)	7	2.88	5	(2.0)	6	2.40	18	(2.4)	20	2.71
Muscle spasms	4	(1.6)	6	2.45	2	(0.8)	2	0.82	4	(1.6)	6	2.40	10	(1.3)	14	1.90
Osteoarthritis	3	(1.2)	3	1.23	5	(2.0)	5	2.06	2	(0.8)	2	0.80	10	(1.3)	10	1.35
Periarthritis	3	(1.2)	3	1.23	5	(2.0)	5	2.06	2	(0.8)	2	0.80	10	(1.3)	10	1.35
Spinal osteoarthritis	4	(1.6)	4	1.63	4	(1.6)	4	1.65	2	(0.8)	2	0.80	10	(1.3)	10	1.35
Myalgia	5	(2.0)	5	2.04	2	(0.8)	2	0.82	2	(0.8)	2	0.80	9	(1.2)	9	1.22
Intervertebral disc protrusion	3	(1.2)	3	1.23	2	(0.8)	2	0.82	2	(0.8)	2	0.80	7	(0.9)	7	0.95
Tenosynovitis	2	(0.8)	2	0.82	2	(0.8)	2	0.82	3	(1.2)	3	1.20	7	(0.9)	7	0.95
Musculoskeletal stiffness	2	(0.8)	2	0.82	1	(0.4)	1	0.41	3	(1.2)	4	1.60	6	(0.8)	7	0.95
Musculoskeletal pain	2	(0.8)	2	0.82	2	(0.8)	3	1.23	1	(0.4)	1	0.40	5	(0.7)	6	0.81
Pain in extremity	2	(0.8)	2	0.82	2	(0.8)	2	0.82	1	(0.4)	1	0.40	5	(0.7)	5	0.68
Trigger finger	0				4	(1.6)	5	2.06	1	(0.4)	1	0.40	5	(0.7)	6	0.81
Arthritis	2	(0.8)	2	0.82	1	(0.4)	1	0.41	1	(0.4)	1	0.40	4	(0.5)	4	0.54
Flank pain	1	(0.4)	1	0.41	2	(0.8)	2	0.82	0				3	(0.4)	3	0.41
Neck pain	1	(0.4)	1	0.41	1	(0.4)	1	0.41	1	(0.4)	1	0.40	3	(0.4)	3	0.41
Osteoporosis	1	(0.4)	1	0.41	2	(0.8)	2	0.82	0				3	(0.4)	3	0.41
Intervertebral disc disorder	0				1	(0.4)	1	0.41	1	(0.4)	1	0.40	2	(0.3)	2	0.27
Joint swelling	1	(0.4)	1	0.41	1	(0.4)	1	0.41	0				2	(0.3)	2	0.27
Lumbar spinal stenosis	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Spinal column stenosis	0				1	(0.4)	1	0.41	1	(0.4)	1	0.40	2	(0.3)	2	0.27

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Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Bone pain	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Cervical spinal stenosis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Fasciitis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Groin pain	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Joint contracture	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Musculoskeletal chest pain	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Nodal osteoarthritis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Osteitis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Plantar fasciitis	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Rhabdomyolysis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Rheumatoid arthritis	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Spondylolisthesis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Synovial cyst	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Tendon pain	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Eye disorders	41	(16.3)	47	19.20	26	(10.4)	35	14.40	38	(15.2)	47	18.79	105	(14.0)	129	17.48
Diabetic retinopathy	15	(6.0)	15	6.13	11	(4.4)	13	5.35	11	(4.4)	11	4.40	37	(4.9)	39	5.28
Cataract	4	(1.6)	4	1.63	4	(1.6)	4	1.65	5	(2.0)	5	2.00	13	(1.7)	13	1.76
Asthenopia	1	(0.4)	1	0.41	3	(1.2)	3	1.23	3	(1.2)	3	1.20	7	(0.9)	7	0.95
Conjunctivitis allergic	3	(1.2)	4	1.63	2	(0.8)	2	0.82	2	(0.8)	2	0.80	7	(0.9)	8	1.08
Dry eye	2	(0.8)	2	0.82	2	(0.8)	2	0.82	1	(0.4)	1	0.40	5	(0.7)	5	0.68
Glaucoma	2	(0.8)	2	0.82	0				3	(1.2)	3	1.20	5	(0.7)	5	0.68
Vitreous floaters	2	(0.8)	2	0.82	1	(0.4)	1	0.41	2	(0.8)	2	0.80	5	(0.7)	5	0.68
Diabetic retinal oedema	2	(0.8)	2	0.82	0				1	(0.4)	1	0.40	3	(0.4)	3	0.41
Macular fibrosis	2	(0.8)	2	0.82	0				1	(0.4)	1	0.40	3	(0.4)	3	0.41
Retinal haemorrhage	1	(0.4)	1	0.41	1	(0.4)	1	0.41	1	(0.4)	1	0.40	3	(0.4)	3	0.41
Vision blurred	1	(0.4)	1	0.41	1	(0.4)	1	0.41	1	(0.4)	1	0.40	3	(0.4)	3	0.41
Blepharitis	0				1	(0.4)	1	0.41	1	(0.4)	1	0.40	2	(0.3)	2	0.27
Conjunctival haemorrhage	1	(0.4)	1	0.41	1	(0.4)	2	0.82	0				2	(0.3)	3	0.41
Keratitis	0				0				2	(0.8)	2	0.80	2	(0.3)	2	0.27
Posterior capsule opacification	1	(0.4)	1	0.41	0				1	(0.4)	1	0.40	2	(0.3)	2	0.27

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PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Retinal detachment	1	(0.4)	1	0.41	0				1	(0.4)	1	0.40	2	(0.3)	2	0.27
Retinopathy	0				0				2	(0.8)	2	0.80	2	(0.3)	2	0.27
Age-related macular degeneration	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Astigmatism	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Blepharitis allergic	0				1	(0.4)	2	0.82	0				1	(0.1)	2	0.27
Blepharospasm	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Chorioretinopathy	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Conjunctivochalasis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Cystoid macular oedema	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Erythema of eyelid	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Exposure keratitis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Eye haemorrhage	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Eye inflammation	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Macular degeneration	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Macular hole	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Macular oedema	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Ocular discomfort	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Retinal degeneration	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Retinal exudates	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Retinal tear	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Retinopathy proliferative	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Visual impairment	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Vitreous haemorrhage	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Skin and subcutaneous tissue disorders	29	(11.6)	32	13.07	32	(12.7)	40	16.45	26	(10.4)	30	11.99	87	(11.6)	102	13.82
Eczema	15	(6.0)	17	6.95	6	(2.4)	6	2.47	8	(3.2)	8	3.20	29	(3.9)	31	4.20
Dermatitis contact	2	(0.8)	2	0.82	1	(0.4)	1	0.41	6	(2.4)	7	2.80	9	(1.2)	10	1.35
Pruritus	3	(1.2)	3	1.23	3	(1.2)	4	1.65	2	(0.8)	2	0.80	8	(1.1)	9	1.22
Rash	2	(0.8)	2	0.82	3	(1.2)	3	1.23	0				5	(0.7)	5	0.68
Urticaria	1	(0.4)	1	0.41	3	(1.2)	4	1.65	0				4	(0.5)	5	0.68

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Asteatosis	0				0				3	(1.2)	3	1.20	3	(0.4)	3	0.41
Dermatitis allergic	1	(0.4)	1	0.41	2	(0.8)	2	0.82	0				3	(0.4)	3	0.41
Hyperkeratosis	0				3	(1.2)	3	1.23	0				3	(0.4)	3	0.41
Miliaria	1	(0.4)	1	0.41	2	(0.8)	2	0.82	0				3	(0.4)	3	0.41
Dermatitis	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Dermatitis atopic	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Haemorrhage subcutaneous	1	(0.4)	1	0.41	1	(0.4)	3	1.23	0				2	(0.3)	4	0.54
Ingrowing nail	0				1	(0.4)	1	0.41	1	(0.4)	1	0.40	2	(0.3)	2	0.27
Skin mass	0				0				2	(0.8)	2	0.80	2	(0.3)	2	0.27
Acne	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Blister	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Chronic pigmented purpura	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Dermal cyst	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Drug eruption	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Dry skin	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Dyshidrotic eczema	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Granuloma annulare	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Hand dermatitis	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Nail hypertrophy	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Onychoclasis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Onycholysis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Pigmentation disorder	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Psoriasis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Scab	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Seborrhoeic dermatitis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Solar dermatitis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Swelling face	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Investigations	26	(10.4)	39	15.93	27	(10.8)	43	17.69	32	(12.8)	37	14.79	85	(11.3)	119	16.12
Weight increased	4	(1.6)	4	1.63	19	(7.6)	19	7.82	1	(0.4)	1	0.40	24	(3.2)	24	3.25
Lipase increased	6	(2.4)	8	3.27	0				15	(6.0)	15	6.00	21	(2.8)	23	3.12
Blood proinsulin decreased	5	(2.0)	5	2.04	3	(1.2)	3	1.23	1	(0.4)	1	0.40	9	(1.2)	9	1.22

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Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Free fatty acids decreased	4	(1.6)	5	2.04	4	(1.6)	5	2.06	1	(0.4)	1	0.40	9	(1.2)	11	1.49
Insulin C-peptide decreased	3	(1.2)	3	1.23	4	(1.6)	4	1.65	0				7	(0.9)	7	0.95
Helicobacter test positive	3	(1.2)	3	1.23	1	(0.4)	1	0.41	2	(0.8)	2	0.80	6	(0.8)	6	0.81
Amylase increased	2	(0.8)	2	0.82	0				3	(1.2)	3	1.20	5	(0.7)	5	0.68
Alanine aminotransferase increased	1	(0.4)	1	0.41	1	(0.4)	1	0.41	2	(0.8)	2	0.80	4	(0.5)	4	0.54
Blood creatine phosphokinase increased	0				3	(1.2)	4	1.65	1	(0.4)	1	0.40	4	(0.5)	5	0.68
Blood triglycerides increased	0				0				2	(0.8)	2	0.80	2	(0.3)	2	0.27
Gamma-glutamyltransferase increased	1	(0.4)	1	0.41	0				1	(0.4)	1	0.40	2	(0.3)	2	0.27
Pancreatic enzymes increased	0				0				2	(0.8)	2	0.80	2	(0.3)	2	0.27
Aspartate aminotransferase increased	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Blood calcitonin increased	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Blood potassium increased	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Blood pressure increased	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
C-reactive protein increased	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Cardiac murmur	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Carotid intima-media thickness increased	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Electrocardiogram QT prolonged	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Electrocardiogram T wave amplitude decreased	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Eosinophil count increased	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Glomerular filtration rate decreased	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Hepatic enzyme increased	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Intraocular pressure increased	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14

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Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Occult blood positive	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Rheumatoid factor increased	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Urine ketone body present	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Waist circumference increased	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Weight decreased	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
White blood cell count increased	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Nervous system disorders	19	(7.6)	27	11.03	34	(13.5)	47	19.33	27	(10.8)	29	11.59	80	(10.6)	103	13.96
Headache	6	(2.4)	10	4.09	7	(2.8)	12	4.94	11	(4.4)	12	4.80	24	(3.2)	34	4.61
Dizziness	3	(1.2)	6	2.45	8	(3.2)	9	3.70	3	(1.2)	3	1.20	14	(1.9)	18	2.44
Hypoaesthesia	2	(0.8)	3	1.23	5	(2.0)	5	2.06	3	(1.2)	3	1.20	10	(1.3)	11	1.49
Diabetic neuropathy	2	(0.8)	2	0.82	4	(1.6)	4	1.65	2	(0.8)	2	0.80	8	(1.1)	8	1.08
Facial paralysis	1	(0.4)	1	0.41	2	(0.8)	2	0.82	1	(0.4)	1	0.40	4	(0.5)	4	0.54
Carotid arteriosclerosis	0				3	(1.2)	3	1.23	0				3	(0.4)	3	0.41
Migraine	0				2	(0.8)	2	0.82	1	(0.4)	1	0.40	3	(0.4)	3	0.41
Dysgeusia	0				0				2	(0.8)	2	0.80	2	(0.3)	2	0.27
Somnolence	1	(0.4)	1	0.41	1	(0.4)	2	0.82	0				2	(0.3)	3	0.41
Balance disorder	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Carotid artery stenosis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Carpal tunnel syndrome	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Cerebral infarction	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Cervicobrachial syndrome	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Head discomfort	0				0				1	(0.4)	2	0.80	1	(0.1)	2	0.27
Hypoglycaemic unconsciousness	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Intercostal neuralgia	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Loss of consciousness	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Neuralgia	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Neuropathy peripheral	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Presyncope	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14

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Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Sciatica	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Thalamic infarction	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Thrombotic cerebral infarction	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Tongue biting	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Injury, poisoning and procedural complications	21	(8.4)	23	9.40	26	(10.4)	32	13.16	27	(10.8)	35	13.99	74	(9.8)	90	12.19
Contusion	5	(2.0)	5	2.04	5	(2.0)	6	2.47	9	(3.6)	10	4.00	19	(2.5)	21	2.85
Ligament sprain	1	(0.4)	2	0.82	3	(1.2)	3	1.23	4	(1.6)	4	1.60	8	(1.1)	9	1.22
Arthropod bite	2	(0.8)	2	0.82	2	(0.8)	2	0.82	1	(0.4)	1	0.40	5	(0.7)	5	0.68
Arthropod sting	1	(0.4)	1	0.41	1	(0.4)	2	0.82	2	(0.8)	2	0.80	4	(0.5)	5	0.68
Rib fracture	1	(0.4)	1	0.41	2	(0.8)	2	0.82	1	(0.4)	1	0.40	4	(0.5)	4	0.54
Heat illness	1	(0.4)	1	0.41	0				2	(0.8)	2	0.80	3	(0.4)	3	0.41
Spinal compression fracture	2	(0.8)	2	0.82	0				1	(0.4)	1	0.40	3	(0.4)	3	0.41
Accidental overdose	1	(0.4)	1	0.41	0				1	(0.4)	1	0.40	2	(0.3)	2	0.27
Foreign body in eye	1	(0.4)	1	0.41	1	(0.4)	1	0.41	0				2	(0.3)	2	0.27
Laceration	1	(0.4)	1	0.41	0				1	(0.4)	1	0.40	2	(0.3)	2	0.27
Skin abrasion	0				0				2	(0.8)	2	0.80	2	(0.3)	2	0.27
Tooth injury	1	(0.4)	1	0.41	1	(0.4)	1	0.41	0				2	(0.3)	2	0.27
Wound	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Avulsion fracture	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Bone contusion	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Chest injury	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Clavicle fracture	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Epicondylitis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Excoriation	0				0				1	(0.4)	2	0.80	1	(0.1)	2	0.27
Femoral neck fracture	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Hand fracture	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Head injury	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Heat stroke	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Incorrect dose administered	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14

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	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Limb injury	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Lip injury	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Lower limb fracture	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Lumbar vertebral fracture	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Median nerve injury	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Meniscus injury	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Muscle injury	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Overdose	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Pubis fracture	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Scratch	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Stab wound	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Suture related complication	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Thermal burn	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Thoracic vertebral fracture	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Tooth fracture	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Wrong drug administered	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
General disorders and administration site conditions	13	(5.2)	13	5.31	24	(9.6)	26	10.69	26	(10.4)	31	12.39	63	(8.4)	70	9.48
Oedema peripheral	4	(1.6)	4	1.63	7	(2.8)	8	3.29	1	(0.4)	1	0.40	12	(1.6)	13	1.76
Malaise	2	(0.8)	2	0.82	3	(1.2)	3	1.23	5	(2.0)	6	2.40	10	(1.3)	11	1.49
Fatigue	0				1	(0.4)	1	0.41	3	(1.2)	3	1.20	4	(0.5)	4	0.54
Injection site bruising	0				2	(0.8)	2	0.82	2	(0.8)	2	0.80	4	(0.5)	4	0.54
Injection site erythema	1	(0.4)	1	0.41	0				3	(1.2)	3	1.20	4	(0.5)	4	0.54
Injection site induration	0				1	(0.4)	1	0.41	3	(1.2)	4	1.60	4	(0.5)	5	0.68
Oedema	0				2	(0.8)	2	0.82	2	(0.8)	2	0.80	4	(0.5)	4	0.54
Injection site reaction	1	(0.4)	1	0.41	0				2	(0.8)	2	0.80	3	(0.4)	3	0.41
Asthenia	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Chest discomfort	0				0				2	(0.8)	2	0.80	2	(0.3)	2	0.27
Injection site pain	1	(0.4)	1	0.41	0				1	(0.4)	1	0.40	2	(0.3)	2	0.27
Injection site pruritus	1	(0.4)	1	0.41	0				1	(0.4)	1	0.40	2	(0.3)	2	0.27

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PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Pyrexia	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Feeling abnormal	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Feeling hot	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Hunger	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Inflammation	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Infusion site bruising	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Injection site haemorrhage	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Injection site mass	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Injection site swelling	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Pain	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Peripheral swelling	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Sense of oppression	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Thirst	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Respiratory, thoracic and mediastinal disorders	24	(9.6)	32	13.07	23	(9.2)	29	11.93	14	(5.6)	17	6.80	61	(8.1)	78	10.57
Upper respiratory tract inflammation	6	(2.4)	8	3.27	6	(2.4)	7	2.88	6	(2.4)	7	2.80	18	(2.4)	22	2.98
Asthma	4	(1.6)	4	1.63	5	(2.0)	5	2.06	2	(0.8)	2	0.80	11	(1.5)	11	1.49
Oropharyngeal pain	2	(0.8)	2	0.82	3	(1.2)	3	1.23	3	(1.2)	3	1.20	8	(1.1)	8	1.08
Rhinitis allergic	5	(2.0)	5	2.04	1	(0.4)	1	0.41	2	(0.8)	2	0.80	8	(1.1)	8	1.08
Cough	2	(0.8)	2	0.82	4	(1.6)	6	2.47	1	(0.4)	1	0.40	7	(0.9)	9	1.22
Sleep apnoea syndrome	1	(0.4)	1	0.41	4	(1.6)	4	1.65	1	(0.4)	1	0.40	6	(0.8)	6	0.81
Rhinorrhoea	2	(0.8)	2	0.82	1	(0.4)	1	0.41	0				3	(0.4)	3	0.41
Emphysema	1	(0.4)	1	0.41	1	(0.4)	1	0.41	0				2	(0.3)	2	0.27
Bronchitis chronic	1	(0.4)	2	0.82	0				0				1	(0.1)	2	0.27
Chronic obstructive pulmonary disease	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Dysphonia	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Pharyngeal oedema	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Productive cough	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Pulmonary fibrosis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Respiratory disorder	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Sneezing	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Vascular disorders	13	(5.2)	13	5.31	15	(6.0)	15	6.17	7	(2.8)	8	3.20	35	(4.7)	36	4.88
Hypertension	8	(3.2)	8	3.27	12	(4.8)	12	4.94	4	(1.6)	4	1.60	24	(3.2)	24	3.25
Arteriosclerosis	2	(0.8)	2	0.82	0				1	(0.4)	1	0.40	3	(0.4)	3	0.41
Hot flush	1	(0.4)	1	0.41	0				1	(0.4)	1	0.40	2	(0.3)	2	0.27
Orthostatic hypotension	1	(0.4)	1	0.41	0				1	(0.4)	1	0.40	2	(0.3)	2	0.27
Peripheral arterial occlusive disease	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Hypotension	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Internal haemorrhage	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Varicose vein	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Hepatobiliary disorders	10	(4.0)	13	5.31	12	(4.8)	17	6.99	11	(4.4)	14	5.60	33	(4.4)	44	5.96
Hepatic steatosis	6	(2.4)	6	2.45	3	(1.2)	3	1.23	2	(0.8)	2	0.80	11	(1.5)	11	1.49
Cholelithiasis	3	(1.2)	3	1.23	3	(1.2)	3	1.23	3	(1.2)	3	1.20	9	(1.2)	9	1.22
Gallbladder polyp	1	(0.4)	1	0.41	5	(2.0)	5	2.06	2	(0.8)	2	0.80	8	(1.1)	8	1.08
Hepatic cyst	1	(0.4)	1	0.41	1	(0.4)	1	0.41	2	(0.8)	2	0.80	4	(0.5)	4	0.54
Non-alcoholic fatty liver	1	(0.4)	1	0.41	1	(0.4)	1	0.41	1	(0.4)	1	0.40	3	(0.4)	3	0.41
Hepatic function abnormal	0				1	(0.4)	1	0.41	1	(0.4)	1	0.40	2	(0.3)	2	0.27
Cholecystitis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Cholecystitis acute	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Chronic hepatitis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Drug-induced liver injury	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Hepatic calcification	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Hepatic mass	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Liver disorder	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Metabolism and nutrition disorders	7	(2.8)	7	2.86	10	(4.0)	11	4.52	15	(6.0)	17	6.80	32	(4.3)	35	4.74
Decreased appetite	1	(0.4)	1	0.41	2	(0.8)	2	0.82	11	(4.4)	11	4.40	14	(1.9)	14	1.90

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Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Dyslipidaemia	1	(0.4)	1	0.41	2	(0.8)	2	0.82	2	(0.8)	2	0.80	5	(0.7)	5	0.68
Hyperuricaemia	1	(0.4)	1	0.41	2	(0.8)	2	0.82	1	(0.4)	1	0.40	4	(0.5)	4	0.54
Dehydration	0				1	(0.4)	1	0.41	1	(0.4)	2	0.80	2	(0.3)	3	0.41
Gout	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Hyperlipidaemia	1	(0.4)	1	0.41	1	(0.4)	1	0.41	0				2	(0.3)	2	0.27
Hyperlipasaemia	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Hypertriglyceridaemia	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Hypokalaemia	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Obesity	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Overweight	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Cardiac disorders	6	(2.4)	6	2.45	9	(3.6)	9	3.70	11	(4.4)	11	4.40	26	(3.5)	26	3.52
Atrial fibrillation	0				2	(0.8)	2	0.82	2	(0.8)	2	0.80	4	(0.5)	4	0.54
Palpitations	0				1	(0.4)	1	0.41	3	(1.2)	3	1.20	4	(0.5)	4	0.54
Angina pectoris	2	(0.8)	2	0.82	0				0				2	(0.3)	2	0.27
Myocardial ischaemia	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Supraventricular extrasystoles	0				0				2	(0.8)	2	0.80	2	(0.3)	2	0.27
Ventricular extrasystoles	2	(0.8)	2	0.82	0				0				2	(0.3)	2	0.27
Acute myocardial infarction	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Atrioventricular block complete	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Atrioventricular block first degree	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Cardiac disorder	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Cardiomegaly	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Coronary artery stenosis	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Sinus arrhythmia	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Sinus node dysfunction	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Supraventricular tachycardia	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Tachycardia	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14

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Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Renal and urinary disorders	8	(3.2)	8	3.27	7	(2.8)	9	3.70	5	(2.0)	6	2.40	20	(2.7)	23	3.12
Renal cyst	5	(2.0)	5	2.04	2	(0.8)	2	0.82	2	(0.8)	2	0.80	9	(1.2)	9	1.22
Nephrolithiasis	1	(0.4)	1	0.41	4	(1.6)	4	1.65	1	(0.4)	1	0.40	6	(0.8)	6	0.81
Calculus urinary	0				0				2	(0.8)	2	0.80	2	(0.3)	2	0.27
Chronic kidney disease	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Diabetic nephropathy	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Hydronephrosis	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Nephrotic syndrome	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Renal impairment	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Urinary retention	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Ear and labyrinth disorders	9	(3.6)	11	4.49	5	(2.0)	6	2.47	5	(2.0)	5	2.00	19	(2.5)	22	2.98
Vertigo	5	(2.0)	7	2.86	2	(0.8)	3	1.23	3	(1.2)	3	1.20	10	(1.3)	13	1.76
Tinnitus	1	(0.4)	1	0.41	2	(0.8)	2	0.82	1	(0.4)	1	0.40	4	(0.5)	4	0.54
Vertigo positional	2	(0.8)	2	0.82	0				1	(0.4)	1	0.40	3	(0.4)	3	0.41
Otorrhoea	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Sudden hearing loss	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Psychiatric disorders	6	(2.4)	6	2.45	8	(3.2)	8	3.29	4	(1.6)	4	1.60	18	(2.4)	18	2.44
Insomnia	6	(2.4)	6	2.45	5	(2.0)	5	2.06	1	(0.4)	1	0.40	12	(1.6)	12	1.63
Depression	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Sleep disorder	0				0				2	(0.8)	2	0.80	2	(0.3)	2	0.27
Anxiety	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Neurosis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	(2.0)	5	2.04	6	(2.4)	8	3.29	5	(2.0)	5	2.00	16	(2.1)	18	2.44
Colon adenoma	0				0				3	(1.2)	3	1.20	3	(0.4)	3	0.41
Benign neoplasm of thyroid gland	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Acrochordon	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14

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	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Adrenal neoplasm	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Basal cell carcinoma	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Benign neoplasm of bladder	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Breast cancer	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Gastric cancer stage I	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Lung adenocarcinoma	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Lung neoplasm malignant	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Metastases to lymph nodes	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Oligodendroglioma	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Skin papilloma	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Thyroid neoplasm	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Uterine leiomyoma	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Reproductive system and breast disorders	4	(1.6)	4	1.63	6	(2.4)	6	2.47	2	(0.8)	2	0.80	12	(1.6)	12	1.63
Pruritus genital	1	(0.4)	1	0.41	2	(0.8)	2	0.82	0				3	(0.4)	3	0.41
Menopausal symptoms	0				1	(0.4)	1	0.41	1	(0.4)	1	0.40	2	(0.3)	2	0.27
Benign prostatic hyperplasia	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Endometrial hyperplasia	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Gynaecomastia	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Menstruation irregular	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Ovarian cyst	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Prostatic calcification	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Uterine disorder	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Endocrine disorders	3	(1.2)	3	1.23	6	(2.4)	7	2.88	2	(0.8)	2	0.80	11	(1.5)	12	1.63
Thyroid cyst	2	(0.8)	2	0.82	5	(2.0)	5	2.06	1	(0.4)	1	0.40	8	(1.1)	8	1.08
Thyroid mass	1	(0.4)	1	0.41	2	(0.8)	2	0.82	0				3	(0.4)	3	0.41
Hyperthyroidism	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Immune system disorders	3	(1.2)	4	1.63	2	(0.8)	2	0.82	2	(0.8)	2	0.80	7	(0.9)	8	1.08
Seasonal allergy	2	(0.8)	2	0.82	1	(0.4)	1	0.41	2	(0.8)	2	0.80	5	(0.7)	5	0.68

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R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Allergy to arthropod sting	1	(0.4)	2	0.82	0				0				1	(0.1)	2	0.27
Hypersensitivity	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Blood and lymphatic system disorders	2	(0.8)	2	0.82	1	(0.4)	1	0.41	3	(1.2)	3	1.20	6	(0.8)	6	0.81
Iron deficiency anaemia	1	(0.4)	1	0.41	1	(0.4)	1	0.41	1	(0.4)	1	0.40	3	(0.4)	3	0.41
Anaemia	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Polycythaemia	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Splenomegaly	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Surgical and medical procedures	1	(0.4)	1	0.41	2	(0.8)	3	1.23	2	(0.8)	2	0.80	5	(0.7)	6	0.81
Tooth extraction	1	(0.4)	1	0.41	1	(0.4)	2	0.82	0				2	(0.3)	3	0.41
Cardiac ablation	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Cataract operation	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Large intestinal polypectomy	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Congenital, familial and genetic disorders	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Epidermolysis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

2.7.4.7.1-33 ベースライン時に正常腎機能を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	12				12				24			
PYE (years)	6.20				6.24				12.43			
Events	12	(100.0)	47	758.58	9	(75.0)	30	481.01	21	(87.5)	77	619.34
Gastrointestinal disorders	7	(58.3)	17	274.38	4	(33.3)	9	144.30	11	(45.8)	26	209.13
Abdominal discomfort	2	(16.7)	2	32.28	2	(16.7)	2	32.07	4	(16.7)	4	32.17
Diarrhoea	3	(25.0)	6	96.84	1	(8.3)	1	16.03	4	(16.7)	7	56.30
Nausea	3	(25.0)	3	48.42	1	(8.3)	1	16.03	4	(16.7)	4	32.17
Vomiting	2	(16.7)	2	32.28	0				2	(8.3)	2	16.09
Abdominal distension	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Chronic gastritis	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Constipation	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Enteritis	1	(8.3)	2	32.28	0				1	(4.2)	2	16.09
Gastritis	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Gastrointestinal motility disorder	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Glossitis	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Stomatitis	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Infections and infestations	7	(58.3)	12	193.68	4	(33.3)	5	80.17	11	(45.8)	17	136.74
Viral upper respiratory tract infection	3	(25.0)	3	48.42	2	(16.7)	2	32.07	5	(20.8)	5	40.22
Gastroenteritis	2	(16.7)	4	64.56	1	(8.3)	1	16.03	3	(12.5)	5	40.22
Bronchitis	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Periodontitis	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Pharyngitis	1	(8.3)	2	32.28	0				1	(4.2)	2	16.09
Tinea pedis	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Upper respiratory tract infection	0				1	(8.3)	2	32.07	1	(4.2)	2	16.09
Eye disorders	4	(33.3)	4	64.56	5	(41.7)	6	96.20	9	(37.5)	10	80.43
Diabetic retinopathy	3	(25.0)	3	48.42	5	(41.7)	6	96.20	8	(33.3)	9	72.39
Blepharospasm	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04

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PYE: Patient years of exposure (1 PYE = 365.25 days),
Normal renal function: eGFR >= 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal renal function at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
General disorders and administration site conditions	2	(16.7)	2	32.28	2	(16.7)	2	32.07	4	(16.7)	4	32.17
Injection site discomfort	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Injection site induration	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Oedema peripheral	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Pyrexia	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Metabolism and nutrition disorders	3	(25.0)	3	48.42	1	(8.3)	1	16.03	4	(16.7)	4	32.17
Dyslipidaemia	1	(8.3)	1	16.14	1	(8.3)	1	16.03	2	(8.3)	2	16.09
Decreased appetite	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Hyperuricaemia	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Nervous system disorders	2	(16.7)	2	32.28	2	(16.7)	2	32.07	4	(16.7)	4	32.17
Headache	1	(8.3)	1	16.14	1	(8.3)	1	16.03	2	(8.3)	2	16.09
Dysgeusia	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Migraine	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Vascular disorders	3	(25.0)	3	48.42	0				3	(12.5)	3	24.13
Hypertension	2	(16.7)	2	32.28	0				2	(8.3)	2	16.09
Orthostatic hypotension	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Injury, poisoning and procedural complications	1	(8.3)	1	16.14	1	(8.3)	1	16.03	2	(8.3)	2	16.09
Laceration	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Thermal burn	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Musculoskeletal and connective tissue disorders	1	(8.3)	1	16.14	1	(8.3)	1	16.03	2	(8.3)	2	16.09
Back pain	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Intervertebral disc protrusion	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Ear and labyrinth disorders	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Vertigo	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04

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PYE: Patient years of exposure (1 PYE = 365.25 days),
Normal renal function: eGFR >= 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal renal function at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Psychiatric disorders	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Insomnia	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Renal and urinary disorders	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Renal cyst	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Respiratory, thoracic and mediastinal disorders	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Cough	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Skin and subcutaneous tissue disorders	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Hyperkeratosis	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04

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R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Normal renal function: eGFR >= 90 mL/min/1.73 m2,
MedDRA version 20.0

2.7.4.7.1-34 ベースライン時に軽度腎機能障害を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	93				93				186			
PYE (years)	48.08				46.03				94.11			
Events	70	(75.3)	233	484.59	71	(76.3)	180	391.06	141	(75.8)	413	438.84
Infections and infestations	28	(30.1)	45	93.59	34	(36.6)	47	102.11	62	(33.3)	92	97.76
Viral upper respiratory tract infection	18	(19.4)	24	49.91	22	(23.7)	28	60.83	40	(21.5)	52	55.25
Bronchitis	0				5	(5.4)	5	10.86	5	(2.7)	5	5.31
Pharyngitis	4	(4.3)	4	8.32	1	(1.1)	2	4.35	5	(2.7)	6	6.38
Gastroenteritis	2	(2.2)	2	4.16	1	(1.1)	1	2.17	3	(1.6)	3	3.19
Herpes zoster	2	(2.2)	2	4.16	1	(1.1)	1	2.17	3	(1.6)	3	3.19
Influenza	1	(1.1)	1	2.08	2	(2.2)	2	4.35	3	(1.6)	3	3.19
Sinusitis	3	(3.2)	3	6.24	0				3	(1.6)	3	3.19
Cystitis	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Upper respiratory tract infection	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Abscess	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Adenoviral conjunctivitis	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Cellulitis	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Gingivitis	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Herpes simplex	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Hordeolum	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Infected dermal cyst	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Otitis externa	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Periodontitis	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Tonsillitis	1	(1.1)	2	4.16	0				1	(0.5)	2	2.13
Upper respiratory tract infection bacterial	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Urinary tract infection	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Gastrointestinal disorders	38	(40.9)	71	147.66	20	(21.5)	31	67.35	58	(31.2)	102	108.38
Diarrhoea	12	(12.9)	14	29.12	4	(4.3)	5	10.86	16	(8.6)	19	20.19
Constipation	9	(9.7)	10	20.80	3	(3.2)	3	6.52	12	(6.5)	13	13.81

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PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Nausea	7	(7.5)	9	18.72	3	(3.2)	4	8.69	10	(5.4)	13	13.81
Abdominal discomfort	6	(6.5)	6	12.48	3	(3.2)	3	6.52	9	(4.8)	9	9.56
Vomiting	7	(7.5)	9	18.72	2	(2.2)	2	4.35	9	(4.8)	11	11.69
Gastrooesophageal reflux disease	3	(3.2)	3	6.24	2	(2.2)	2	4.35	5	(2.7)	5	5.31
Dyspepsia	3	(3.2)	4	8.32	1	(1.1)	1	2.17	4	(2.2)	5	5.31
Chronic gastritis	2	(2.2)	3	6.24	1	(1.1)	1	2.17	3	(1.6)	4	4.25
Hiatus hernia	3	(3.2)	3	6.24	0				3	(1.6)	3	3.19
Abdominal pain	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Dental caries	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Faeces soft	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Gastritis	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Gastritis erosive	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Duodenal ulcer	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Enteritis	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Epigastric discomfort	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Food poisoning	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Hyperchlorhydria	1	(1.1)	2	4.16	0				1	(0.5)	2	2.13
Large intestine polyp	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Oesophageal disorder	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Periodontal disease	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Varices oesophageal	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Eye disorders	18	(19.4)	20	41.60	15	(16.1)	17	36.93	33	(17.7)	37	39.32
Diabetic retinopathy	14	(15.1)	15	31.20	12	(12.9)	12	26.07	26	(14.0)	27	28.69
Cataract	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Cataract nuclear	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Conjunctival haemorrhage	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Dry eye	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Pingueculitis	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Posterior capsule opacification	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Retinal detachment	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Retinal haemorrhage	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06

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PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Retinopathy	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Musculoskeletal and connective tissue disorders	13	(14.0)	17	35.36	13	(14.0)	14	30.42	26	(14.0)	31	32.94
Back pain	5	(5.4)	6	12.48	4	(4.3)	4	8.69	9	(4.8)	10	10.63
Arthralgia	3	(3.2)	3	6.24	1	(1.1)	1	2.17	4	(2.2)	4	4.25
Muscle spasms	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Musculoskeletal pain	2	(2.2)	2	4.16	0				2	(1.1)	2	2.13
Periarthritis	0				2	(2.2)	2	4.35	2	(1.1)	2	2.13
Tenosynovitis	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Arthritis	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Flank pain	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Intervertebral disc protrusion	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Musculoskeletal stiffness	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Myalgia	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Neck pain	1	(1.1)	2	4.16	0				1	(0.5)	2	2.13
Osteoarthritis	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Trigger finger	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Injury, poisoning and procedural complications	9	(9.7)	13	27.04	9	(9.7)	10	21.73	18	(9.7)	23	24.44
Contusion	2	(2.2)	2	4.16	3	(3.2)	3	6.52	5	(2.7)	5	5.31
Fall	3	(3.2)	3	6.24	0				3	(1.6)	3	3.19
Laceration	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Arthropod bite	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Excoriation	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Foot fracture	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Fractured coccyx	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Heat illness	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Heat stroke	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Hip fracture	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Ligament sprain	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Postoperative fever	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Tibia fracture	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06

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R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Tooth fracture	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Tooth injury	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Wrong drug administered	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Nervous system disorders	7	(7.5)	9	18.72	9	(9.7)	12	26.07	16	(8.6)	21	22.31
Dizziness	2	(2.2)	2	4.16	4	(4.3)	5	10.86	6	(3.2)	7	7.44
Hypoaesthesia	2	(2.2)	2	4.16	1	(1.1)	1	2.17	3	(1.6)	3	3.19
Carpal tunnel syndrome	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Diabetic neuropathy	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Headache	2	(2.2)	2	4.16	0				2	(1.1)	2	2.13
Lacunar infarction	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Loss of consciousness	0				1	(1.1)	2	4.35	1	(0.5)	2	2.13
Neuropathy peripheral	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Sciatica	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
General disorders and administration site conditions	7	(7.5)	8	16.64	8	(8.6)	8	17.38	15	(8.1)	16	17.00
Inflammation	1	(1.1)	1	2.08	2	(2.2)	2	4.35	3	(1.6)	3	3.19
Malaise	2	(2.2)	3	6.24	1	(1.1)	1	2.17	3	(1.6)	4	4.25
Pyrexia	1	(1.1)	1	2.08	2	(2.2)	2	4.35	3	(1.6)	3	3.19
Administration site induration	0				2	(2.2)	2	4.35	2	(1.1)	2	2.13
Oedema peripheral	2	(2.2)	2	4.16	0				2	(1.1)	2	2.13
Generalised oedema	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Induration	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Metabolism and nutrition disorders	12	(12.9)	12	24.96	2	(2.2)	2	4.35	14	(7.5)	14	14.88
Decreased appetite	7	(7.5)	7	14.56	0				7	(3.8)	7	7.44
Gout	2	(2.2)	2	4.16	1	(1.1)	1	2.17	3	(1.6)	3	3.19
Hyperuricaemia	2	(2.2)	2	4.16	0				2	(1.1)	2	2.13
Dehydration	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Dyslipidaemia	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06

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Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Skin and subcutaneous tissue disorders	3	(3.2)	4	8.32	10	(10.8)	10	21.73	13	(7.0)	14	14.88
Eczema	2	(2.2)	2	4.16	4	(4.3)	4	8.69	6	(3.2)	6	6.38
Acne	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Dermatitis	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Miliaria	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Penile ulceration	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Pustular psoriasis	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Rash	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Skin irritation	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Skin swelling	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Investigations	7	(7.5)	7	14.56	5	(5.4)	5	10.86	12	(6.5)	12	12.75
Helicobacter test positive	1	(1.1)	1	2.08	2	(2.2)	2	4.35	3	(1.6)	3	3.19
Lipase increased	2	(2.2)	2	4.16	0				2	(1.1)	2	2.13
Electrocardiogram ST-T segment depression	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Electrocardiogram T wave inversion	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Free fatty acids decreased	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Gamma-glutamyltransferase increased	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Glomerular filtration rate decreased	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Oxygen saturation decreased	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Weight decreased	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Respiratory, thoracic and mediastinal disorders	6	(6.5)	9	18.72	5	(5.4)	5	10.86	11	(5.9)	14	14.88
Upper respiratory tract inflammation	1	(1.1)	2	4.16	3	(3.2)	3	6.52	4	(2.2)	5	5.31
Oropharyngeal pain	2	(2.2)	2	4.16	0				2	(1.1)	2	2.13
Atelectasis	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Bronchitis chronic	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Cough	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Pleural effusion	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Respiratory tract inflammation	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Sputum increased	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Sputum retention	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06

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PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Renal and urinary disorders	4	(4.3)	7	14.56	2	(2.2)	2	4.35	6	(3.2)	9	9.56
Nephrolithiasis	2	(2.2)	2	4.16	2	(2.2)	2	4.35	4	(2.2)	4	4.25
Renal cyst	2	(2.2)	2	4.16	0				2	(1.1)	2	2.13
Acute kidney injury	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Haematuria	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Ureterolithiasis	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Hepatobiliary disorders	1	(1.1)	1	2.08	3	(3.2)	3	6.52	4	(2.2)	4	4.25
Cholecystitis acute	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Cholelithiasis	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Hepatic cirrhosis	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Hepatic steatosis	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(2.2)	2	4.16	2	(2.2)	2	4.35	4	(2.2)	4	4.25
Adenocarcinoma	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Pancreatic carcinoma	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Renal cell carcinoma	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Uterine leiomyoma	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Vascular disorders	2	(2.2)	2	4.16	2	(2.2)	2	4.35	4	(2.2)	4	4.25
Hypertension	1	(1.1)	1	2.08	2	(2.2)	2	4.35	3	(1.6)	3	3.19
Arteriosclerosis	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Cardiac disorders	2	(2.2)	3	6.24	0				2	(1.1)	3	3.19
Acute myocardial infarction	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Cardiac failure congestive	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Supraventricular extrasystoles	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Ear and labyrinth disorders	0				2	(2.2)	3	6.52	2	(1.1)	3	3.19
Vertigo	0				2	(2.2)	3	6.52	2	(1.1)	3	3.19

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PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Psychiatric disorders	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Insomnia	1	(1.1)	1	2.08	1	(1.1)	1	2.17	2	(1.1)	2	2.13
Blood and lymphatic system disorders	0				1	(1.1)	3	6.52	1	(0.5)	3	3.19
Leukopenia	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Lymphopenia	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Neutropenia	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Endocrine disorders	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Thyroid mass	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Immune system disorders	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Seasonal allergy	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Reproductive system and breast disorders	0				1	(1.1)	3	6.52	1	(0.5)	3	3.19
Uterine cyst	0				1	(1.1)	2	4.35	1	(0.5)	2	2.13
Uterine mass	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06

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R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
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Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

2.7.4.7.1-35 ベースライン時に正常肝機能を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	226				222				213				661			
PYE (years)	219.62				213.34				212.03				645.00			
Events	188	(83.2)	660	300.51	176	(79.3)	685	321.08	177	(83.1)	703	331.55	541	(81.8)	2048	317.52
Infections and infestations	121	(53.5)	211	96.07	112	(50.5)	217	101.71	116	(54.5)	220	103.76	349	(52.8)	648	100.47
Viral upper respiratory tract infection	80	(35.4)	114	51.91	78	(35.1)	136	63.75	76	(35.7)	126	59.42	234	(35.4)	376	58.29
Pharyngitis	8	(3.5)	9	4.10	11	(5.0)	11	5.16	8	(3.8)	8	3.77	27	(4.1)	28	4.34
Gastroenteritis	9	(4.0)	9	4.10	5	(2.3)	5	2.34	10	(4.7)	11	5.19	24	(3.6)	25	3.88
Influenza	9	(4.0)	9	4.10	6	(2.7)	6	2.81	6	(2.8)	6	2.83	21	(3.2)	21	3.26
Bronchitis	6	(2.7)	8	3.64	4	(1.8)	4	1.87	6	(2.8)	6	2.83	16	(2.4)	18	2.79
Periodontitis	5	(2.2)	5	2.28	5	(2.3)	9	4.22	4	(1.9)	4	1.89	14	(2.1)	18	2.79
Cystitis	2	(0.9)	4	1.82	7	(3.2)	9	4.22	1	(0.5)	1	0.47	10	(1.5)	14	2.17
Conjunctivitis	1	(0.4)	1	0.46	3	(1.4)	3	1.41	5	(2.3)	5	2.36	9	(1.4)	9	1.40
Herpes zoster	3	(1.3)	3	1.37	3	(1.4)	3	1.41	1	(0.5)	1	0.47	7	(1.1)	7	1.09
Tonsillitis	2	(0.9)	2	0.91	3	(1.4)	3	1.41	2	(0.9)	2	0.94	7	(1.1)	7	1.09
Upper respiratory tract infection	1	(0.4)	1	0.46	2	(0.9)	3	1.41	4	(1.9)	5	2.36	7	(1.1)	9	1.40
Helicobacter infection	1	(0.4)	1	0.46	3	(1.4)	3	1.41	2	(0.9)	2	0.94	6	(0.9)	6	0.93
Nasopharyngitis	3	(1.3)	7	3.19	0				3	(1.4)	3	1.41	6	(0.9)	10	1.55
Sinusitis	4	(1.8)	5	2.28	0				2	(0.9)	4	1.89	6	(0.9)	9	1.40
Gingivitis	2	(0.9)	2	0.91	1	(0.5)	1	0.47	2	(0.9)	3	1.41	5	(0.8)	6	0.93
Otitis externa	3	(1.3)	3	1.37	0				2	(0.9)	3	1.41	5	(0.8)	6	0.93
Pneumonia	1	(0.4)	1	0.46	1	(0.5)	1	0.47	3	(1.4)	3	1.41	5	(0.8)	5	0.78
Tinea pedis	0				0				4	(1.9)	4	1.89	4	(0.6)	4	0.62
Gastroenteritis viral	1	(0.4)	1	0.46	1	(0.5)	1	0.47	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Helicobacter gastritis	0				1	(0.5)	1	0.47	2	(0.9)	2	0.94	3	(0.5)	3	0.47
Herpes virus infection	1	(0.4)	1	0.46	0				2	(0.9)	2	0.94	3	(0.5)	3	0.47
Hordeolum	1	(0.4)	1	0.46	0				2	(0.9)	2	0.94	3	(0.5)	3	0.47
Oral herpes	2	(0.9)	2	0.91	0				1	(0.5)	1	0.47	3	(0.5)	3	0.47

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Normal hepatic function: Baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Urinary tract infection	0				3	(1.4)	3	1.41	0				3	(0.5)	3	0.47
Cellulitis	0				0				2	(0.9)	2	0.94	2	(0.3)	2	0.31
Gingival abscess	2	(0.9)	2	0.91	0				0				2	(0.3)	2	0.31
Otitis media	0				1	(0.5)	1	0.47	1	(0.5)	1	0.47	2	(0.3)	2	0.31
Pulpitis dental	0				0				2	(0.9)	2	0.94	2	(0.3)	2	0.31
Purulence	2	(0.9)	2	0.91	0				0				2	(0.3)	2	0.31
Rhinitis	1	(0.4)	1	0.46	0				1	(0.5)	1	0.47	2	(0.3)	2	0.31
Skin infection	2	(0.9)	2	0.91	0				0				2	(0.3)	2	0.31
Tinea infection	0				2	(0.9)	2	0.94	0				2	(0.3)	2	0.31
Acute sinusitis	0				1	(0.5)	2	0.94	0				1	(0.2)	2	0.31
Beta haemolytic streptococcal infection	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Body tinea	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Bronchitis bacterial	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Conjunctivitis viral	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Dermatitis infected	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Dermatophytosis of nail	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Eczema impetiginous	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Eczema infected	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Empyema	1	(0.4)	2	0.91	0				0				1	(0.2)	2	0.31
Enterocolitis bacterial	0				0				1	(0.5)	2	0.94	1	(0.2)	2	0.31
Folliculitis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Fungal cystitis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Furuncle	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Gastroenteritis bacterial	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Gastroenteritis norovirus	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Genital herpes	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Herpes zoster meningitis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Infectious colitis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Localised infection	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Mycoplasma infection	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Oesophageal candidiasis	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16

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PYE: Patient years of exposure (1 PYE = 365.25 days),
Normal hepatic function: Baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Paronychia	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Peritonsillitis	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Pneumonia haemophilus	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Pyelonephritis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Respiratory tract infection	1	(0.4)	2	0.91	0				0				1	(0.2)	2	0.31
Sycosis barbae	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Tinea capitis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Ureteritis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Urethritis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Vaginal infection	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Gastrointestinal disorders	77	(34.1)	147	66.93	54	(24.3)	89	41.72	90	(42.3)	162	76.40	221	(33.4)	398	61.71
Constipation	19	(8.4)	19	8.65	11	(5.0)	11	5.16	28	(13.1)	32	15.09	58	(8.8)	62	9.61
Diarrhoea	11	(4.9)	15	6.83	10	(4.5)	12	5.62	18	(8.5)	24	11.32	39	(5.9)	51	7.91
Nausea	7	(3.1)	10	4.55	4	(1.8)	4	1.87	16	(7.5)	22	10.38	27	(4.1)	36	5.58
Gastrooesophageal reflux disease	12	(5.3)	12	5.46	6	(2.7)	6	2.81	6	(2.8)	6	2.83	24	(3.6)	24	3.72
Chronic gastritis	8	(3.5)	8	3.64	7	(3.2)	7	3.28	6	(2.8)	7	3.30	21	(3.2)	22	3.41
Dental caries	9	(4.0)	9	4.10	6	(2.7)	6	2.81	6	(2.8)	7	3.30	21	(3.2)	22	3.41
Dyspepsia	6	(2.7)	7	3.19	0				9	(4.2)	11	5.19	15	(2.3)	18	2.79
Abdominal distension	7	(3.1)	7	3.19	3	(1.4)	3	1.41	3	(1.4)	3	1.41	13	(2.0)	13	2.02
Abdominal discomfort	1	(0.4)	1	0.46	4	(1.8)	5	2.34	6	(2.8)	6	2.83	11	(1.7)	12	1.86
Stomatitis	8	(3.5)	8	3.64	3	(1.4)	4	1.87	0				11	(1.7)	12	1.86
Abdominal pain upper	4	(1.8)	5	2.28	4	(1.8)	4	1.87	2	(0.9)	2	0.94	10	(1.5)	11	1.71
Vomiting	0				2	(0.9)	2	0.94	8	(3.8)	10	4.72	10	(1.5)	12	1.86
Gastric polyps	2	(0.9)	2	0.91	3	(1.4)	3	1.41	4	(1.9)	4	1.89	9	(1.4)	9	1.40
Large intestine polyp	6	(2.7)	6	2.73	2	(0.9)	2	0.94	1	(0.5)	1	0.47	9	(1.4)	9	1.40
Abdominal pain	3	(1.3)	3	1.37	2	(0.9)	2	0.94	2	(0.9)	3	1.41	7	(1.1)	8	1.24
Gastritis	3	(1.3)	3	1.37	1	(0.5)	1	0.47	3	(1.4)	3	1.41	7	(1.1)	7	1.09
Periodontal disease	1	(0.4)	1	0.46	3	(1.4)	3	1.41	3	(1.4)	3	1.41	7	(1.1)	7	1.09
Colitis	3	(1.3)	3	1.37	1	(0.5)	1	0.47	2	(0.9)	2	0.94	6	(0.9)	6	0.93
Toothache	1	(0.4)	1	0.46	1	(0.5)	1	0.47	3	(1.4)	3	1.41	5	(0.8)	5	0.78

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hiatus hernia	2	(0.9)	2	0.91	2	(0.9)	2	0.94	0				4	(0.6)	4	0.62
Faeces soft	1	(0.4)	1	0.46	1	(0.5)	1	0.47	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Hyperchlorhydria	1	(0.4)	1	0.46	1	(0.5)	1	0.47	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Anal fissure	0				2	(0.9)	2	0.94	0				2	(0.3)	2	0.31
Barrett's oesophagus	2	(0.9)	2	0.91	0				0				2	(0.3)	2	0.31
Enteritis	1	(0.4)	2	0.91	1	(0.5)	1	0.47	0				2	(0.3)	3	0.47
Enterocolitis	2	(0.9)	3	1.37	0				0				2	(0.3)	3	0.47
Food poisoning	2	(0.9)	2	0.91	0				0				2	(0.3)	2	0.31
Gastric ulcer	1	(0.4)	1	0.46	1	(0.5)	1	0.47	0				2	(0.3)	2	0.31
Gastritis erosive	1	(0.4)	1	0.46	0				1	(0.5)	1	0.47	2	(0.3)	2	0.31
Gastrointestinal disorder	0				0				2	(0.9)	3	1.41	2	(0.3)	3	0.47
Parotid gland enlargement	2	(0.9)	2	0.91	0				0				2	(0.3)	2	0.31
Proctitis	2	(0.9)	2	0.91	0				0				2	(0.3)	2	0.31
Autoimmune pancreatitis	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Diverticulum intestinal	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Dry mouth	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Duodenal polyp	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Duodenitis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Eructation	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Faecaloma	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Gastroduodenitis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Haematochezia	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Haemorrhoidal haemorrhage	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Haemorrhoids	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Hypoaesthesia oral	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Inguinal hernia	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Mouth ulceration	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Oral discomfort	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Pancreatic atrophy	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Pancreatic cyst	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Pancreatitis acute	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Periodontal inflammation	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16

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Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Musculoskeletal and connective tissue disorders	42	(18.6)	49	22.31	44	(19.8)	64	30.00	33	(15.5)	49	23.11	119	(18.0)	162	25.12
Back pain	9	(4.0)	9	4.10	11	(5.0)	11	5.16	11	(5.2)	14	6.60	31	(4.7)	34	5.27
Arthralgia	5	(2.2)	5	2.28	5	(2.3)	6	2.81	4	(1.9)	5	2.36	14	(2.1)	16	2.48
Muscle spasms	3	(1.3)	5	2.28	2	(0.9)	2	0.94	4	(1.9)	6	2.83	9	(1.4)	13	2.02
Osteoarthritis	3	(1.3)	3	1.37	4	(1.8)	4	1.87	2	(0.9)	2	0.94	9	(1.4)	9	1.40
Periarthritis	2	(0.9)	2	0.91	5	(2.3)	5	2.34	2	(0.9)	2	0.94	9	(1.4)	9	1.40
Spinal osteoarthritis	4	(1.8)	4	1.82	3	(1.4)	3	1.41	2	(0.9)	2	0.94	9	(1.4)	9	1.40
Myalgia	3	(1.3)	3	1.37	3	(1.4)	3	1.41	2	(0.9)	2	0.94	8	(1.2)	8	1.24
Intervertebral disc protrusion	3	(1.3)	3	1.37	2	(0.9)	2	0.94	1	(0.5)	1	0.47	6	(0.9)	6	0.93
Musculoskeletal stiffness	3	(1.3)	3	1.37	0				3	(1.4)	4	1.89	6	(0.9)	7	1.09
Tenosynovitis	2	(0.9)	2	0.91	2	(0.9)	2	0.94	1	(0.5)	1	0.47	5	(0.8)	5	0.78
Musculoskeletal pain	1	(0.4)	1	0.46	2	(0.9)	3	1.41	1	(0.5)	1	0.47	4	(0.6)	5	0.78
Pain in extremity	2	(0.9)	2	0.91	2	(0.9)	2	0.94	0				4	(0.6)	4	0.62
Trigger finger	0				3	(1.4)	4	1.87	1	(0.5)	1	0.47	4	(0.6)	5	0.78
Arthritis	1	(0.4)	1	0.46	1	(0.5)	1	0.47	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Flank pain	1	(0.4)	1	0.46	2	(0.9)	2	0.94	0				3	(0.5)	3	0.47
Joint swelling	1	(0.4)	1	0.46	1	(0.5)	1	0.47	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Lumbar spinal stenosis	0				2	(0.9)	2	0.94	0				2	(0.3)	2	0.31
Osteoporosis	0				2	(0.9)	2	0.94	0				2	(0.3)	2	0.31
Spinal column stenosis	0				1	(0.5)	1	0.47	1	(0.5)	1	0.47	2	(0.3)	2	0.31
Bone pain	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Cervical spinal stenosis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Fasciitis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Intervertebral disc disorder	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Joint contracture	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Musculoskeletal chest pain	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Myalgia intercostal	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Neck pain	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Nodal osteoarthritis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Osteitis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16

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Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Plantar fasciitis	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Rhabdomyolysis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Rheumatoid arthritis	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Spondylolisthesis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Synovial cyst	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Tendon pain	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Tendonitis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Eye disorders	33	(14.6)	38	17.30	22	(9.9)	31	14.53	33	(15.5)	42	19.81	88	(13.3)	111	17.21
Diabetic retinopathy	12	(5.3)	12	5.46	10	(4.5)	12	5.62	7	(3.3)	7	3.30	29	(4.4)	31	4.81
Cataract	3	(1.3)	3	1.37	3	(1.4)	3	1.41	5	(2.3)	5	2.36	11	(1.7)	11	1.71
Asthenopia	1	(0.4)	1	0.46	3	(1.4)	3	1.41	4	(1.9)	4	1.89	8	(1.2)	8	1.24
Conjunctivitis allergic	4	(1.8)	5	2.28	2	(0.9)	2	0.94	2	(0.9)	2	0.94	8	(1.2)	9	1.40
Retinal haemorrhage	2	(0.9)	2	0.91	1	(0.5)	1	0.47	1	(0.5)	1	0.47	4	(0.6)	4	0.62
Vitreous floaters	1	(0.4)	1	0.46	1	(0.5)	1	0.47	2	(0.9)	2	0.94	4	(0.6)	4	0.62
Dry eye	2	(0.9)	2	0.91	0				1	(0.5)	1	0.47	3	(0.5)	3	0.47
Glaucoma	1	(0.4)	1	0.46	0				2	(0.9)	2	0.94	3	(0.5)	3	0.47
Vision blurred	1	(0.4)	1	0.46	1	(0.5)	1	0.47	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Blepharitis	0				1	(0.5)	1	0.47	1	(0.5)	1	0.47	2	(0.3)	2	0.31
Diabetic retinal oedema	1	(0.4)	1	0.46	0				1	(0.5)	1	0.47	2	(0.3)	2	0.31
Macular fibrosis	1	(0.4)	1	0.46	0				1	(0.5)	1	0.47	2	(0.3)	2	0.31
Posterior capsule opacification	1	(0.4)	1	0.46	0				1	(0.5)	1	0.47	2	(0.3)	2	0.31
Retinal detachment	1	(0.4)	1	0.46	0				1	(0.5)	1	0.47	2	(0.3)	2	0.31
Retinopathy	0				0				2	(0.9)	2	0.94	2	(0.3)	2	0.31
Age-related macular degeneration	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Astigmatism	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Blepharitis allergic	0				1	(0.5)	2	0.94	0				1	(0.2)	2	0.31
Blepharospasm	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Chorioretinopathy	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Conjunctival haemorrhage	0				1	(0.5)	2	0.94	0				1	(0.2)	2	0.31

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Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Conjunctivochalasis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Cystoid macular oedema	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Erythema of eyelid	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Eye haemorrhage	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Eye inflammation	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Keratitis	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Macular degeneration	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Macular hole	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Macular oedema	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Ocular discomfort	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Retinal degeneration	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Retinal exudates	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Retinopathy proliferative	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Visual impairment	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Vitreous haemorrhage	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Skin and subcutaneous tissue disorders	25	(11.1)	27	12.29	26	(11.7)	32	15.00	20	(9.4)	25	11.79	71	(10.7)	84	13.02
Eczema	11	(4.9)	12	5.46	6	(2.7)	6	2.81	6	(2.8)	7	3.30	23	(3.5)	25	3.88
Dermatitis contact	2	(0.9)	2	0.91	0				5	(2.3)	6	2.83	7	(1.1)	8	1.24
Pruritus	3	(1.3)	3	1.37	1	(0.5)	2	0.94	2	(0.9)	2	0.94	6	(0.9)	7	1.09
Rash	1	(0.4)	1	0.46	3	(1.4)	3	1.41	0				4	(0.6)	4	0.62
Urticaria	1	(0.4)	1	0.46	3	(1.4)	4	1.87	0				4	(0.6)	5	0.78
Asteatosis	0				0				3	(1.4)	3	1.41	3	(0.5)	3	0.47
Dermatitis allergic	1	(0.4)	1	0.46	2	(0.9)	2	0.94	0				3	(0.5)	3	0.47
Dermatitis atopic	1	(0.4)	1	0.46	2	(0.9)	2	0.94	0				3	(0.5)	3	0.47
Hyperkeratosis	0				3	(1.4)	3	1.41	0				3	(0.5)	3	0.47
Miliaria	1	(0.4)	1	0.46	2	(0.9)	2	0.94	0				3	(0.5)	3	0.47
Dermatitis	0				2	(0.9)	2	0.94	0				2	(0.3)	2	0.31
Ingrowing nail	0				1	(0.5)	1	0.47	1	(0.5)	1	0.47	2	(0.3)	2	0.31
Dermal cyst	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Drug eruption	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Dry skin	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Dyshidrotic eczema	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Granuloma annulare	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Haemorrhage subcutaneous	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Hand dermatitis	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Nail hypertrophy	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Onychoclasis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Onycholysis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Pigmentation disorder	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Psoriasis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Scab	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Skin mass	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Solar dermatitis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Swelling face	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Nervous system disorders	14	(6.2)	19	8.65	31	(14.0)	43	20.16	25	(11.7)	28	13.21	70	(10.6)	90	13.95
Headache	6	(2.7)	8	3.64	6	(2.7)	11	5.16	11	(5.2)	13	6.13	23	(3.5)	32	4.96
Dizziness	2	(0.9)	5	2.28	8	(3.6)	9	4.22	3	(1.4)	3	1.41	13	(2.0)	17	2.64
Hypoaesthesia	1	(0.4)	1	0.46	4	(1.8)	4	1.87	3	(1.4)	3	1.41	8	(1.2)	8	1.24
Diabetic neuropathy	2	(0.9)	2	0.91	3	(1.4)	3	1.41	1	(0.5)	1	0.47	6	(0.9)	6	0.93
Carotid arteriosclerosis	0				3	(1.4)	3	1.41	0				3	(0.5)	3	0.47
Facial paralysis	0				2	(0.9)	2	0.94	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Migraine	0				2	(0.9)	2	0.94	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Head discomfort	0				1	(0.5)	1	0.47	1	(0.5)	2	0.94	2	(0.3)	3	0.47
Somnolence	1	(0.4)	1	0.46	1	(0.5)	2	0.94	0				2	(0.3)	3	0.47
Balance disorder	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Carotid artery stenosis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Carpal tunnel syndrome	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Cervicobrachial syndrome	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Dysgeusia	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Intercostal neuralgia	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Loss of consciousness	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16

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Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Neuralgia	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Presyncope	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Sciatica	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Thrombotic cerebral infarction	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Tongue biting	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Investigations	21	(9.3)	33	15.03	19	(8.6)	32	15.00	27	(12.7)	30	14.15	67	(10.1)	95	14.73
Lipase increased	6	(2.7)	8	3.64	0				14	(6.6)	14	6.60	20	(3.0)	22	3.41
Weight increased	2	(0.9)	2	0.91	11	(5.0)	11	5.16	1	(0.5)	1	0.47	14	(2.1)	14	2.17
Blood proinsulin decreased	4	(1.8)	4	1.82	2	(0.9)	2	0.94	1	(0.5)	1	0.47	7	(1.1)	7	1.09
Insulin C-peptide decreased	3	(1.3)	3	1.37	3	(1.4)	3	1.41	0				6	(0.9)	6	0.93
Amylase increased	2	(0.9)	2	0.91	0				3	(1.4)	3	1.41	5	(0.8)	5	0.78
Free fatty acids decreased	2	(0.9)	3	1.37	3	(1.4)	4	1.87	0				5	(0.8)	7	1.09
Helicobacter test positive	2	(0.9)	2	0.91	1	(0.5)	1	0.47	2	(0.9)	2	0.94	5	(0.8)	5	0.78
Blood creatine phosphokinase increased	0				3	(1.4)	4	1.87	1	(0.5)	1	0.47	4	(0.6)	5	0.78
Blood calcitonin increased	1	(0.4)	1	0.46	0				2	(0.9)	2	0.94	3	(0.5)	3	0.47
Alanine aminotransferase increased	1	(0.4)	1	0.46	1	(0.5)	1	0.47	0				2	(0.3)	2	0.31
Aspartate aminotransferase increased	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Blood creatine phosphokinase MM increased	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Blood potassium increased	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Blood triglycerides increased	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
C-reactive protein increased	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Carbohydrate antigen 125 increased	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Cardiac murmur	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16

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Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Carotid intima-media thickness increased	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Electrocardiogram T wave amplitude decreased	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Eosinophil count increased	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Gamma-glutamyltransferase increased	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Hepatic enzyme increased	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Intraocular pressure increased	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Occult blood positive	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Rheumatoid factor increased	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Urine ketone body present	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Waist circumference increased	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Weight decreased	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
White blood cell count increased	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Injury, poisoning and procedural complications	17	(7.5)	18	8.20	25	(11.3)	33	15.47	21	(9.9)	29	13.68	63	(9.5)	80	12.40
Contusion	5	(2.2)	5	2.28	6	(2.7)	7	3.28	7	(3.3)	8	3.77	18	(2.7)	20	3.10
Ligament sprain	0				3	(1.4)	4	1.87	4	(1.9)	4	1.89	7	(1.1)	8	1.24
Accidental overdose	1	(0.4)	1	0.46	1	(0.5)	1	0.47	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Arthropod bite	1	(0.4)	1	0.46	2	(0.9)	2	0.94	0				3	(0.5)	3	0.47
Arthropod sting	0				1	(0.5)	2	0.94	2	(0.9)	2	0.94	3	(0.5)	4	0.62
Heat illness	1	(0.4)	1	0.46	0				2	(0.9)	2	0.94	3	(0.5)	3	0.47
Rib fracture	1	(0.4)	1	0.46	2	(0.9)	2	0.94	0				3	(0.5)	3	0.47
Laceration	1	(0.4)	1	0.46	0				1	(0.5)	1	0.47	2	(0.3)	2	0.31
Skin abrasion	0				0				2	(0.9)	2	0.94	2	(0.3)	2	0.31
Spinal compression fracture	1	(0.4)	1	0.46	0				1	(0.5)	1	0.47	2	(0.3)	2	0.31
Wound	0				2	(0.9)	2	0.94	0				2	(0.3)	2	0.31

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	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Avulsion fracture	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Bone contusion	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Chest injury	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Clavicle fracture	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Epicondylitis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Excoriation	0				0				1	(0.5)	2	0.94	1	(0.2)	2	0.31
Foreign body in eye	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Hand fracture	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Head injury	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Heat stroke	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Incorrect dose administered	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Limb injury	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Lip injury	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Median nerve injury	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Meniscus injury	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Muscle strain	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Overdose	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Pubis fracture	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Scratch	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Stab wound	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Subcutaneous haematoma	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Suture related complication	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Thermal burn	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Thoracic vertebral fracture	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Tooth fracture	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Tooth injury	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Wrong drug administered	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
General disorders and administration site conditions	16	(7.1)	16	7.29	21	(9.5)	23	10.78	25	(11.7)	28	13.21	62	(9.4)	67	10.39
Malaise	2	(0.9)	2	0.91	3	(1.4)	3	1.41	5	(2.3)	6	2.83	10	(1.5)	11	1.71

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Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Oedema peripheral	4	(1.8)	4	1.82	5	(2.3)	6	2.81	1	(0.5)	1	0.47	10	(1.5)	11	1.71
Oedema	0				3	(1.4)	3	1.41	2	(0.9)	2	0.94	5	(0.8)	5	0.78
Injection site bruising	0				2	(0.9)	2	0.94	2	(0.9)	2	0.94	4	(0.6)	4	0.62
Injection site erythema	1	(0.4)	1	0.46	0				3	(1.4)	3	1.41	4	(0.6)	4	0.62
Fatigue	0				1	(0.5)	1	0.47	2	(0.9)	2	0.94	3	(0.5)	3	0.47
Injection site induration	0				1	(0.5)	1	0.47	2	(0.9)	2	0.94	3	(0.5)	3	0.47
Injection site reaction	2	(0.9)	2	0.91	0				1	(0.5)	1	0.47	3	(0.5)	3	0.47
Pyrexia	0				2	(0.9)	2	0.94	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Asthenia	0				2	(0.9)	2	0.94	0				2	(0.3)	2	0.31
Chest discomfort	0				0				2	(0.9)	2	0.94	2	(0.3)	2	0.31
Injection site pain	1	(0.4)	1	0.46	0				1	(0.5)	1	0.47	2	(0.3)	2	0.31
Administration site mass	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Chills	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Fat tissue increased	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Feeling abnormal	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Feeling hot	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Hunger	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Inflammation	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Infusion site bruising	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Injection site discolouration	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Injection site haemorrhage	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Injection site pruritus	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Injection site swelling	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Pain	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Thirst	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Respiratory, thoracic and mediastinal disorders	25	(11.1)	32	14.57	18	(8.1)	24	11.25	13	(6.1)	17	8.02	56	(8.5)	73	11.32
Upper respiratory tract inflammation	5	(2.2)	7	3.19	3	(1.4)	4	1.87	5	(2.3)	6	2.83	13	(2.0)	17	2.64
Asthma	3	(1.3)	3	1.37	4	(1.8)	4	1.87	3	(1.4)	3	1.41	10	(1.5)	10	1.55

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	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Rhinitis allergic	6	(2.7)	6	2.73	2	(0.9)	2	0.94	2	(0.9)	2	0.94	10	(1.5)	10	1.55
Oropharyngeal pain	2	(0.9)	2	0.91	3	(1.4)	3	1.41	4	(1.9)	4	1.89	9	(1.4)	9	1.40
Cough	3	(1.3)	3	1.37	4	(1.8)	6	2.81	1	(0.5)	1	0.47	8	(1.2)	10	1.55
Sleep apnoea syndrome	2	(0.9)	2	0.91	2	(0.9)	2	0.94	0				4	(0.6)	4	0.62
Emphysema	1	(0.4)	1	0.46	1	(0.5)	1	0.47	0				2	(0.3)	2	0.31
Rhinorrhoea	1	(0.4)	1	0.46	1	(0.5)	1	0.47	0				2	(0.3)	2	0.31
Bronchitis chronic	1	(0.4)	2	0.91	0				0				1	(0.2)	2	0.31
Chronic obstructive pulmonary disease	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Dysphonia	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Pleuritic pain	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Productive cough	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Pulmonary fibrosis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Respiratory disorder	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Sneezing	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Vascular disorders	11	(4.9)	11	5.01	15	(6.8)	15	7.03	7	(3.3)	8	3.77	33	(5.0)	34	5.27
Hypertension	7	(3.1)	7	3.19	11	(5.0)	11	5.16	4	(1.9)	4	1.89	22	(3.3)	22	3.41
Arteriosclerosis	1	(0.4)	1	0.46	1	(0.5)	1	0.47	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Hot flush	1	(0.4)	1	0.46	0				1	(0.5)	1	0.47	2	(0.3)	2	0.31
Orthostatic hypotension	1	(0.4)	1	0.46	0				1	(0.5)	1	0.47	2	(0.3)	2	0.31
Peripheral arterial occlusive disease	0				2	(0.9)	2	0.94	0				2	(0.3)	2	0.31
Hypotension	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Internal haemorrhage	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Varicose vein	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Metabolism and nutrition disorders	7	(3.1)	7	3.19	9	(4.1)	10	4.69	11	(5.2)	13	6.13	27	(4.1)	30	4.65
Decreased appetite	0				2	(0.9)	2	0.94	8	(3.8)	8	3.77	10	(1.5)	10	1.55
Dyslipidaemia	2	(0.9)	2	0.91	2	(0.9)	2	0.94	2	(0.9)	2	0.94	6	(0.9)	6	0.93
Hyperuricaemia	1	(0.4)	1	0.46	3	(1.4)	3	1.41	1	(0.5)	1	0.47	5	(0.8)	5	0.78

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Normal hepatic function: Baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Dehydration	0				1	(0.5)	1	0.47	1	(0.5)	2	0.94	2	(0.3)	3	0.47
Hyperlipidaemia	1	(0.4)	1	0.46	1	(0.5)	1	0.47	0				2	(0.3)	2	0.31
Overweight	2	(0.9)	2	0.91	0				0				2	(0.3)	2	0.31
Gout	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Hypoglycaemia	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Hepatobiliary disorders	8	(3.5)	11	5.01	11	(5.0)	16	7.50	6	(2.8)	8	3.77	25	(3.8)	35	5.43
Hepatic steatosis	5	(2.2)	5	2.28	3	(1.4)	3	1.41	2	(0.9)	2	0.94	10	(1.5)	10	1.55
Cholelithiasis	2	(0.9)	2	0.91	3	(1.4)	3	1.41	2	(0.9)	2	0.94	7	(1.1)	7	1.09
Gallbladder polyp	1	(0.4)	1	0.46	5	(2.3)	5	2.34	1	(0.5)	1	0.47	7	(1.1)	7	1.09
Hepatic cyst	1	(0.4)	1	0.46	1	(0.5)	1	0.47	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Cholecystitis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Cholecystitis acute	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Chronic hepatitis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Drug-induced liver injury	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Hepatic calcification	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Hepatic function abnormal	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Liver disorder	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Non-alcoholic fatty liver	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Cardiac disorders	5	(2.2)	5	2.28	9	(4.1)	9	4.22	8	(3.8)	8	3.77	22	(3.3)	22	3.41
Atrial fibrillation	0				2	(0.9)	2	0.94	2	(0.9)	2	0.94	4	(0.6)	4	0.62
Palpitations	1	(0.4)	1	0.46	1	(0.5)	1	0.47	2	(0.9)	2	0.94	4	(0.6)	4	0.62
Angina pectoris	2	(0.9)	2	0.91	0				0				2	(0.3)	2	0.31
Myocardial ischaemia	0				2	(0.9)	2	0.94	0				2	(0.3)	2	0.31
Acute myocardial infarction	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Atrioventricular block complete	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Atrioventricular block first degree	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Cardiac disorder	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Cardiomegaly	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Coronary artery stenosis	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Sinus arrhythmia	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Sinus node dysfunction	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Supraventricular tachycardia	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Ventricular extrasystoles	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Renal and urinary disorders	8	(3.5)	8	3.64	6	(2.7)	8	3.75	6	(2.8)	7	3.30	20	(3.0)	23	3.57
Renal cyst	4	(1.8)	4	1.82	1	(0.5)	1	0.47	2	(0.9)	2	0.94	7	(1.1)	7	1.09
Nephrolithiasis	1	(0.4)	1	0.46	4	(1.8)	4	1.87	1	(0.5)	1	0.47	6	(0.9)	6	0.93
Calculus urinary	0				0				2	(0.9)	2	0.94	2	(0.3)	2	0.31
Chronic kidney disease	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Diabetic nephropathy	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Hydronephrosis	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Nephrocalcinosis	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Nephrotic syndrome	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Renal impairment	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Ureterolithiasis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Urinary retention	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Ear and labyrinth disorders	7	(3.1)	7	3.19	5	(2.3)	6	2.81	5	(2.3)	5	2.36	17	(2.6)	18	2.79
Vertigo	4	(1.8)	4	1.82	2	(0.9)	3	1.41	3	(1.4)	3	1.41	9	(1.4)	10	1.55
Tinnitus	1	(0.4)	1	0.46	2	(0.9)	2	0.94	1	(0.5)	1	0.47	4	(0.6)	4	0.62
Vertigo positional	2	(0.9)	2	0.91	0				1	(0.5)	1	0.47	3	(0.5)	3	0.47
Otorrhoea	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Psychiatric disorders	4	(1.8)	4	1.82	5	(2.3)	5	2.34	6	(2.8)	6	2.83	15	(2.3)	15	2.33
Insomnia	4	(1.8)	4	1.82	3	(1.4)	3	1.41	2	(0.9)	2	0.94	9	(1.4)	9	1.40
Sleep disorder	0				0				2	(0.9)	2	0.94	2	(0.3)	2	0.31
Anxiety	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Depression	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Neurosis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Suicide attempt	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16

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Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Reproductive system and breast disorders	5	(2.2)	5	2.28	7	(3.2)	9	4.22	3	(1.4)	7	3.30	15	(2.3)	21	3.26
Pruritus genital	1	(0.4)	1	0.46	3	(1.4)	3	1.41	0				4	(0.6)	4	0.62
Ovarian cyst	1	(0.4)	1	0.46	1	(0.5)	1	0.47	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Menopausal symptoms	0				1	(0.5)	1	0.47	1	(0.5)	1	0.47	2	(0.3)	2	0.31
Balanoposthitis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Benign prostatic hyperplasia	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Cervical cyst	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Cervical polyp	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Endometrial hyperplasia	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Gynaecomastia	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Menorrhagia	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Menstruation irregular	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Prostatic calcification	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Uterine disorder	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Uterine haemorrhage	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Uterine prolapse	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	(1.8)	4	1.82	6	(2.7)	8	3.75	3	(1.4)	3	1.41	13	(2.0)	15	2.33
Colon adenoma	0				0				3	(1.4)	3	1.41	3	(0.5)	3	0.47
Benign neoplasm of thyroid gland	0				2	(0.9)	2	0.94	0				2	(0.3)	2	0.31
Acrochordon	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Adrenal neoplasm	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Benign neoplasm of bladder	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Gastric cancer stage I	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Lung adenocarcinoma	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Lung neoplasm malignant	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Metastases to lymph nodes	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Oligodendroglioma	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16

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Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Thyroid neoplasm	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Uterine leiomyoma	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Endocrine disorders	4	(1.8)	4	1.82	4	(1.8)	5	2.34	2	(0.9)	2	0.94	10	(1.5)	11	1.71
Thyroid cyst	2	(0.9)	2	0.91	4	(1.8)	4	1.87	1	(0.5)	1	0.47	7	(1.1)	7	1.09
Thyroid mass	1	(0.4)	1	0.46	1	(0.5)	1	0.47	0				2	(0.3)	2	0.31
Hyperthyroidism	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Silent thyroiditis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Blood and lymphatic system disorders	2	(0.9)	2	0.91	1	(0.5)	1	0.47	4	(1.9)	4	1.89	7	(1.1)	7	1.09
Iron deficiency anaemia	1	(0.4)	1	0.46	1	(0.5)	1	0.47	2	(0.9)	2	0.94	4	(0.6)	4	0.62
Anaemia	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Polycythaemia	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Splenomegaly	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Surgical and medical procedures	1	(0.4)	1	0.46	2	(0.9)	3	1.41	1	(0.5)	1	0.47	4	(0.6)	5	0.78
Tooth extraction	1	(0.4)	1	0.46	1	(0.5)	2	0.94	0				2	(0.3)	3	0.47
Cataract operation	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Large intestinal polypectomy	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Immune system disorders	1	(0.4)	1	0.46	1	(0.5)	1	0.47	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Seasonal allergy	1	(0.4)	1	0.46	0				1	(0.5)	1	0.47	2	(0.3)	2	0.31
Hypersensitivity	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Congenital, familial and genetic disorders	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Epidermolysis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16

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2.7.4.7.1-36 ベースライン時に肝機能障害を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	49				49				60				158			
PYE (years)	48.38				48.47				59.81				156.65			
Events	41	(83.7)	213	440.31	40	(81.6)	144	297.12	52	(86.7)	182	304.32	133	(84.2)	539	344.09
Infections and infestations	34	(69.4)	80	165.37	27	(55.1)	57	117.61	31	(51.7)	51	85.28	92	(58.2)	188	120.02
Viral upper respiratory tract infection	26	(53.1)	52	107.49	13	(26.5)	25	51.58	18	(30.0)	29	48.49	57	(36.1)	106	67.67
Influenza	6	(12.2)	6	12.40	3	(6.1)	3	6.19	3	(5.0)	3	5.02	12	(7.6)	12	7.66
Pharyngitis	3	(6.1)	4	8.27	4	(8.2)	7	14.44	1	(1.7)	1	1.67	8	(5.1)	12	7.66
Gastroenteritis	3	(6.1)	3	6.20	2	(4.1)	3	6.19	1	(1.7)	1	1.67	6	(3.8)	7	4.47
Bronchitis	1	(2.0)	1	2.07	2	(4.1)	3	6.19	2	(3.3)	2	3.34	5	(3.2)	6	3.83
Cystitis	2	(4.1)	2	4.13	1	(2.0)	1	2.06	2	(3.3)	2	3.34	5	(3.2)	5	3.19
Conjunctivitis	2	(4.1)	2	4.13	1	(2.0)	1	2.06	1	(1.7)	1	1.67	4	(2.5)	4	2.55
Helicobacter infection	0				1	(2.0)	1	2.06	2	(3.3)	2	3.34	3	(1.9)	3	1.92
Herpes zoster	1	(2.0)	1	2.07	2	(4.1)	2	4.13	0				3	(1.9)	3	1.92
Nasopharyngitis	0				3	(6.1)	5	10.32	0				3	(1.9)	5	3.19
Periodontitis	1	(2.0)	1	2.07	1	(2.0)	1	2.06	1	(1.7)	1	1.67	3	(1.9)	3	1.92
Tinea pedis	1	(2.0)	1	2.07	1	(2.0)	1	2.06	1	(1.7)	1	1.67	3	(1.9)	3	1.92
Cellulitis	0				1	(2.0)	1	2.06	1	(1.7)	1	1.67	2	(1.3)	2	1.28
Otitis externa	1	(2.0)	1	2.07	0				1	(1.7)	1	1.67	2	(1.3)	2	1.28
Abdominal abscess	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Acute sinusitis	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Dermatitis infected	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Enteritis infectious	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Folliculitis	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Gingivitis	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Hordeolum	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Infected dermal cyst	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Oral herpes	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Paronychia	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64

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Adverse events by system organ class and preferred term - treatment emergent - subjects with hepatic impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Pharyngotonsillitis	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Pneumonia mycoplasmal	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Pulpitis dental	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Sinusitis	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Tonsillitis	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Gastrointestinal disorders	19	(38.8)	40	82.69	8	(16.3)	21	43.33	24	(40.0)	56	93.64	51	(32.3)	117	74.69
Constipation	8	(16.3)	9	18.60	1	(2.0)	1	2.06	10	(16.7)	10	16.72	19	(12.0)	20	12.77
Diarrhoea	4	(8.2)	5	10.34	2	(4.1)	2	4.13	6	(10.0)	7	11.70	12	(7.6)	14	8.94
Nausea	2	(4.1)	3	6.20	1	(2.0)	3	6.19	7	(11.7)	8	13.38	10	(6.3)	14	8.94
Abdominal discomfort	2	(4.1)	3	6.20	2	(4.1)	2	4.13	3	(5.0)	3	5.02	7	(4.4)	8	5.11
Abdominal pain upper	3	(6.1)	3	6.20	1	(2.0)	1	2.06	1	(1.7)	1	1.67	5	(3.2)	5	3.19
Periodontal disease	3	(6.1)	4	8.27	0				2	(3.3)	2	3.34	5	(3.2)	6	3.83
Vomiting	2	(4.1)	4	8.27	1	(2.0)	1	2.06	2	(3.3)	2	3.34	5	(3.2)	7	4.47
Gastritis	2	(4.1)	2	4.13	1	(2.0)	1	2.06	1	(1.7)	1	1.67	4	(2.5)	4	2.55
Gastrooesophageal reflux disease	1	(2.0)	1	2.07	1	(2.0)	1	2.06	2	(3.3)	2	3.34	4	(2.5)	4	2.55
Large intestine polyp	0				1	(2.0)	1	2.06	3	(5.0)	3	5.02	4	(2.5)	4	2.55
Stomatitis	2	(4.1)	3	6.20	0				1	(1.7)	1	1.67	3	(1.9)	4	2.55
Abdominal pain	0				1	(2.0)	3	6.19	1	(1.7)	1	1.67	2	(1.3)	4	2.55
Chronic gastritis	0				1	(2.0)	1	2.06	1	(1.7)	1	1.67	2	(1.3)	2	1.28
Dental caries	0				1	(2.0)	1	2.06	1	(1.7)	1	1.67	2	(1.3)	2	1.28
Dyspepsia	0				1	(2.0)	1	2.06	1	(1.7)	1	1.67	2	(1.3)	2	1.28
Eructation	0				0				2	(3.3)	2	3.34	2	(1.3)	2	1.28
Faeces soft	0				0				2	(3.3)	3	5.02	2	(1.3)	3	1.92
Abdominal distension	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Abdominal pain lower	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Brunner's gland hyperplasia	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Colitis	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Flatulence	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Functional gastrointestinal disorder	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64

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	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Gastric polyps	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Gastric ulcer	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Gingival swelling	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Melaena	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Oesophageal polyp	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Pancreatic cyst	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Musculoskeletal and connective tissue disorders	11	(22.4)	14	28.94	7	(14.3)	7	14.44	8	(13.3)	11	18.39	26	(16.5)	32	20.43
Back pain	3	(6.1)	3	6.20	1	(2.0)	1	2.06	2	(3.3)	2	3.34	6	(3.8)	6	3.83
Arthralgia	2	(4.1)	2	4.13	1	(2.0)	1	2.06	1	(1.7)	1	1.67	4	(2.5)	4	2.55
Myalgia	3	(6.1)	3	6.20	0				0				3	(1.9)	3	1.92
Musculoskeletal stiffness	0				1	(2.0)	1	2.06	1	(1.7)	1	1.67	2	(1.3)	2	1.28
Neck pain	1	(2.0)	1	2.07	0				1	(1.7)	1	1.67	2	(1.3)	2	1.28
Osteoarthritis	0				2	(4.1)	2	4.13	0				2	(1.3)	2	1.28
Tenosynovitis	0				0				2	(3.3)	2	3.34	2	(1.3)	2	1.28
Arthritis	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Groin pain	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Intervertebral disc disorder	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Intervertebral disc protrusion	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Muscle spasms	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Musculoskeletal pain	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Osteoporosis	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Pain in extremity	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Periarthritis	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Spinal osteoarthritis	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Trigger finger	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Eye disorders	12	(24.5)	14	28.94	6	(12.2)	6	12.38	6	(10.0)	6	10.03	24	(15.2)	26	16.60
Diabetic retinopathy	5	(10.2)	5	10.34	2	(4.1)	2	4.13	4	(6.7)	4	6.69	11	(7.0)	11	7.02
Dry eye	1	(2.0)	1	2.07	2	(4.1)	2	4.13	0				3	(1.9)	3	1.92

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	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Cataract	1	(2.0)	1	2.07	1	(2.0)	1	2.06	0				2	(1.3)	2	1.28
Glaucoma	1	(2.0)	1	2.07	0				1	(1.7)	1	1.67	2	(1.3)	2	1.28
Conjunctival haemorrhage	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Diabetic retinal oedema	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Exposure keratitis	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Keratitis	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Macular fibrosis	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Retinal tear	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Vision blurred	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Vitreous floaters	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Investigations	9	(18.4)	10	20.67	8	(16.3)	11	22.70	7	(11.7)	9	15.05	24	(15.2)	30	19.15
Weight increased	2	(4.1)	2	4.13	8	(16.3)	8	16.51	0				10	(6.3)	10	6.38
Free fatty acids decreased	2	(4.1)	2	4.13	1	(2.0)	1	2.06	1	(1.7)	1	1.67	4	(2.5)	4	2.55
Alanine aminotransferase increased	0				0				2	(3.3)	2	3.34	2	(1.3)	2	1.28
Blood proinsulin decreased	1	(2.0)	1	2.07	1	(2.0)	1	2.06	0				2	(1.3)	2	1.28
Blood triglycerides increased	0				0				2	(3.3)	2	3.34	2	(1.3)	2	1.28
Pancreatic enzymes increased	0				0				2	(3.3)	2	3.34	2	(1.3)	2	1.28
Blood pressure increased	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Electrocardiogram QT prolonged	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Electrocardiogram T wave amplitude decreased	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Gamma-glutamyltransferase increased	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Glomerular filtration rate decreased	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Helicobacter test positive	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Insulin C-peptide decreased	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Lipase increased	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64

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	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Skin and subcutaneous tissue disorders	7	(14.3)	8	16.54	6	(12.2)	8	16.51	8	(13.3)	8	13.38	21	(13.3)	24	15.32
Eczema	5	(10.2)	6	12.40	0				3	(5.0)	3	5.02	8	(5.1)	9	5.75
Pruritus	0				2	(4.1)	2	4.13	1	(1.7)	1	1.67	3	(1.9)	3	1.92
Dermatitis contact	0				1	(2.0)	1	2.06	1	(1.7)	1	1.67	2	(1.3)	2	1.28
Acne	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Blister	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Chronic pigmented purpura	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Dermal cyst	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Haemorrhage subcutaneous	0				1	(2.0)	3	6.19	0				1	(0.6)	3	1.92
Rash	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Seborrhoeic dermatitis	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Skin mass	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Nervous system disorders	7	(14.3)	10	20.67	5	(10.2)	6	12.38	6	(10.0)	7	11.70	18	(11.4)	23	14.68
Headache	1	(2.0)	3	6.20	1	(2.0)	1	2.06	4	(6.7)	4	6.69	6	(3.8)	8	5.11
Hypoaesthesia	1	(2.0)	2	4.13	2	(4.1)	2	4.13	0				3	(1.9)	4	2.55
Diabetic neuropathy	0				1	(2.0)	1	2.06	1	(1.7)	1	1.67	2	(1.3)	2	1.28
Dysgeusia	0				0				2	(3.3)	2	3.34	2	(1.3)	2	1.28
Cerebral infarction	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Dizziness	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Facial paralysis	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Hypoglycaemic unconsciousness	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Lumbar radiculopathy	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Neuropathy peripheral	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Thalamic infarction	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Injury, poisoning and procedural complications	5	(10.2)	6	12.40	4	(8.2)	4	8.25	7	(11.7)	7	11.70	16	(10.1)	17	10.85
Arthropod bite	1	(2.0)	1	2.07	0				1	(1.7)	1	1.67	2	(1.3)	2	1.28
Arthropod sting	1	(2.0)	1	2.07	0				1	(1.7)	1	1.67	2	(1.3)	2	1.28

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	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Contusion	0				0				2	(3.3)	2	3.34	2	(1.3)	2	1.28
Ligament sprain	1	(2.0)	2	4.13	1	(2.0)	1	2.06	0				2	(1.3)	3	1.92
Femoral neck fracture	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Foreign body in eye	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Lower limb fracture	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Lumbar vertebral fracture	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Muscle injury	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Rib fracture	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Spinal compression fracture	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Tooth injury	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Respiratory, thoracic and mediastinal disorders	3	(6.1)	4	8.27	6	(12.2)	6	12.38	3	(5.0)	3	5.02	12	(7.6)	13	8.30
Upper respiratory tract inflammation	1	(2.0)	1	2.07	3	(6.1)	3	6.19	1	(1.7)	1	1.67	5	(3.2)	5	3.19
Sleep apnoea syndrome	0				2	(4.1)	2	4.13	1	(1.7)	1	1.67	3	(1.9)	3	1.92
Asthma	1	(2.0)	1	2.07	1	(2.0)	1	2.06	0				2	(1.3)	2	1.28
Pharyngeal oedema	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Rhinitis allergic	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Rhinorrhoea	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Metabolism and nutrition disorders	3	(6.1)	3	6.20	4	(8.2)	4	8.25	4	(6.7)	4	6.69	11	(7.0)	11	7.02
Decreased appetite	1	(2.0)	1	2.07	1	(2.0)	1	2.06	3	(5.0)	3	5.02	5	(3.2)	5	3.19
Gout	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Hyperlipasaemia	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Hypertriglyceridaemia	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Hypokalaemia	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Obesity	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Overweight	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64

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General disorders and administration site conditions	2	(4.1)	3	6.20	4	(8.2)	4	8.25	4	(6.7)	6	10.03	10	(6.3)	13	8.30
Injection site pruritus	1	(2.0)	1	2.07	0				1	(1.7)	1	1.67	2	(1.3)	2	1.28
Oedema peripheral	0				2	(4.1)	2	4.13	0				2	(1.3)	2	1.28
Fatigue	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Injection site induration	0				0				1	(1.7)	2	3.34	1	(0.6)	2	1.28
Injection site mass	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Injection site reaction	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Injection site swelling	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Malaise	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Peripheral swelling	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Sense of oppression	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Hepatobiliary disorders	2	(4.1)	2	4.13	1	(2.0)	1	2.06	6	(10.0)	7	11.70	9	(5.7)	10	6.38
Cholelithiasis	1	(2.0)	1	2.07	0				1	(1.7)	1	1.67	2	(1.3)	2	1.28
Hepatic steatosis	1	(2.0)	1	2.07	0				1	(1.7)	1	1.67	2	(1.3)	2	1.28
Non-alcoholic fatty liver	0				1	(2.0)	1	2.06	1	(1.7)	1	1.67	2	(1.3)	2	1.28
Gallbladder polyp	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Hepatic cyst	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Hepatic function abnormal	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Hepatic mass	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Psychiatric disorders	2	(4.1)	2	4.13	4	(8.2)	4	8.25	0				6	(3.8)	6	3.83
Insomnia	2	(4.1)	2	4.13	3	(6.1)	3	6.19	0				5	(3.2)	5	3.19
Depression	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Cardiac disorders	2	(4.1)	2	4.13	0				3	(5.0)	3	5.02	5	(3.2)	5	3.19
Supraventricular extrasystoles	0				0				2	(3.3)	2	3.34	2	(1.3)	2	1.28
Palpitations	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Tachycardia	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64

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PYE: Patient years of exposure (1 PYE = 365.25 days),
Hepatic impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with hepatic impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Ventricular extrasystoles	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Vascular disorders	4	(8.2)	4	8.27	1	(2.0)	1	2.06	0				5	(3.2)	5	3.19
Hypertension	3	(6.1)	3	6.20	1	(2.0)	1	2.06	0				4	(2.5)	4	2.55
Arteriosclerosis	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Immune system disorders	2	(4.1)	3	6.20	1	(2.0)	1	2.06	1	(1.7)	1	1.67	4	(2.5)	5	3.19
Seasonal allergy	1	(2.0)	1	2.07	1	(2.0)	1	2.06	1	(1.7)	1	1.67	3	(1.9)	3	1.92
Allergy to arthropod sting	1	(2.0)	2	4.13	0				0				1	(0.6)	2	1.28
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(4.1)	2	4.13	0				2	(3.3)	2	3.34	4	(2.5)	4	2.55
Skin papilloma	2	(4.1)	2	4.13	0				0				2	(1.3)	2	1.28
Basal cell carcinoma	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Breast cancer	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Renal and urinary disorders	2	(4.1)	2	4.13	1	(2.0)	1	2.06	0				3	(1.9)	3	1.92
Renal cyst	1	(2.0)	1	2.07	1	(2.0)	1	2.06	0				2	(1.3)	2	1.28
Ureterolithiasis	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Ear and labyrinth disorders	2	(4.1)	4	8.27	0				0				2	(1.3)	4	2.55
Sudden hearing loss	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Vertigo	1	(2.0)	3	6.20	0				0				1	(0.6)	3	1.92
Endocrine disorders	0				2	(4.1)	2	4.13	0				2	(1.3)	2	1.28
Thyroid cyst	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Thyroid mass	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Surgical and medical procedures	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Cardiac ablation	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64

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2.7.4.7.1-37 ベースライン時に正常肝機能を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	79				88				167			
PYE (years)	40.82				43.70				84.52			
Events	64	(81.0)	226	553.63	66	(75.0)	172	393.58	130	(77.8)	398	470.88
Gastrointestinal disorders	38	(48.1)	70	171.48	22	(25.0)	34	77.80	60	(35.9)	104	123.04
Diarrhoea	11	(13.9)	15	36.75	3	(3.4)	3	6.86	14	(8.4)	18	21.30
Constipation	8	(10.1)	9	22.05	4	(4.5)	4	9.15	12	(7.2)	13	15.38
Nausea	8	(10.1)	9	22.05	4	(4.5)	5	11.44	12	(7.2)	14	16.56
Abdominal discomfort	7	(8.9)	7	17.15	4	(4.5)	4	9.15	11	(6.6)	11	13.01
Vomiting	7	(8.9)	7	17.15	1	(1.1)	1	2.29	8	(4.8)	8	9.46
Chronic gastritis	3	(3.8)	4	9.80	1	(1.1)	1	2.29	4	(2.4)	5	5.92
Gastrooesophageal reflux disease	2	(2.5)	2	4.90	2	(2.3)	2	4.58	4	(2.4)	4	4.73
Dyspepsia	2	(2.5)	3	7.35	1	(1.1)	1	2.29	3	(1.8)	4	4.73
Hiatus hernia	3	(3.8)	3	7.35	0				3	(1.8)	3	3.55
Abdominal pain	1	(1.3)	1	2.45	1	(1.1)	1	2.29	2	(1.2)	2	2.37
Dental caries	1	(1.3)	1	2.45	1	(1.1)	1	2.29	2	(1.2)	2	2.37
Faeces soft	1	(1.3)	1	2.45	1	(1.1)	1	2.29	2	(1.2)	2	2.37
Gastritis	1	(1.3)	1	2.45	1	(1.1)	1	2.29	2	(1.2)	2	2.37
Gastritis erosive	1	(1.3)	1	2.45	1	(1.1)	1	2.29	2	(1.2)	2	2.37
Abdominal distension	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Duodenal ulcer	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Enteritis	1	(1.3)	2	4.90	0				1	(0.6)	2	2.37
Epigastric discomfort	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Food poisoning	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Gastrointestinal motility disorder	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Glossitis	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Hyperchlorhydria	1	(1.3)	2	4.90	0				1	(0.6)	2	2.37
Large intestine polyp	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Oesophageal disorder	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Periodontal disease	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Stomatitis	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Infections and infestations	29	(36.7)	46	112.69	27	(30.7)	38	86.95	56	(33.5)	84	99.38
Viral upper respiratory tract infection	16	(20.3)	21	51.44	17	(19.3)	21	48.05	33	(19.8)	42	49.69
Pharyngitis	5	(6.3)	6	14.70	1	(1.1)	2	4.58	6	(3.6)	8	9.46
Bronchitis	1	(1.3)	1	2.45	3	(3.4)	3	6.86	4	(2.4)	4	4.73
Gastroenteritis	2	(2.5)	4	9.80	2	(2.3)	2	4.58	4	(2.4)	6	7.10
Herpes zoster	2	(2.5)	2	4.90	1	(1.1)	1	2.29	3	(1.8)	3	3.55
Influenza	1	(1.3)	1	2.45	2	(2.3)	2	4.58	3	(1.8)	3	3.55
Upper respiratory tract infection	1	(1.3)	1	2.45	2	(2.3)	3	6.86	3	(1.8)	4	4.73
Periodontitis	2	(2.5)	2	4.90	0				2	(1.2)	2	2.37
Sinusitis	2	(2.5)	2	4.90	0				2	(1.2)	2	2.37
Adenoviral conjunctivitis	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Cellulitis	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Cystitis	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Gingivitis	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Infected dermal cyst	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Otitis externa	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Tinea pedis	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Tonsillitis	1	(1.3)	2	4.90	0				1	(0.6)	2	2.37
Upper respiratory tract infection bacterial	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Eye disorders	18	(22.8)	19	46.54	15	(17.0)	17	38.90	33	(19.8)	36	42.59
Diabetic retinopathy	13	(16.5)	14	34.30	12	(13.6)	13	29.75	25	(15.0)	27	31.94
Blepharospasm	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Cataract	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Cataract nuclear	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Conjunctival haemorrhage	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Pingueculitis	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Posterior capsule opacification	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Retinal detachment	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Retinal haemorrhage	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Retinopathy	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Musculoskeletal and connective tissue disorders	11	(13.9)	14	34.30	13	(14.8)	14	32.04	24	(14.4)	28	33.13
Back pain	4	(5.1)	5	12.25	5	(5.7)	5	11.44	9	(5.4)	10	11.83
Arthralgia	1	(1.3)	1	2.45	1	(1.1)	1	2.29	2	(1.2)	2	2.37
Intervertebral disc protrusion	1	(1.3)	1	2.45	1	(1.1)	1	2.29	2	(1.2)	2	2.37
Periarthritis	0				2	(2.3)	2	4.58	2	(1.2)	2	2.37
Tenosynovitis	1	(1.3)	1	2.45	1	(1.1)	1	2.29	2	(1.2)	2	2.37
Arthritis	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Flank pain	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Muscle spasms	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Musculoskeletal pain	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Musculoskeletal stiffness	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Myalgia	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Neck pain	1	(1.3)	2	4.90	0				1	(0.6)	2	2.37
Osteoarthritis	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Trigger finger	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Injury, poisoning and procedural complications	9	(11.4)	13	31.85	8	(9.1)	9	20.59	17	(10.2)	22	26.03
Contusion	2	(2.5)	2	4.90	3	(3.4)	3	6.86	5	(3.0)	5	5.92
Laceration	2	(2.5)	2	4.90	1	(1.1)	1	2.29	3	(1.8)	3	3.55
Fall	2	(2.5)	2	4.90	0				2	(1.2)	2	2.37
Arthropod bite	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Excoriation	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Fractured coccyx	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Heat illness	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Heat stroke	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Hip fracture	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Ligament sprain	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Postoperative fever	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Thermal burn	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Tooth fracture	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18

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Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Tooth injury	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Wrong drug administered	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Nervous system disorders	9	(11.4)	11	26.95	8	(9.1)	10	22.88	17	(10.2)	21	24.85
Headache	3	(3.8)	3	7.35	1	(1.1)	1	2.29	4	(2.4)	4	4.73
Dizziness	2	(2.5)	2	4.90	1	(1.1)	1	2.29	3	(1.8)	3	3.55
Hypoaesthesia	2	(2.5)	2	4.90	1	(1.1)	1	2.29	3	(1.8)	3	3.55
Carpal tunnel syndrome	1	(1.3)	1	2.45	1	(1.1)	1	2.29	2	(1.2)	2	2.37
Diabetic neuropathy	1	(1.3)	1	2.45	1	(1.1)	1	2.29	2	(1.2)	2	2.37
Dysgeusia	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Lacunar infarction	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Loss of consciousness	0				1	(1.1)	2	4.58	1	(0.6)	2	2.37
Migraine	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Neuropathy peripheral	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Sciatica	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
General disorders and administration site conditions	7	(8.9)	8	19.60	8	(9.1)	8	18.31	15	(9.0)	16	18.93
Inflammation	1	(1.3)	1	2.45	2	(2.3)	2	4.58	3	(1.8)	3	3.55
Pyrexia	2	(2.5)	2	4.90	1	(1.1)	1	2.29	3	(1.8)	3	3.55
Administration site induration	0				2	(2.3)	2	4.58	2	(1.2)	2	2.37
Oedema peripheral	1	(1.3)	1	2.45	1	(1.1)	1	2.29	2	(1.2)	2	2.37
Generalised oedema	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Induration	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Injection site discomfort	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Injection site induration	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Malaise	1	(1.3)	2	4.90	0				1	(0.6)	2	2.37
Metabolism and nutrition disorders	10	(12.7)	10	24.50	3	(3.4)	3	6.86	13	(7.8)	13	15.38
Decreased appetite	5	(6.3)	5	12.25	0				5	(3.0)	5	5.92
Dyslipidaemia	2	(2.5)	2	4.90	1	(1.1)	1	2.29	3	(1.8)	3	3.55
Gout	2	(2.5)	2	4.90	1	(1.1)	1	2.29	3	(1.8)	3	3.55

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Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Dehydration	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Hyperuricaemia	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Investigations	7	(8.9)	7	17.15	5	(5.7)	5	11.44	12	(7.2)	12	14.20
Helicobacter test positive	1	(1.3)	1	2.45	2	(2.3)	2	4.58	3	(1.8)	3	3.55
Lipase increased	2	(2.5)	2	4.90	0				2	(1.2)	2	2.37
Electrocardiogram ST-T segment depression	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Electrocardiogram T wave inversion	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Free fatty acids decreased	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Gamma-glutamyltransferase increased	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Glomerular filtration rate decreased	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Oxygen saturation decreased	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Weight decreased	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Skin and subcutaneous tissue disorders	3	(3.8)	3	7.35	8	(9.1)	8	18.31	11	(6.6)	11	13.01
Eczema	1	(1.3)	1	2.45	3	(3.4)	3	6.86	4	(2.4)	4	4.73
Dermatitis	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Hyperkeratosis	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Penile ulceration	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Pustular psoriasis	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Rash	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Skin irritation	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Skin swelling	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Respiratory, thoracic and mediastinal disorders	2	(2.5)	4	9.80	6	(6.8)	6	13.73	8	(4.8)	10	11.83
Upper respiratory tract inflammation	0				3	(3.4)	3	6.86	3	(1.8)	3	3.55
Atelectasis	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Bronchitis chronic	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Cough	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Oropharyngeal pain	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Pleural effusion	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Respiratory tract inflammation	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Normal hepatic function: Baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Sputum increased	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Vascular disorders	5	(6.3)	5	12.25	2	(2.3)	2	4.58	7	(4.2)	7	8.28
Hypertension	3	(3.8)	3	7.35	2	(2.3)	2	4.58	5	(3.0)	5	5.92
Arteriosclerosis	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Orthostatic hypotension	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Renal and urinary disorders	4	(5.1)	7	17.15	2	(2.3)	2	4.58	6	(3.6)	9	10.65
Nephrolithiasis	2	(2.5)	2	4.90	1	(1.1)	1	2.29	3	(1.8)	3	3.55
Renal cyst	2	(2.5)	2	4.90	1	(1.1)	1	2.29	3	(1.8)	3	3.55
Acute kidney injury	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Haematuria	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Ureterolithiasis	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(2.5)	2	4.90	2	(2.3)	2	4.58	4	(2.4)	4	4.73
Adenocarcinoma	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Pancreatic carcinoma	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Renal cell carcinoma	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Uterine leiomyoma	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Ear and labyrinth disorders	1	(1.3)	1	2.45	2	(2.3)	3	6.86	3	(1.8)	4	4.73
Vertigo	1	(1.3)	1	2.45	2	(2.3)	3	6.86	3	(1.8)	4	4.73
Hepatobiliary disorders	0				3	(3.4)	3	6.86	3	(1.8)	3	3.55
Cholecystitis acute	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Cholelithiasis	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Hepatic steatosis	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Psychiatric disorders	1	(1.3)	1	2.45	2	(2.3)	2	4.58	3	(1.8)	3	3.55
Insomnia	1	(1.3)	1	2.45	2	(2.3)	2	4.58	3	(1.8)	3	3.55

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Normal hepatic function: Baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Cardiac disorders	2	(2.5)	3	7.35	0				2	(1.2)	3	3.55
Acute myocardial infarction	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Cardiac failure congestive	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Supraventricular extrasystoles	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Blood and lymphatic system disorders	0				1	(1.1)	3	6.86	1	(0.6)	3	3.55
Leukopenia	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Lymphopenia	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Neutropenia	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Endocrine disorders	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Thyroid mass	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Immune system disorders	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Seasonal allergy	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Reproductive system and breast disorders	0				1	(1.1)	3	6.86	1	(0.6)	3	3.55
Uterine cyst	0				1	(1.1)	2	4.58	1	(0.6)	2	2.37
Uterine mass	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
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Normal hepatic function: Baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower,
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2.7.4.7.1-38 ベースライン時に肝機能障害を有する被験者における有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	26				17				43			
PYE (years)	13.46				8.56				22.02			
Events	18	(69.2)	54	401.29	14	(82.4)	38	443.72	32	(74.4)	92	417.79
Infections and infestations	6	(23.1)	11	81.74	11	(64.7)	14	163.48	17	(39.5)	25	113.53
Viral upper respiratory tract infection	5	(19.2)	6	44.59	7	(41.2)	9	105.09	12	(27.9)	15	68.12
Bronchitis	0				2	(11.8)	2	23.35	2	(4.7)	2	9.08
Gastroenteritis	2	(7.7)	2	14.86	0				2	(4.7)	2	9.08
Abscess	0				1	(5.9)	1	11.68	1	(2.3)	1	4.54
Cystitis	0				1	(5.9)	1	11.68	1	(2.3)	1	4.54
Herpes simplex	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Hordeolum	0				1	(5.9)	1	11.68	1	(2.3)	1	4.54
Sinusitis	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Urinary tract infection	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Eye disorders	4	(15.4)	5	37.16	5	(29.4)	6	70.06	9	(20.9)	11	49.95
Diabetic retinopathy	4	(15.4)	4	29.73	5	(29.4)	5	58.38	9	(20.9)	9	40.87
Cataract	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Dry eye	0				1	(5.9)	1	11.68	1	(2.3)	1	4.54
Gastrointestinal disorders	7	(26.9)	18	133.76	2	(11.8)	6	70.06	9	(20.9)	24	108.99
Diarrhoea	4	(15.4)	5	37.16	2	(11.8)	3	35.03	6	(14.0)	8	36.33
Vomiting	2	(7.7)	4	29.73	1	(5.9)	1	11.68	3	(7.0)	5	22.71
Abdominal discomfort	1	(3.8)	1	7.43	1	(5.9)	1	11.68	2	(4.7)	2	9.08
Nausea	2	(7.7)	3	22.29	0				2	(4.7)	3	13.62
Constipation	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Dyspepsia	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Enteritis	0				1	(5.9)	1	11.68	1	(2.3)	1	4.54
Gastritis	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Gastrooesophageal reflux disease	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54

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PYE: Patient years of exposure (1 PYE = 365.25 days),
Hepatic impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with hepatic impairment at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Varices oesophageal	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Metabolism and nutrition disorders	5	(19.2)	5	37.16	0				5	(11.6)	5	22.71
Decreased appetite	3	(11.5)	3	22.29	0				3	(7.0)	3	13.62
Hyperuricaemia	2	(7.7)	2	14.86	0				2	(4.7)	2	9.08
General disorders and administration site conditions	2	(7.7)	2	14.86	2	(11.8)	2	23.35	4	(9.3)	4	18.16
Malaise	1	(3.8)	1	7.43	1	(5.9)	1	11.68	2	(4.7)	2	9.08
Oedema peripheral	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Pyrexia	0				1	(5.9)	1	11.68	1	(2.3)	1	4.54
Musculoskeletal and connective tissue disorders	3	(11.5)	4	29.73	1	(5.9)	1	11.68	4	(9.3)	5	22.71
Arthralgia	2	(7.7)	2	14.86	0				2	(4.7)	2	9.08
Back pain	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Muscle spasms	0				1	(5.9)	1	11.68	1	(2.3)	1	4.54
Musculoskeletal pain	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Respiratory, thoracic and mediastinal disorders	4	(15.4)	5	37.16	0				4	(9.3)	5	22.71
Cough	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Oropharyngeal pain	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Sputum retention	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Upper respiratory tract inflammation	1	(3.8)	2	14.86	0				1	(2.3)	2	9.08
Injury, poisoning and procedural complications	1	(3.8)	1	7.43	2	(11.8)	2	23.35	3	(7.0)	3	13.62
Fall	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Foot fracture	0				1	(5.9)	1	11.68	1	(2.3)	1	4.54
Tibia fracture	0				1	(5.9)	1	11.68	1	(2.3)	1	4.54
Nervous system disorders	0				3	(17.6)	4	46.71	3	(7.0)	4	18.16
Dizziness	0				3	(17.6)	4	46.71	3	(7.0)	4	18.16

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Hepatic impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with hepatic impairment at baseline - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Skin and subcutaneous tissue disorders	1	(3.8)	2	14.86	2	(11.8)	2	23.35	3	(7.0)	4	18.16
Eczema	1	(3.8)	1	7.43	1	(5.9)	1	11.68	2	(4.7)	2	9.08
Acne	0				1	(5.9)	1	11.68	1	(2.3)	1	4.54
Miliaria	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Hepatobiliary disorders	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Hepatic cirrhosis	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Renal and urinary disorders	0				1	(5.9)	1	11.68	1	(2.3)	1	4.54
Nephrolithiasis	0				1	(5.9)	1	11.68	1	(2.3)	1	4.54

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Hepatic impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range,
MedDRA version 20.0

2.7.4.7.1-39 有害事象（器官別大分類及び基本語別）ー前治療：メトホルミン+Basal インスリンーSAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	46				46				92			
PYE (years)	23.85				22.70				46.56			
Events	36	(78.3)	141	591.07	36	(78.3)	97	427.27	72	(78.3)	238	511.20
Infections and infestations	18	(39.1)	32	134.14	20	(43.5)	28	123.34	38	(41.3)	60	128.87
Viral upper respiratory tract infection	11	(23.9)	13	54.50	11	(23.9)	15	66.07	22	(23.9)	28	60.14
Gastroenteritis	3	(6.5)	5	20.96	1	(2.2)	1	4.40	4	(4.3)	6	12.89
Pharyngitis	3	(6.5)	3	12.58	1	(2.2)	2	8.81	4	(4.3)	5	10.74
Bronchitis	1	(2.2)	1	4.19	2	(4.3)	2	8.81	3	(3.3)	3	6.44
Cystitis	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Herpes zoster	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Sinusitis	2	(4.3)	2	8.38	0				2	(2.2)	2	4.30
Abscess	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Adenoviral conjunctivitis	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Cellulitis	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Herpes simplex	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Influenza	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Periodontitis	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Tonsillitis	1	(2.2)	2	8.38	0				1	(1.1)	2	4.30
Upper respiratory tract infection	0				1	(2.2)	2	8.81	1	(1.1)	2	4.30
Upper respiratory tract infection bacterial	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Urinary tract infection	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Gastrointestinal disorders	19	(41.3)	40	167.68	10	(21.7)	15	66.07	29	(31.5)	55	118.13
Diarrhoea	8	(17.4)	12	50.30	3	(6.5)	4	17.62	11	(12.0)	16	34.37
Vomiting	5	(10.9)	5	20.96	2	(4.3)	2	8.81	7	(7.6)	7	15.04
Abdominal discomfort	4	(8.7)	4	16.77	2	(4.3)	2	8.81	6	(6.5)	6	12.89
Constipation	4	(8.7)	5	20.96	0				4	(4.3)	5	10.74
Nausea	3	(6.5)	4	16.77	1	(2.2)	1	4.40	4	(4.3)	5	10.74
Dental caries	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Dyspepsia	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30

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Adverse events by system organ class and preferred term - treatment emergent - pre-trial metformin and basal insulin users - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Gastritis erosive	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Gastrooesophageal reflux disease	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Hiatus hernia	2	(4.3)	2	8.38	0				2	(2.2)	2	4.30
Abdominal pain	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Chronic gastritis	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Enteritis	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Food poisoning	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Gastritis	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Oesophageal disorder	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Eye disorders	9	(19.6)	10	41.92	5	(10.9)	7	30.83	14	(15.2)	17	36.51
Diabetic retinopathy	7	(15.2)	8	33.54	4	(8.7)	5	22.02	11	(12.0)	13	27.92
Blepharospasm	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Cataract nuclear	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Conjunctival haemorrhage	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Retinal detachment	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Metabolism and nutrition disorders	9	(19.6)	9	37.73	3	(6.5)	3	13.21	12	(13.0)	12	25.77
Decreased appetite	4	(8.7)	4	16.77	0				4	(4.3)	4	8.59
Gout	2	(4.3)	2	8.38	1	(2.2)	1	4.40	3	(3.3)	3	6.44
Dyslipidaemia	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Hyperuricaemia	2	(4.3)	2	8.38	0				2	(2.2)	2	4.30
Dehydration	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Injury, poisoning and procedural complications	5	(10.9)	8	33.54	6	(13.0)	6	26.43	11	(12.0)	14	30.07
Contusion	1	(2.2)	1	4.19	2	(4.3)	2	8.81	3	(3.3)	3	6.44
Fall	2	(4.3)	2	8.38	0				2	(2.2)	2	4.30
Laceration	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Arthropod bite	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Excoriation	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Foot fracture	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Fractured coccyx	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Heat illness	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15

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Adverse events by system organ class and preferred term - treatment emergent - pre-trial metformin and basal insulin users - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Postoperative fever	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Tooth injury	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Musculoskeletal and connective tissue disorders	6	(13.0)	10	41.92	5	(10.9)	6	26.43	11	(12.0)	16	34.37
Back pain	3	(6.5)	4	16.77	3	(6.5)	3	13.21	6	(6.5)	7	15.04
Arthralgia	2	(4.3)	2	8.38	1	(2.2)	1	4.40	3	(3.3)	3	6.44
Arthritis	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Musculoskeletal pain	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Musculoskeletal stiffness	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Neck pain	1	(2.2)	2	8.38	0				1	(1.1)	2	4.30
Osteoarthritis	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Nervous system disorders	3	(6.5)	5	20.96	7	(15.2)	10	44.05	10	(10.9)	15	32.22
Dizziness	1	(2.2)	1	4.19	2	(4.3)	3	13.21	3	(3.3)	4	8.59
Headache	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Hypoaesthesia	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Carpal tunnel syndrome	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Diabetic neuropathy	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Lacunar infarction	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Loss of consciousness	0				1	(2.2)	2	8.81	1	(1.1)	2	4.30
Migraine	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Neuropathy peripheral	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
General disorders and administration site conditions	4	(8.7)	4	16.77	3	(6.5)	3	13.21	7	(7.6)	7	15.04
Pyrexia	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Generalised oedema	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Induration	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Injection site discomfort	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Malaise	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Oedema peripheral	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Investigations	5	(10.9)	5	20.96	2	(4.3)	2	8.81	7	(7.6)	7	15.04

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - pre-trial metformin and basal insulin users - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Helicobacter test positive	1	(2.2)	1	4.19	2	(4.3)	2	8.81	3	(3.3)	3	6.44
Gamma-glutamyltransferase increased	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Lipase increased	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Oxygen saturation decreased	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Weight decreased	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Renal and urinary disorders	3	(6.5)	4	16.77	3	(6.5)	3	13.21	6	(6.5)	7	15.04
Nephrolithiasis	1	(2.2)	1	4.19	2	(4.3)	2	8.81	3	(3.3)	3	6.44
Renal cyst	2	(4.3)	2	8.38	1	(2.2)	1	4.40	3	(3.3)	3	6.44
Acute kidney injury	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Respiratory, thoracic and mediastinal disorders	2	(4.3)	4	16.77	4	(8.7)	4	17.62	6	(6.5)	8	17.18
Cough	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Upper respiratory tract inflammation	0				2	(4.3)	2	8.81	2	(2.2)	2	4.30
Atelectasis	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Pleural effusion	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Respiratory tract inflammation	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Sputum increased	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Skin and subcutaneous tissue disorders	2	(4.3)	3	12.58	4	(8.7)	4	17.62	6	(6.5)	7	15.04
Eczema	1	(2.2)	1	4.19	2	(4.3)	2	8.81	3	(3.3)	3	6.44
Dermatitis	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Miliaria	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Penile ulceration	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Pustular psoriasis	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Vascular disorders	2	(4.3)	2	8.38	1	(2.2)	1	4.40	3	(3.3)	3	6.44
Hypertension	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Orthostatic hypotension	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Ear and labyrinth disorders	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Vertigo	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - pre-trial metformin and basal insulin users - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(2.2)	1	4.19	1	(2.2)	1	4.40	2	(2.2)	2	4.30
Pancreatic carcinoma	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Uterine leiomyoma	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Psychiatric disorders	0				2	(4.3)	2	8.81	2	(2.2)	2	4.30
Insomnia	0				2	(4.3)	2	8.81	2	(2.2)	2	4.30
Cardiac disorders	1	(2.2)	2	8.38	0				1	(1.1)	2	4.30
Acute myocardial infarction	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Cardiac failure congestive	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Hepatobiliary disorders	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Cholecystitis acute	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Immune system disorders	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Seasonal allergy	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
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MedDRA version 20.0

2.7.4.7.1-40 有害事象（器官別大分類及び基本語別）－前治療：メトホルミン+Basal インスリン+その他の経口糖尿病薬 1 剤－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	20				21				41			
PYE (years)	10.34				10.92				21.26			
Events	19	(95.0)	50	483.52	16	(76.2)	45	412.14	35	(85.4)	95	446.86
Gastrointestinal disorders	10	(50.0)	15	145.06	5	(23.8)	10	91.59	15	(36.6)	25	117.59
Nausea	3	(15.0)	3	29.01	2	(9.5)	3	27.48	5	(12.2)	6	28.22
Diarrhoea	3	(15.0)	3	29.01	0				3	(7.3)	3	14.11
Chronic gastritis	1	(5.0)	1	9.67	1	(4.8)	1	9.16	2	(4.9)	2	9.41
Constipation	1	(5.0)	1	9.67	1	(4.8)	1	9.16	2	(4.9)	2	9.41
Dyspepsia	2	(10.0)	3	29.01	0				2	(4.9)	3	14.11
Abdominal discomfort	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Abdominal distension	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Abdominal pain	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Faeces soft	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Gastritis	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Gastrointestinal motility disorder	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Gastrooesophageal reflux disease	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Vomiting	1	(5.0)	2	19.34	0				1	(2.4)	2	9.41
Infections and infestations	7	(35.0)	10	96.70	6	(28.6)	7	64.11	13	(31.7)	17	79.96
Viral upper respiratory tract infection	4	(20.0)	5	48.35	4	(19.0)	4	36.63	8	(19.5)	9	42.33
Bronchitis	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Gastroenteritis	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Herpes zoster	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Hordeolum	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Otitis externa	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Sinusitis	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Tinea pedis	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Upper respiratory tract infection	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Eye disorders	5	(25.0)	6	58.02	6	(28.6)	7	64.11	11	(26.8)	13	61.15

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PYE: Patient years of exposure (1 PYE = 365.25 days), OAD: Oral anti-diabetic drug,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - pre-trial metformin, basal insulin and one other OAD users - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Diabetic retinopathy	4	(20.0)	4	38.68	5	(23.8)	5	45.79	9	(22.0)	9	42.33
Cataract	1	(5.0)	1	9.67	1	(4.8)	1	9.16	2	(4.9)	2	9.41
Dry eye	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Retinal haemorrhage	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Musculoskeletal and connective tissue disorders	2	(10.0)	2	19.34	5	(23.8)	5	45.79	7	(17.1)	7	32.93
Intervertebral disc protrusion	1	(5.0)	1	9.67	1	(4.8)	1	9.16	2	(4.9)	2	9.41
Back pain	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Flank pain	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Musculoskeletal pain	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Periarthritis	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Tenosynovitis	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
General disorders and administration site conditions	1	(5.0)	1	9.67	4	(19.0)	4	36.63	5	(12.2)	5	23.52
Administration site induration	0				2	(9.5)	2	18.32	2	(4.9)	2	9.41
Inflammation	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Malaise	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Pyrexia	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Nervous system disorders	2	(10.0)	2	19.34	1	(4.8)	1	9.16	3	(7.3)	3	14.11
Dizziness	1	(5.0)	1	9.67	1	(4.8)	1	9.16	2	(4.9)	2	9.41
Hypoaesthesia	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Respiratory, thoracic and mediastinal disorders	2	(10.0)	3	29.01	1	(4.8)	1	9.16	3	(7.3)	4	18.82
Bronchitis chronic	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Oropharyngeal pain	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Upper respiratory tract inflammation	1	(5.0)	2	19.34	0				1	(2.4)	2	9.41
Skin and subcutaneous tissue disorders	1	(5.0)	1	9.67	2	(9.5)	2	18.32	3	(7.3)	3	14.11
Acne	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Eczema	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Hyperkeratosis	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70

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PYE: Patient years of exposure (1 PYE = 365.25 days), OAD: Oral anti-diabetic drug,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - pre-trial metformin, basal insulin and one other OAD users - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Injury, poisoning and procedural complications	1	(5.0)	1	9.67	1	(4.8)	2	18.32	2	(4.9)	3	14.11
Contusion	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Hip fracture	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Tooth fracture	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Investigations	1	(5.0)	1	9.67	1	(4.8)	1	9.16	2	(4.9)	2	9.41
Glomerular filtration rate decreased	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Lipase increased	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Metabolism and nutrition disorders	2	(10.0)	2	19.34	0				2	(4.9)	2	9.41
Decreased appetite	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Hyperuricaemia	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Vascular disorders	2	(10.0)	2	19.34	0				2	(4.9)	2	9.41
Arteriosclerosis	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Hypertension	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Ear and labyrinth disorders	0				1	(4.8)	2	18.32	1	(2.4)	2	9.41
Vertigo	0				1	(4.8)	2	18.32	1	(2.4)	2	9.41
Psychiatric disorders	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Insomnia	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Renal and urinary disorders	1	(5.0)	3	29.01	0				1	(2.4)	3	14.11
Haematuria	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Nephrolithiasis	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Ureterolithiasis	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Reproductive system and breast disorders	0				1	(4.8)	3	27.48	1	(2.4)	3	14.11
Uterine cyst	0				1	(4.8)	2	18.32	1	(2.4)	2	9.41
Uterine mass	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70

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MedDRA version 20.0

2.7.4.7.1-41 有害事象（器官別大分類及び基本語別）－前治療：メトホルミン +混合／配合インスリン－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	26				25				51			
PYE (years)	13.39				11.92				25.31			
Events	18	(69.2)	60	448.25	18	(72.0)	44	369.11	36	(70.6)	104	410.97
Infections and infestations	7	(26.9)	9	67.24	9	(36.0)	14	117.44	16	(31.4)	23	90.89
Viral upper respiratory tract infection	5	(19.2)	7	52.30	7	(28.0)	9	75.50	12	(23.5)	16	63.23
Influenza	0				2	(8.0)	2	16.78	2	(3.9)	2	7.90
Bronchitis	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Gastroenteritis	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Infected dermal cyst	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Pharyngitis	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Upper respiratory tract infection	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Gastrointestinal disorders	10	(38.5)	23	171.83	4	(16.0)	8	67.11	14	(27.5)	31	122.50
Constipation	3	(11.5)	3	22.41	2	(8.0)	2	16.78	5	(9.8)	5	19.76
Abdominal discomfort	2	(7.7)	2	14.94	1	(4.0)	1	8.39	3	(5.9)	3	11.85
Nausea	2	(7.7)	3	22.41	1	(4.0)	1	8.39	3	(5.9)	4	15.81
Diarrhoea	2	(7.7)	3	22.41	0				2	(3.9)	3	11.85
Gastrooesophageal reflux disease	2	(7.7)	2	14.94	0				2	(3.9)	2	7.90
Vomiting	2	(7.7)	3	22.41	0				2	(3.9)	3	11.85
Chronic gastritis	1	(3.8)	2	14.94	0				1	(2.0)	2	7.90
Duodenal ulcer	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Epigastric discomfort	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Glossitis	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Hiatus hernia	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Hyperchlorhydria	1	(3.8)	2	14.94	0				1	(2.0)	2	7.90
Large intestine polyp	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Stomatitis	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Varices oesophageal	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Eye disorders	5	(19.2)	5	37.35	5	(20.0)	5	41.94	10	(19.6)	10	39.52

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - pre-trial metformin and pre-mix/combination insulin users - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Diabetic retinopathy	3	(11.5)	3	22.41	5	(20.0)	5	41.94	8	(15.7)	8	31.61
Pingueculitis	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Retinopathy	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Musculoskeletal and connective tissue disorders	5	(19.2)	5	37.35	3	(12.0)	3	25.17	8	(15.7)	8	31.61
Back pain	2	(7.7)	2	14.94	1	(4.0)	1	8.39	3	(5.9)	3	11.85
Arthralgia	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Muscle spasms	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Myalgia	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Periarthritis	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Trigger finger	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Injury, poisoning and procedural complications	3	(11.5)	4	29.88	3	(12.0)	3	25.17	6	(11.8)	7	27.66
Contusion	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Fall	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Heat stroke	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Ligament sprain	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Thermal burn	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Tibia fracture	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Wrong drug administered	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Nervous system disorders	3	(11.5)	3	22.41	2	(8.0)	2	16.78	5	(9.8)	5	19.76
Carpal tunnel syndrome	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Diabetic neuropathy	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Dizziness	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Dysgeusia	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Headache	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
General disorders and administration site conditions	2	(7.7)	2	14.94	2	(8.0)	2	16.78	4	(7.8)	4	15.81
Oedema peripheral	1	(3.8)	1	7.47	1	(4.0)	1	8.39	2	(3.9)	2	7.90
Inflammation	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Pyrexia	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - pre-trial metformin and pre-mix/combination insulin users - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Respiratory, thoracic and mediastinal disorders	2	(7.7)	2	14.94	1	(4.0)	1	8.39	3	(5.9)	3	11.85
Oropharyngeal pain	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Sputum retention	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Upper respiratory tract inflammation	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Hepatobiliary disorders	1	(3.8)	1	7.47	1	(4.0)	1	8.39	2	(3.9)	2	7.90
Hepatic cirrhosis	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Hepatic steatosis	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Investigations	0				2	(8.0)	2	16.78	2	(3.9)	2	7.90
Electrocardiogram T wave inversion	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Free fatty acids decreased	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Metabolism and nutrition disorders	2	(7.7)	2	14.94	0				2	(3.9)	2	7.90
Decreased appetite	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Dyslipidaemia	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(3.8)	1	7.47	1	(4.0)	1	8.39	2	(3.9)	2	7.90
Adenocarcinoma	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Renal cell carcinoma	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Skin and subcutaneous tissue disorders	1	(3.8)	1	7.47	1	(4.0)	1	8.39	2	(3.9)	2	7.90
Eczema	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Skin swelling	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Cardiac disorders	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Supraventricular extrasystoles	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Endocrine disorders	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Thyroid mass	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Vascular disorders	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent – pre-trial metformin and pre-mix/combination insulin users - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hypertension	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-42 有害事象（器官別大分類及び基本語別）－前治療：メトホルミン +混合／配合インスリン+その他の経口糖尿病薬 1 剤－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	13				13				26			
PYE (years)	6.70				6.72				13.42			
Events	9	(69.2)	29	433.04	10	(76.9)	24	356.92	19	(73.1)	53	394.91
Gastrointestinal disorders	6	(46.2)	10	149.33	5	(38.5)	7	104.10	11	(42.3)	17	126.67
Diarrhoea	2	(15.4)	2	29.87	2	(15.4)	2	29.74	4	(15.4)	4	29.80
Abdominal discomfort	2	(15.4)	2	29.87	1	(7.7)	1	14.87	3	(11.5)	3	22.35
Constipation	1	(7.7)	1	14.93	1	(7.7)	1	14.87	2	(7.7)	2	14.90
Nausea	2	(15.4)	2	29.87	0				2	(7.7)	2	14.90
Enteritis	1	(7.7)	2	29.87	0				1	(3.8)	2	14.90
Faeces soft	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Gastritis	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Periodontal disease	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Vomiting	1	(7.7)	1	14.93	0				1	(3.8)	1	7.45
Eye disorders	3	(23.1)	3	44.80	4	(30.8)	4	59.49	7	(26.9)	7	52.16
Diabetic retinopathy	3	(23.1)	3	44.80	3	(23.1)	3	44.62	6	(23.1)	6	44.71
Posterior capsule opacification	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Infections and infestations	3	(23.1)	6	89.60	3	(23.1)	3	44.62	6	(23.1)	9	67.06
Viral upper respiratory tract infection	1	(7.7)	2	29.87	2	(15.4)	2	29.74	3	(11.5)	4	29.80
Bronchitis	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Gingivitis	1	(7.7)	1	14.93	0				1	(3.8)	1	7.45
Periodontitis	1	(7.7)	1	14.93	0				1	(3.8)	1	7.45
Pharyngitis	1	(7.7)	2	29.87	0				1	(3.8)	2	14.90
General disorders and administration site conditions	2	(15.4)	3	44.80	1	(7.7)	1	14.87	3	(11.5)	4	29.80
Inflammation	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Injection site induration	1	(7.7)	1	14.93	0				1	(3.8)	1	7.45
Malaise	1	(7.7)	2	29.87	0				1	(3.8)	2	14.90

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), OAD: Oral anti-diabetic drug,
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - pre-trial metformin, pre-mix/combination insulin and one other OAD users - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Skin and subcutaneous tissue disorders	0				3	(23.1)	3	44.62	3	(11.5)	3	22.35
Eczema	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Rash	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Skin irritation	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Metabolism and nutrition disorders	2	(15.4)	2	29.87	0				2	(7.7)	2	14.90
Decreased appetite	2	(15.4)	2	29.87	0				2	(7.7)	2	14.90
Musculoskeletal and connective tissue disorders	1	(7.7)	1	14.93	1	(7.7)	1	14.87	2	(7.7)	2	14.90
Muscle spasms	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Tenosynovitis	1	(7.7)	1	14.93	0				1	(3.8)	1	7.45
Nervous system disorders	1	(7.7)	1	14.93	1	(7.7)	1	14.87	2	(7.7)	2	14.90
Headache	1	(7.7)	1	14.93	0				1	(3.8)	1	7.45
Sciatica	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Blood and lymphatic system disorders	0				1	(7.7)	3	44.62	1	(3.8)	3	22.35
Leukopenia	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Lymphopenia	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Neutropenia	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Hepatobiliary disorders	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Cholelithiasis	0				1	(7.7)	1	14.87	1	(3.8)	1	7.45
Injury, poisoning and procedural complications	1	(7.7)	1	14.93	0				1	(3.8)	1	7.45
Laceration	1	(7.7)	1	14.93	0				1	(3.8)	1	7.45
Investigations	1	(7.7)	1	14.93	0				1	(3.8)	1	7.45
Electrocardiogram ST-T segment depression	1	(7.7)	1	14.93	0				1	(3.8)	1	7.45
Vascular disorders	1	(7.7)	1	14.93	0				1	(3.8)	1	7.45
Hypertension	1	(7.7)	1	14.93	0				1	(3.8)	1	7.45

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), OAD: Oral anti-diabetic drug,
MedDRA version 20.0

2.7.4.7.1-43 男性被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	194				195				192				581			
PYE (years)	189.96				188.09				192.61				570.66			
Events	15	(7.7)	16	8.42	10	(5.1)	13	6.91	5	(2.6)	5	2.60	30	(5.2)	34	5.96
Cardiac disorders	2	(1.0)	2	1.05	3	(1.5)	3	1.60	1	(0.5)	1	0.52	6	(1.0)	6	1.05
Angina pectoris	2	(1.0)	2	1.05	0				0				2	(0.3)	2	0.35
Acute myocardial infarction	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Atrioventricular block complete	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Myocardial ischaemia	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Sinus node dysfunction	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Injury, poisoning and procedural complications	3	(1.5)	3	1.58	0				1	(0.5)	1	0.52	4	(0.7)	4	0.70
Femoral neck fracture	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Meniscus injury	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Spinal compression fracture	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Thoracic vertebral fracture	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(1.0)	2	1.05	2	(1.0)	4	2.13	0				4	(0.7)	6	1.05
Adrenal neoplasm	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Benign neoplasm of bladder	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Gastric cancer stage I	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Lung adenocarcinoma	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Lung neoplasm malignant	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Metastases to lymph nodes	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Nervous system disorders	2	(1.0)	2	1.05	2	(1.0)	2	1.06	0				4	(0.7)	4	0.70
Cerebral infarction	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Hypoglycaemic unconsciousness	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Thalamic infarction	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Thrombotic cerebral infarction	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Gastrointestinal disorders	3	(1.5)	3	1.58	0				0				3	(0.5)	3	0.53
Gastrooesophageal reflux disease	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Large intestine polyp	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Pancreatitis acute	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Infections and infestations	1	(0.5)	1	0.53	2	(1.0)	2	1.06	0				3	(0.5)	3	0.53
Herpes zoster meningitis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Pneumonia haemophilus	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Tonsillitis	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Hepatobiliary disorders	1	(0.5)	1	0.53	0				1	(0.5)	1	0.52	2	(0.3)	2	0.35
Cholecystitis	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Cholecystitis acute	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Respiratory, thoracic and mediastinal disorders	1	(0.5)	1	0.53	0				1	(0.5)	1	0.52	2	(0.3)	2	0.35
Sleep apnoea syndrome	1	(0.5)	1	0.53	0				1	(0.5)	1	0.52	2	(0.3)	2	0.35
Vascular disorders	0				2	(1.0)	2	1.06	0				2	(0.3)	2	0.35
Peripheral arterial occlusive disease	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Varicose vein	0				1	(0.5)	1	0.53	0				1	(0.2)	1	0.18
Eye disorders	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18
Retinal detachment	1	(0.5)	1	0.53	0				0				1	(0.2)	1	0.18

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - male subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Surgical and medical procedures	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18
Large intestinal polypectomy	0				0				1	(0.5)	1	0.52	1	(0.2)	1	0.18

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-44 女性被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	81				76				81				238			
PYE (years)	78.04				73.72				79.23				230.99			
Events	2	(2.5)	2	2.56	3	(3.9)	3	4.07	9	(11.1)	9	11.36	14	(5.9)	14	6.06
Infections and infestations	0				0				2	(2.5)	2	2.52	2	(0.8)	2	0.87
Cellulitis	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Pneumonia	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Nervous system disorders	0				1	(1.3)	1	1.36	1	(1.2)	1	1.26	2	(0.8)	2	0.87
Carpal tunnel syndrome	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Facial paralysis	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Reproductive system and breast disorders	0				1	(1.3)	1	1.36	1	(1.2)	1	1.26	2	(0.8)	2	0.87
Endometrial hyperplasia	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Uterine prolapse	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Cardiac disorders	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Cardiac disorder	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Gastrointestinal disorders	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Autoimmune pancreatitis	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
General disorders and administration site conditions	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Chills	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Metabolism and nutrition disorders	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43
Hypoglycaemia	1	(1.2)	1	1.28	0				0				1	(0.4)	1	0.43

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - female subjects - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Breast cancer	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Psychiatric disorders	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Suicide attempt	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Respiratory, thoracic and mediastinal disorders	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Sleep apnoea syndrome	0				1	(1.3)	1	1.36	0				1	(0.4)	1	0.43
Surgical and medical procedures	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43
Cardiac ablation	0				0				1	(1.2)	1	1.26	1	(0.4)	1	0.43

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-45 男性被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	70				63				133			
PYE (years)	36.19				31.53				67.73			
Events	2	(2.9)	2	5.53	3	(4.8)	5	15.86	5	(3.8)	7	10.34
Eye disorders	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Retinal detachment	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Hepatobiliary disorders	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Cholecystitis acute	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Infections and infestations	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Gastroenteritis	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Injury, poisoning and procedural complications	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Hip fracture	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Pancreatic carcinoma	0				1	(1.6)	1	3.17	1	(0.8)	1	1.48
Nervous system disorders	0				1	(1.6)	2	6.34	1	(0.8)	2	2.95
Loss of consciousness	0				1	(1.6)	2	6.34	1	(0.8)	2	2.95

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-46 女性被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	35				42				77			
PYE (years)	18.09				20.73				38.82			
Events	1	(2.9)	2	11.06	1	(2.4)	1	4.82	2	(2.6)	3	7.73
Cardiac disorders	1	(2.9)	2	11.06	0				1	(1.3)	2	5.15
Acute myocardial infarction	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Cardiac failure congestive	1	(2.9)	1	5.53	0				1	(1.3)	1	2.58
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58
Renal cell carcinoma	0				1	(2.4)	1	4.82	1	(1.3)	1	2.58

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-47 ベースラインの BMI（kg/m^2）が 25 未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	122				117				118				357			
PYE (years)	117.94				111.20				117.32				346.46			
Events	12	(9.8)	13	11.02	5	(4.3)	7	6.29	4	(3.4)	4	3.41	21	(5.9)	24	6.93
Cardiac disorders	3	(2.5)	3	2.54	1	(0.9)	1	0.90	0				4	(1.1)	4	1.15
Angina pectoris	2	(1.6)	2	1.70	0				0				2	(0.6)	2	0.58
Acute myocardial infarction	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Cardiac disorder	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Gastrointestinal disorders	3	(2.5)	3	2.54	0				1	(0.8)	1	0.85	4	(1.1)	4	1.15
Autoimmune pancreatitis	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Gastrooesophageal reflux disease	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Large intestine polyp	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Pancreatitis acute	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Nervous system disorders	2	(1.6)	2	1.70	1	(0.9)	1	0.90	0				3	(0.8)	3	0.87
Cerebral infarction	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Thalamic infarction	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Thrombotic cerebral infarction	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Infections and infestations	1	(0.8)	1	0.85	1	(0.9)	1	0.90	0				2	(0.6)	2	0.58
Herpes zoster meningitis	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Pneumonia haemophilus	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Injury, poisoning and procedural complications	2	(1.6)	2	1.70	0				0				2	(0.6)	2	0.58
Spinal compression fracture	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Thoracic vertebral fracture	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline < 25 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.8)	1	0.85	1	(0.9)	3	2.70	0				2	(0.6)	4	1.15
Adrenal neoplasm	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Gastric cancer stage I	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Lung adenocarcinoma	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Metastases to lymph nodes	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Hepatobiliary disorders	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Cholecystitis acute	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Reproductive system and breast disorders	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Uterine prolapse	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Respiratory, thoracic and mediastinal disorders	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Sleep apnoea syndrome	1	(0.8)	1	0.85	0				0				1	(0.3)	1	0.29
Surgical and medical procedures	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Large intestinal polypectomy	0				0				1	(0.8)	1	0.85	1	(0.3)	1	0.29
Vascular disorders	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
Varicose vein	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

2.7.4.7.1-48 ベースラインの BMI（kg/m^2）が 25 以上 30 未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	112				107				109				328			
PYE (years)	110.64				105.69				109.04				325.37			
Events	5	(4.5)	5	4.52	5	(4.7)	6	5.68	7	(6.4)	7	6.42	17	(5.2)	18	5.53
Cardiac disorders	0				2	(1.9)	2	1.89	1	(0.9)	1	0.92	3	(0.9)	3	0.92
Atrioventricular block complete	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Myocardial ischaemia	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Sinus node dysfunction	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.9)	1	0.90	1	(0.9)	1	0.95	1	(0.9)	1	0.92	3	(0.9)	3	0.92
Benign neoplasm of bladder	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Breast cancer	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Lung neoplasm malignant	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Injury, poisoning and procedural complications	1	(0.9)	1	0.90	0				1	(0.9)	1	0.92	2	(0.6)	2	0.61
Femoral neck fracture	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Meniscus injury	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Nervous system disorders	0				1	(0.9)	1	0.95	1	(0.9)	1	0.92	2	(0.6)	2	0.61
Carpal tunnel syndrome	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Facial paralysis	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Respiratory, thoracic and mediastinal disorders	0				1	(0.9)	1	0.95	1	(0.9)	1	0.92	2	(0.6)	2	0.61
Sleep apnoea syndrome	0				1	(0.9)	1	0.95	1	(0.9)	1	0.92	2	(0.6)	2	0.61
Eye disorders	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - subjects with BMI at baseline 25 <= < 30 kg/m^2 - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Retinal detachment	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
General disorders and administration site conditions	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Chills	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Hepatobiliary disorders	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Cholecystitis	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Infections and infestations	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Pneumonia	0				0				1	(0.9)	1	0.92	1	(0.3)	1	0.31
Metabolism and nutrition disorders	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Hypoglycaemia	1	(0.9)	1	0.90	0				0				1	(0.3)	1	0.31
Vascular disorders	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31
Peripheral arterial occlusive disease	0				1	(0.9)	1	0.95	0				1	(0.3)	1	0.31

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

2.7.4.7.1-49 ベースラインの BMI（kg/m^2）が 30 以上の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	41				47				46				134			
PYE (years)	39.42				44.91				45.48				129.82			
Events	0				3	(6.4)	3	6.68	3	(6.5)	3	6.60	6	(4.5)	6	4.62
Infections and infestations	0				1	(2.1)	1	2.23	1	(2.2)	1	2.20	2	(1.5)	2	1.54
Cellulitis	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Tonsillitis	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Nervous system disorders	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Hypoglycaemic unconsciousness	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Psychiatric disorders	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Suicide attempt	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Reproductive system and breast disorders	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Endometrial hyperplasia	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Surgical and medical procedures	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77
Cardiac ablation	0				0				1	(2.2)	1	2.20	1	(0.7)	1	0.77

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

2.7.4.7.1-50 ベースラインの BMI（kg/m^2）が 25 未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	26				28				54			
PYE (years)	13.42				13.74				27.16			
Events	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68
Renal cell carcinoma	0				1	(3.6)	1	7.28	1	(1.9)	1	3.68

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

2.7.4.7.1-51 ベースラインの BMI（kg/m^2）が 25 以上 30 未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	64				53				117			
PYE (years)	33.06				26.07				59.13			
Events	3	(4.7)	4	12.10	1	(1.9)	1	3.84	4	(3.4)	5	8.46
Cardiac disorders	1	(1.6)	2	6.05	0				1	(0.9)	2	3.38
Acute myocardial infarction	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Cardiac failure congestive	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Infections and infestations	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Gastroenteritis	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Injury, poisoning and procedural complications	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Hip fracture	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
Pancreatic carcinoma	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

2.7.4.7.1-52 ベースラインの BMI（kg/m^2）が 30 以上の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	15				24				39			
PYE (years)	7.79				12.46				20.25			
Events	0				2	(8.3)	4	32.11	2	(5.1)	4	19.75
Eye disorders	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Retinal detachment	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Hepatobiliary disorders	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Cholecystitis acute	0				1	(4.2)	1	8.03	1	(2.6)	1	4.94
Nervous system disorders	0				1	(4.2)	2	16.05	1	(2.6)	2	9.88
Loss of consciousness	0				1	(4.2)	2	16.05	1	(2.6)	2	9.88

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index (kg/m^2) at baseline,
MedDRA version 20.0

2.7.4.7.1-53 ベースラインの年齢が 65 歳未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	197				183				202				582			
PYE (years)	193.01				179.38				202.03				574.43			
Events	5	(2.5)	5	2.59	5	(2.7)	5	2.79	11	(5.4)	11	5.44	21	(3.6)	21	3.66
Infections and infestations	1	(0.5)	1	0.52	1	(0.5)	1	0.56	2	(1.0)	2	0.99	4	(0.7)	4	0.70
Cellulitis	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Pneumonia	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Pneumonia haemophilus	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Tonsillitis	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Nervous system disorders	2	(1.0)	2	1.04	2	(1.1)	2	1.11	0				4	(0.7)	4	0.70
Cerebral infarction	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Hypoglycaemic unconsciousness	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Thalamic infarction	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Thrombotic cerebral infarction	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Reproductive system and breast disorders	0				1	(0.5)	1	0.56	1	(0.5)	1	0.49	2	(0.3)	2	0.35
Endometrial hyperplasia	0				1	(0.5)	1	0.56	0				1	(0.2)	1	0.17
Uterine prolapse	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Respiratory, thoracic and mediastinal disorders	0				1	(0.5)	1	0.56	1	(0.5)	1	0.49	2	(0.3)	2	0.35
Sleep apnoea syndrome	0				1	(0.5)	1	0.56	1	(0.5)	1	0.49	2	(0.3)	2	0.35
Cardiac disorders	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Sinus node dysfunction	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Eye disorders	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline < 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Retinal detachment	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
General disorders and administration site conditions	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Chills	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Hepatobiliary disorders	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Cholecystitis acute	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Injury, poisoning and procedural complications	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Femoral neck fracture	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Metabolism and nutrition disorders	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Hypoglycaemia	1	(0.5)	1	0.52	0				0				1	(0.2)	1	0.17
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Breast cancer	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Psychiatric disorders	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Suicide attempt	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Surgical and medical procedures	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17
Large intestinal polypectomy	0				0				1	(0.5)	1	0.49	1	(0.2)	1	0.17

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-54 ベースラインの年齢が 65 歳以上の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	78				88				71				237			
PYE (years)	74.99				82.43				69.80				227.22			
Events	12	(15.4)	13	17.34	8	(9.1)	11	13.35	3	(4.2)	3	4.30	23	(9.7)	27	11.88
Cardiac disorders	3	(3.8)	3	4.00	3	(3.4)	3	3.64	0				6	(2.5)	6	2.64
Angina pectoris	2	(2.6)	2	2.67	0				0				2	(0.8)	2	0.88
Acute myocardial infarction	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Atrioventricular block complete	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Cardiac disorder	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Myocardial ischaemia	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Gastrointestinal disorders	3	(3.8)	3	4.00	0				1	(1.4)	1	1.43	4	(1.7)	4	1.76
Autoimmune pancreatitis	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Gastrooesophageal reflux disease	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Large intestine polyp	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Pancreatitis acute	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(2.6)	2	2.67	2	(2.3)	4	4.85	0				4	(1.7)	6	2.64
Adrenal neoplasm	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Benign neoplasm of bladder	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Gastric cancer stage I	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Lung adenocarcinoma	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Lung neoplasm malignant	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Metastases to lymph nodes	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Injury, poisoning and procedural complications	3	(3.8)	3	4.00	0				0				3	(1.3)	3	1.32

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline >= 65 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Meniscus injury	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Spinal compression fracture	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Thoracic vertebral fracture	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Nervous system disorders	0				1	(1.1)	1	1.21	1	(1.4)	1	1.43	2	(0.8)	2	0.88
Carpal tunnel syndrome	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Facial paralysis	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Vascular disorders	0				2	(2.3)	2	2.43	0				2	(0.8)	2	0.88
Peripheral arterial occlusive disease	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Varicose vein	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Hepatobiliary disorders	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Cholecystitis	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Infections and infestations	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Herpes zoster meningitis	0				1	(1.1)	1	1.21	0				1	(0.4)	1	0.44
Respiratory, thoracic and mediastinal disorders	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Sleep apnoea syndrome	1	(1.3)	1	1.33	0				0				1	(0.4)	1	0.44
Surgical and medical procedures	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44
Cardiac ablation	0				0				1	(1.4)	1	1.43	1	(0.4)	1	0.44

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-55 ベースラインの年齢が 65 歳以上 75 歳未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	76				84				66				226			
PYE (years)	73.16				79.21				64.70				217.07			
Events	10	(13.2)	11	15.03	8	(9.5)	11	13.89	3	(4.5)	3	4.64	21	(9.3)	25	11.52
Cardiac disorders	2	(2.6)	2	2.73	3	(3.6)	3	3.79	0				5	(2.2)	5	2.30
Angina pectoris	2	(2.6)	2	2.73	0				0				2	(0.9)	2	0.92
Acute myocardial infarction	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Atrioventricular block complete	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Myocardial ischaemia	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Gastrointestinal disorders	3	(3.9)	3	4.10	0				1	(1.5)	1	1.55	4	(1.8)	4	1.84
Autoimmune pancreatitis	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Gastrooesophageal reflux disease	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Large intestine polyp	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Pancreatitis acute	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Injury, poisoning and procedural complications	3	(3.9)	3	4.10	0				0				3	(1.3)	3	1.38
Meniscus injury	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Spinal compression fracture	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Thoracic vertebral fracture	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(1.3)	1	1.37	2	(2.4)	4	5.05	0				3	(1.3)	5	2.30
Adrenal neoplasm	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Gastric cancer stage I	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Lung adenocarcinoma	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Lung neoplasm malignant	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - subjects with age at baseline 65 <= < 75 years - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Metastases to lymph nodes	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Nervous system disorders	0				1	(1.2)	1	1.26	1	(1.5)	1	1.55	2	(0.9)	2	0.92
Carpal tunnel syndrome	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Facial paralysis	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Vascular disorders	0				2	(2.4)	2	2.53	0				2	(0.9)	2	0.92
Peripheral arterial occlusive disease	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Varicose vein	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Hepatobiliary disorders	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Cholecystitis	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Infections and infestations	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Herpes zoster meningitis	0				1	(1.2)	1	1.26	0				1	(0.4)	1	0.46
Respiratory, thoracic and mediastinal disorders	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Sleep apnoea syndrome	1	(1.3)	1	1.37	0				0				1	(0.4)	1	0.46
Surgical and medical procedures	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46
Cardiac ablation	0				0				1	(1.5)	1	1.55	1	(0.4)	1	0.46

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-56 ベースラインの年齢が 75 歳以上の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	2				4				5				11			
PYE (years)	1.83				3.22				5.10				10.15			
Events	2	(100.0)	2	109.52	0				0				2	(18.2)	2	19.71
Cardiac disorders	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85
Cardiac disorder	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85
Benign neoplasm of bladder	1	(50.0)	1	54.76	0				0				1	(9.1)	1	9.85

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-57 ベースラインの年齢が 65 歳未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	75				85				160			
PYE (years)	38.80				43.35				82.16			
Events	2	(2.7)	2	5.15	3	(3.5)	5	11.53	5	(3.1)	7	8.52
Eye disorders	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Retinal detachment	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Hepatobiliary disorders	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Cholecystitis acute	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Infections and infestations	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Gastroenteritis	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Injury, poisoning and procedural complications	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Hip fracture	1	(1.3)	1	2.58	0				1	(0.6)	1	1.22
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Pancreatic carcinoma	0				1	(1.2)	1	2.31	1	(0.6)	1	1.22
Nervous system disorders	0				1	(1.2)	2	4.61	1	(0.6)	2	2.43
Loss of consciousness	0				1	(1.2)	2	4.61	1	(0.6)	2	2.43

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-58 ベースラインの年齢が 65 歳以上の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	30				20				50			
PYE (years)	15.47				8.91				24.39			
Events	1	(3.3)	2	12.92	1	(5.0)	1	11.22	2	(4.0)	3	12.30
Cardiac disorders	1	(3.3)	2	12.92	0				1	(2.0)	2	8.20
Acute myocardial infarction	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Cardiac failure congestive	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10
Renal cell carcinoma	0				1	(5.0)	1	11.22	1	(2.0)	1	4.10

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-59 ベースラインの年齢が 65 歳以上 75 歳未満の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	28				19				47			
PYE (years)	14.44				8.66				23.10			
Events	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33
Renal cell carcinoma	0				1	(5.3)	1	11.54	1	(2.1)	1	4.33

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-60 ベースラインの年齢が 75 歳以上の被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	2				1				3			
PYE (years)	1.03				0.25				1.28			
Events	1	(50.0)	2	193.25	0				1	(33.3)	2	155.76
Cardiac disorders	1	(50.0)	2	193.25	0				1	(33.3)	2	155.76
Acute myocardial infarction	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88
Cardiac failure congestive	1	(50.0)	1	96.63	0				1	(33.3)	1	77.88

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-61 ベースライン時に正常腎機能を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	24				20				23				67			
PYE (years)	23.25				18.69				21.69				63.62			
Events	1	(4.2)	1	4.30	0				3	(13.0)	3	13.83	4	(6.0)	4	6.29
General disorders and administration site conditions	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Chills	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Metabolism and nutrition disorders	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Hypoglycaemia	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Psychiatric disorders	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Suicide attempt	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Reproductive system and breast disorders	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57
Uterine prolapse	0				0				1	(4.3)	1	4.61	1	(1.5)	1	1.57

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Normal renal function: eGFR >= 90 mL/min/1.73 m2,
MedDRA version 20.0

2.7.4.7.1-62 ベースライン時に軽度腎機能障害を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	251				251				250				752			
PYE (years)	244.75				243.12				250.15				738.02			
Events	16	(6.4)	17	6.95	13	(5.2)	16	6.58	11	(4.4)	11	4.40	40	(5.3)	44	5.96
Cardiac disorders	3	(1.2)	3	1.23	3	(1.2)	3	1.23	1	(0.4)	1	0.40	7	(0.9)	7	0.95
Angina pectoris	2	(0.8)	2	0.82	0				0				2	(0.3)	2	0.27
Acute myocardial infarction	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Atrioventricular block complete	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Cardiac disorder	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Myocardial ischaemia	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Sinus node dysfunction	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Nervous system disorders	2	(0.8)	2	0.82	3	(1.2)	3	1.23	1	(0.4)	1	0.40	6	(0.8)	6	0.81
Carpal tunnel syndrome	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Cerebral infarction	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Facial paralysis	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Hypoglycaemic unconsciousness	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Thalamic infarction	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Thrombotic cerebral infarction	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Infections and infestations	1	(0.4)	1	0.41	2	(0.8)	2	0.82	2	(0.8)	2	0.80	5	(0.7)	5	0.68
Cellulitis	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Herpes zoster meningitis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Pneumonia	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Pneumonia haemophilus	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Tonsillitis	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(0.8)	2	0.82	2	(0.8)	4	1.65	1	(0.4)	1	0.40	5	(0.7)	7	0.95
Adrenal neoplasm	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Benign neoplasm of bladder	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Breast cancer	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Gastric cancer stage I	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Lung adenocarcinoma	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Lung neoplasm malignant	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Metastases to lymph nodes	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Gastrointestinal disorders	3	(1.2)	3	1.23	0				1	(0.4)	1	0.40	4	(0.5)	4	0.54
Autoimmune pancreatitis	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Gastrooesophageal reflux disease	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Large intestine polyp	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Pancreatitis acute	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Injury, poisoning and procedural complications	3	(1.2)	3	1.23	0				1	(0.4)	1	0.40	4	(0.5)	4	0.54
Femoral neck fracture	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Meniscus injury	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Spinal compression fracture	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Thoracic vertebral fracture	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Respiratory, thoracic and mediastinal disorders	1	(0.4)	1	0.41	1	(0.4)	1	0.41	1	(0.4)	1	0.40	3	(0.4)	3	0.41
Sleep apnoea syndrome	1	(0.4)	1	0.41	1	(0.4)	1	0.41	1	(0.4)	1	0.40	3	(0.4)	3	0.41
Hepatobiliary disorders	1	(0.4)	1	0.41	0				1	(0.4)	1	0.40	2	(0.3)	2	0.27
Cholecystitis	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Cholecystitis acute	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - subjects with mild renal impairment at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Surgical and medical procedures	0				0				2	(0.8)	2	0.80	2	(0.3)	2	0.27
Cardiac ablation	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Large intestinal polypectomy	0				0				1	(0.4)	1	0.40	1	(0.1)	1	0.14
Vascular disorders	0				2	(0.8)	2	0.82	0				2	(0.3)	2	0.27
Peripheral arterial occlusive disease	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Varicose vein	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Eye disorders	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Retinal detachment	1	(0.4)	1	0.41	0				0				1	(0.1)	1	0.14
Reproductive system and breast disorders	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14
Endometrial hyperplasia	0				1	(0.4)	1	0.41	0				1	(0.1)	1	0.14

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

2.7.4.7.1-63 ベースライン時に正常腎機能を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

There is no data for this Table

2.7.4.7.1-64 ベースライン時に軽度腎機能障害を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	93				93				186			
PYE (years)	48.08				46.03				94.11			
Events	3	(3.2)	4	8.32	4	(4.3)	6	13.04	7	(3.8)	10	10.63
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				2	(2.2)	2	4.35	2	(1.1)	2	2.13
Pancreatic carcinoma	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Renal cell carcinoma	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Cardiac disorders	1	(1.1)	2	4.16	0				1	(0.5)	2	2.13
Acute myocardial infarction	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Cardiac failure congestive	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Eye disorders	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Retinal detachment	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Hepatobiliary disorders	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Cholecystitis acute	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Infections and infestations	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Gastroenteritis	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Injury, poisoning and procedural complications	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Hip fracture	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Nervous system disorders	0				1	(1.1)	2	4.35	1	(0.5)	2	2.13
Loss of consciousness	0				1	(1.1)	2	4.35	1	(0.5)	2	2.13

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Mild renal impairment: eGFR >= 60 - < 90 mL/min/1.73 m2,
MedDRA version 20.0

2.7.4.7.1-65 ベースライン時に正常肝機能を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	226				222				213				661			
PYE (years)	219.62				213.34				212.03				645.00			
Events	15	(6.6)	16	7.29	11	(5.0)	14	6.56	10	(4.7)	10	4.72	36	(5.4)	40	6.20
Cardiac disorders	3	(1.3)	3	1.37	3	(1.4)	3	1.41	1	(0.5)	1	0.47	7	(1.1)	7	1.09
Angina pectoris	2	(0.9)	2	0.91	0				0				2	(0.3)	2	0.31
Acute myocardial infarction	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Atrioventricular block complete	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Cardiac disorder	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Myocardial ischaemia	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Sinus node dysfunction	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Gastrointestinal disorders	3	(1.3)	3	1.37	0				1	(0.5)	1	0.47	4	(0.6)	4	0.62
Autoimmune pancreatitis	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Gastrooesophageal reflux disease	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Large intestine polyp	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Pancreatitis acute	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Infections and infestations	1	(0.4)	1	0.46	1	(0.5)	1	0.47	2	(0.9)	2	0.94	4	(0.6)	4	0.62
Cellulitis	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Herpes zoster meningitis	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Pneumonia	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Pneumonia haemophilus	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(0.9)	2	0.91	2	(0.9)	4	1.87	0				4	(0.6)	6	0.93
Adrenal neoplasm	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Normal hepatic function: Baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower,
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Benign neoplasm of bladder	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Gastric cancer stage I	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Lung adenocarcinoma	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Lung neoplasm malignant	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Metastases to lymph nodes	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Injury, poisoning and procedural complications	3	(1.3)	3	1.37	0				0				3	(0.5)	3	0.47
Meniscus injury	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Spinal compression fracture	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Thoracic vertebral fracture	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Nervous system disorders	0				2	(0.9)	2	0.94	1	(0.5)	1	0.47	3	(0.5)	3	0.47
Carpal tunnel syndrome	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Facial paralysis	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Thrombotic cerebral infarction	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Hepatobiliary disorders	1	(0.4)	1	0.46	0				1	(0.5)	1	0.47	2	(0.3)	2	0.31
Cholecystitis	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Cholecystitis acute	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Reproductive system and breast disorders	0				1	(0.5)	1	0.47	1	(0.5)	1	0.47	2	(0.3)	2	0.31
Endometrial hyperplasia	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Uterine prolapse	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Respiratory, thoracic and mediastinal disorders	1	(0.4)	1	0.46	1	(0.5)	1	0.47	0				2	(0.3)	2	0.31
Sleep apnoea syndrome	1	(0.4)	1	0.46	1	(0.5)	1	0.47	0				2	(0.3)	2	0.31
Vascular disorders	0				2	(0.9)	2	0.94	0				2	(0.3)	2	0.31

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Normal hepatic function: Baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower,
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - subjects with normal hepatic function at baseline - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Peripheral arterial occlusive disease	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Varicose vein	0				1	(0.5)	1	0.47	0				1	(0.2)	1	0.16
Eye disorders	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Retinal detachment	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
General disorders and administration site conditions	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Chills	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Metabolism and nutrition disorders	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Hypoglycaemia	1	(0.4)	1	0.46	0				0				1	(0.2)	1	0.16
Psychiatric disorders	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Suicide attempt	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Surgical and medical procedures	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16
Large intestinal polypectomy	0				0				1	(0.5)	1	0.47	1	(0.2)	1	0.16

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Normal hepatic function: Baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower,
MedDRA version 20.0

2.7.4.7.1-66 ベースライン時に肝機能障害を有する被験者における重篤な有害事象（器官別大分類及び基本語別）ーSAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	49				49				60				158			
PYE (years)	48.38				48.47				59.81				156.65			
Events	2	(4.1)	2	4.13	2	(4.1)	2	4.13	4	(6.7)	4	6.69	8	(5.1)	8	5.11
Nervous system disorders	2	(4.1)	2	4.13	1	(2.0)	1	2.06	0				3	(1.9)	3	1.92
Cerebral infarction	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Hypoglycaemic unconsciousness	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Thalamic infarction	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Infections and infestations	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Tonsillitis	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Injury, poisoning and procedural complications	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Femoral neck fracture	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Breast cancer	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Respiratory, thoracic and mediastinal disorders	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Sleep apnoea syndrome	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Surgical and medical procedures	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64
Cardiac ablation	0				0				1	(1.7)	1	1.67	1	(0.6)	1	0.64

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Hepatic impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range,
MedDRA version 20.0

2.7.4.7.1-67 ベースライン時に正常肝機能を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	79				88				167			
PYE (years)	40.82				43.70				84.52			
Events	2	(2.5)	3	7.35	4	(4.5)	6	13.73	6	(3.6)	9	10.65
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				2	(2.3)	2	4.58	2	(1.2)	2	2.37
Pancreatic carcinoma	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Renal cell carcinoma	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Cardiac disorders	1	(1.3)	2	4.90	0				1	(0.6)	2	2.37
Acute myocardial infarction	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Cardiac failure congestive	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Eye disorders	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Retinal detachment	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Hepatobiliary disorders	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Cholecystitis acute	0				1	(1.1)	1	2.29	1	(0.6)	1	1.18
Injury, poisoning and procedural complications	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Hip fracture	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Nervous system disorders	0				1	(1.1)	2	4.58	1	(0.6)	2	2.37
Loss of consciousness	0				1	(1.1)	2	4.58	1	(0.6)	2	2.37

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Normal hepatic function: Baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower,
MedDRA version 20.0

2.7.4.7.1-68 ベースライン時に肝機能障害を有する被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	26				17				43			
PYE (years)	13.46				8.56				22.02			
Events	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Infections and infestations	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54
Gastroenteritis	1	(3.8)	1	7.43	0				1	(2.3)	1	4.54

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
Hepatic impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range,
MedDRA version 20.0

2.7.4.7.1-69 重篤な有害事象（器官別大分類及び基本語別）ー前治療：メトホルミン+Basal インスリンーSAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	46				46				92			
PYE (years)	23.85				22.70				46.56			
Events	1	(2.2)	2	8.38	3	(6.5)	5	22.02	4	(4.3)	7	15.04
Cardiac disorders	1	(2.2)	2	8.38	0				1	(1.1)	2	4.30
Acute myocardial infarction	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Cardiac failure congestive	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Eye disorders	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Retinal detachment	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Hepatobiliary disorders	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Cholecystitis acute	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Pancreatic carcinoma	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Nervous system disorders	0				1	(2.2)	2	8.81	1	(1.1)	2	4.30
Loss of consciousness	0				1	(2.2)	2	8.81	1	(1.1)	2	4.30

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-70 重篤な有害事象（器官別大分類及び基本語別）ー前治療：メトホルミン+Basal インスリン+その他の経口糖尿病薬 1 剤ーSAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	20				21				41			
PYE (years)	10.34				10.92				21.26			
Events	2	(10.0)	2	19.34	0				2	(4.9)	2	9.41
Infections and infestations	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Gastroenteritis	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Injury, poisoning and procedural complications	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70
Hip fracture	1	(5.0)	1	9.67	0				1	(2.4)	1	4.70

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), OAD: Oral anti-diabetic drug,
MedDRA version 20.0

2.7.4.7.1-71 重篤な有害事象（器官別大分類及び基本語別）ー前治療：メトホルミン +混合／配合インスリンーSAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	26				25				51			
PYE (years)	13.39				11.92				25.31			
Events	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Renal cell carcinoma	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-72 重篤な有害事象（器官別大分類及び基本語別）ー前治療：メトホルミン +混合／配合インスリン+その他の経口糖尿病薬 1 剤ー SAS（4184 試験）

There is no data for this Table

2.7.4.7.1-73 男女別の低血糖－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
Male	194				195				192				581			
Female	81				76				81				238			
PYE (years)																
Male	189.96				188.09				192.61				570.66			
Female	78.04				73.72				79.23				230.99			
Severe or BG confirmed symptomatic hypoglycaemia																
Male	45	(23.2)	110	57.91	65	(33.3)	311	165.35	2	(1.0)	3	1.56	112	(19.3)	424	74.30
Female	8	(9.9)	25	32.03	15	(19.7)	51	69.18	1	(1.2)	1	1.26	24	(10.1)	77	33.33
Severe or BG confirmed hypoglycaemia																
Male	88	(45.4)	392	206.36	115	(59.0)	703	373.76	4	(2.1)	10	5.19	207	(35.6)	1105	193.64
Female	18	(22.2)	75	96.10	33	(43.4)	166	225.18	2	(2.5)	3	3.79	53	(22.3)	244	105.63
ADA																
Male	173	(89.2)	3782	1990.94	183	(93.8)	4639	2466.40	35	(18.2)	88	45.69	391	(67.3)	8509	1491.09
Female	67	(82.7)	1048	1342.91	67	(88.2)	1701	2307.40	25	(30.9)	74	93.40	159	(66.8)	2823	1222.13

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Hypoglycaemic episodes by classification and sex - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe hypoglycaemia																
Male	0				3	(1.5)	3	1.60	0				3	(0.5)	3	0.53
Female	1	(1.2)	1	1.28	1	(1.3)	3	4.07	0				2	(0.8)	4	1.73
Documented symptomatic hypoglycaemia																
Male	80	(41.2)	598	314.80	107	(54.9)	1001	532.20	10	(5.2)	16	8.31	197	(33.9)	1615	283.01
Female	37	(45.7)	193	247.31	37	(48.7)	374	507.33	6	(7.4)	10	12.62	80	(33.6)	577	249.79
Asymptomatic hypoglycaemia																
Male	166	(85.6)	2881	1516.63	168	(86.2)	3274	1740.68	26	(13.5)	61	31.67	360	(62.0)	6216	1089.27
Female	63	(77.8)	789	1011.02	56	(73.7)	1079	1463.66	17	(21.0)	52	65.63	136	(57.1)	1920	831.21
Probable symptomatic hypoglycaemia																
Male	32	(16.5)	83	43.69	23	(11.8)	159	84.54	5	(2.6)	6	3.12	60	(10.3)	248	43.46
Female	12	(14.8)	23	29.47	7	(9.2)	12	16.28	3	(3.7)	3	3.79	22	(9.2)	38	16.45
Pseudo-hypoglycaemia																
Male	27	(13.9)	220	115.81	34	(17.4)	202	107.40	4	(2.1)	5	2.60	65	(11.2)	427	74.83
Female	10	(12.3)	42	53.82	17	(22.4)	233	316.06	4	(4.9)	9	11.36	31	(13.0)	284	122.95

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Hypoglycaemic episodes by classification and sex - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia																
Male	0				0				0				0			
Female	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

2.7.4.7.1-74 男女別の低血糖－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Male	70				63				133			
Female	35				42				77			
PYE (years)												
Male	36.19				31.53				67.73			
Female	18.09				20.73				38.82			
Severe or BG confirmed symptomatic hypoglycaemia												
Male	7	(10.0)	30	82.89	11	(17.5)	28	88.79	18	(13.5)	58	85.64
Female	8	(22.9)	22	121.64	7	(16.7)	15	72.36	15	(19.5)	37	95.32
Severe or BG confirmed hypoglycaemia												
Male	18	(25.7)	77	212.76	20	(31.7)	67	212.47	38	(28.6)	144	212.62
Female	12	(34.3)	47	259.87	12	(28.6)	42	202.60	24	(31.2)	89	229.28
ADA												
Male	50	(71.4)	486	1342.85	43	(68.3)	403	1277.96	93	(69.9)	889	1312.64
Female	28	(80.0)	294	1625.54	26	(61.9)	314	1514.64	54	(70.1)	608	1566.31

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Hypoglycaemic episodes by classification and sex - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe hypoglycaemia												
Male	1	(1.4)	1	2.76	0				1	(0.8)	1	1.48
Female	0				0				0			
Documented symptomatic hypoglycaemia												
Male	22	(31.4)	118	326.04	24	(38.1)	142	450.30	46	(34.6)	260	383.90
Female	17	(48.6)	93	514.20	18	(42.9)	113	545.08	35	(45.5)	206	530.69
Asymptomatic hypoglycaemia												
Male	41	(58.6)	347	958.78	36	(57.1)	251	795.95	77	(57.9)	598	882.97
Female	23	(65.7)	185	1022.88	20	(47.6)	181	873.09	43	(55.8)	366	942.88
Probable symptomatic hypoglycaemia												
Male	6	(8.6)	10	27.63	2	(3.2)	2	6.34	8	(6.0)	12	17.72
Female	6	(17.1)	9	49.76	3	(7.1)	5	24.12	9	(11.7)	14	36.07
Pseudo-hypoglycaemia												
Male	6	(8.6)	10	27.63	5	(7.9)	8	25.37	11	(8.3)	18	26.58
Female	5	(14.3)	7	38.70	3	(7.1)	15	72.36	8	(10.4)	22	56.68

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Hypoglycaemic episodes by classification and sex - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia												
Male	0				0				0			
Female	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

2.7.4.7.1-75 ベースラインの BMI（kg/m^2）別の低血糖－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
<25	122				117				118				357			
25<= <30	112				107				109				328			
>=30	41				47				46				134			
PYE (years)																
<25	117.94				111.20				117.32				346.46			
25<= <30	110.64				105.69				109.04				325.37			
>=30	39.42				44.91				45.48				129.82			
Severe or BG confirmed symptomatic hypoglycaemia																
<25	35	(28.7)	107	90.73	42	(35.9)	192	172.66	0				77	(21.6)	299	86.30
25<= <30	17	(15.2)	25	22.59	27	(25.2)	138	130.57	2	(1.8)	3	2.75	46	(14.0)	166	51.02
>=30	1	(2.4)	3	7.61	11	(23.4)	32	71.25	1	(2.2)	1	2.20	13	(9.7)	36	27.73
Severe or BG confirmed hypoglycaemia																
<25	61	(50.0)	286	242.51	73	(62.4)	406	365.10	3	(2.5)	6	5.11	137	(38.4)	698	201.47
25<= <30	43	(38.4)	177	159.97	54	(50.5)	358	338.73	2	(1.8)	5	4.59	99	(30.2)	540	165.96
>=30	2	(4.9)	4	10.15	21	(44.7)	105	233.78	1	(2.2)	2	4.40	24	(17.9)	111	85.51

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
BMI: Body mass index (kg/m^2) at baseline

Hypoglycaemic episodes by classification and BMI (kg/m^2) at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA																
<25	118	(96.7)	2623	2224.09	112	(95.7)	3072	2762.51	34	(28.8)	80	68.19	264	(73.9)	5775	1666.87
25<= <30	96	(85.7)	1914	1729.86	98	(91.6)	2435	2303.92	19	(17.4)	63	57.78	213	(64.9)	4412	1355.99
>=30	26	(63.4)	293	743.29	40	(85.1)	833	1854.64	7	(15.2)	19	41.78	73	(54.5)	1145	882.02
Severe hypoglycaemia																
<25	0				1	(0.9)	1	0.90	0				1	(0.3)	1	0.29
25<= <30	1	(0.9)	1	0.90	1	(0.9)	3	2.84	0				2	(0.6)	4	1.23
>=30	0				2	(4.3)	2	4.45	0				2	(1.5)	2	1.54
Documented symptomatic hypoglycaemia																
<25	67	(54.9)	547	463.81	70	(59.8)	740	665.45	8	(6.8)	10	8.52	145	(40.6)	1297	374.36
25<= <30	40	(35.7)	175	158.16	52	(48.6)	507	479.71	6	(5.5)	13	11.92	98	(29.9)	695	213.60
>=30	10	(24.4)	69	175.04	22	(46.8)	128	284.99	2	(4.3)	3	6.60	34	(25.4)	200	154.07
Asymptomatic hypoglycaemia																
<25	116	(95.1)	1951	1654.29	106	(90.6)	2022	1818.29	25	(21.2)	59	50.29	247	(69.2)	4032	1163.78
25<= <30	89	(79.5)	1566	1415.34	87	(81.3)	1753	1658.64	11	(10.1)	39	35.77	187	(57.0)	3358	1032.05
>=30	24	(58.5)	153	388.13	31	(66.0)	578	1286.89	7	(15.2)	15	32.98	62	(46.3)	746	574.66

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
BMI: Body mass index (kg/m^2) at baseline

Hypoglycaemic episodes by classification and BMI (kg/m^2) at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Probable symptomatic hypoglycaemia																
<25	23	(18.9)	65	55.11	14	(12.0)	53	47.66	6	(5.1)	7	5.97	43	(12.0)	125	36.08
25<= <30	16	(14.3)	31	28.02	12	(11.2)	60	56.77	1	(0.9)	1	0.92	29	(8.8)	92	28.28
>=30	5	(12.2)	10	25.37	4	(8.5)	58	129.13	1	(2.2)	1	2.20	10	(7.5)	69	53.15
Pseudo-hypoglycaemia																
<25	15	(12.3)	60	50.88	21	(17.9)	256	230.21	2	(1.7)	4	3.41	38	(10.6)	320	92.36
25<= <30	15	(13.4)	141	127.43	18	(16.8)	112	105.97	6	(5.5)	10	9.17	39	(11.9)	263	80.83
>=30	7	(17.1)	61	154.75	12	(25.5)	67	149.17	0				19	(14.2)	128	98.60
ADA unclassifiable hypoglycaemia																
<25	0				0				0				0			
25<= <30	0				0				0				0			
>=30	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
BMI: Body mass index (kg/m^2) at baseline

2.7.4.7.1-76 ベースラインの BMI（kg/m^2）別の低血糖－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
<25	26				28				54			
25<= <30	64				53				117			
>=30	15				24				39			
PYE (years)												
<25	13.42				13.74				27.16			
25<= <30	33.06				26.07				59.13			
>=30	7.79				12.46				20.25			
Severe or BG confirmed symptomatic hypoglycaemia												
<25	4	(15.4)	10	74.50	7	(25.0)	11	80.08	11	(20.4)	21	77.32
25<= <30	10	(15.6)	41	124.02	9	(17.0)	29	111.23	19	(16.2)	70	118.38
>=30	1	(6.7)	1	12.83	2	(8.3)	3	24.08	3	(7.7)	4	19.75
Severe or BG confirmed hypoglycaemia												
<25	12	(46.2)	53	394.82	10	(35.7)	33	240.25	22	(40.7)	86	316.65
25<= <30	15	(23.4)	67	202.66	18	(34.0)	71	272.32	33	(28.2)	138	233.38
>=30	3	(20.0)	4	51.32	4	(16.7)	5	40.14	7	(17.9)	9	44.44

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
BMI: Body mass index (kg/m^2) at baseline

Hypoglycaemic episodes by classification and BMI (kg/m^2) at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA												
<25	22	(84.6)	330	2458.34	21	(75.0)	230	1674.46	43	(79.6)	560	2061.90
25<= <30	46	(71.9)	408	1234.14	39	(73.6)	431	1653.08	85	(72.6)	839	1418.86
>=30	10	(66.7)	42	538.83	9	(37.5)	56	449.54	19	(48.7)	98	483.91
Severe hypoglycaemia												
<25	0				0				0			
25<= <30	1	(1.6)	1	3.02	0				1	(0.9)	1	1.69
>=30	0				0				0			
Documented symptomatic hypoglycaemia												
<25	11	(42.3)	59	439.52	14	(50.0)	84	611.54	25	(46.3)	143	526.52
25<= <30	22	(34.4)	142	429.53	24	(45.3)	147	563.81	46	(39.3)	289	488.74
>=30	6	(40.0)	10	128.29	4	(16.7)	24	192.66	10	(25.6)	34	167.89
Asymptomatic hypoglycaemia												
<25	17	(65.4)	264	1966.67	16	(57.1)	129	939.15	33	(61.1)	393	1447.01
25<= <30	40	(62.5)	248	750.16	33	(62.3)	272	1043.24	73	(62.4)	520	879.39
>=30	7	(46.7)	20	256.59	7	(29.2)	31	248.85	14	(35.9)	51	251.83

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
BMI: Body mass index (kg/m^2) at baseline

Hypoglycaemic episodes by classification and BMI (kg/m^2) at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Probable symptomatic hypoglycaemia												
<25	4	(15.4)	4	29.80	1	(3.6)	3	21.84	5	(9.3)	7	25.77
25<= <30	5	(7.8)	8	24.20	3	(5.7)	3	11.51	8	(6.8)	11	18.60
>=30	3	(20.0)	7	89.81	1	(4.2)	1	8.03	4	(10.3)	8	39.50
Pseudo-hypoglycaemia												
<25	2	(7.7)	3	22.35	3	(10.7)	14	101.92	5	(9.3)	17	62.59
25<= <30	6	(9.4)	9	27.22	5	(9.4)	9	34.52	11	(9.4)	18	30.44
>=30	3	(20.0)	5	64.15	0				3	(7.7)	5	24.69
ADA unclassifiable hypoglycaemia												
<25	0				0				0			
25<= <30	0				0				0			
>=30	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
BMI: Body mass index (kg/m^2) at baseline

2.7.4.7.1-77 ベースラインの年齢（歳）別の低血糖－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
<65	197				183				202				582			
>=65	78				88				71				237			
65<= <75	76				84				66				226			
>=75	2				4				5				11			
PYE (years)																
<65	193.01				179.38				202.03				574.43			
>=65	74.99				82.43				69.80				227.22			
65<= <75	73.16				79.21				64.70				217.07			
>=75	1.83				3.22				5.10				10.15			
Severe or BG confirmed symptomatic hypoglycaemia																
<65	35	(17.8)	79	40.93	52	(28.4)	248	138.25	2	(1.0)	3	1.48	89	(15.3)	330	57.45
>=65	18	(23.1)	56	74.68	28	(31.8)	114	138.31	1	(1.4)	1	1.43	47	(19.8)	171	75.26
65<= <75	18	(23.7)	56	76.54	28	(33.3)	114	143.93	1	(1.5)	1	1.55	47	(20.8)	171	78.78
>=75	0				0				0				0			
Severe or BG confirmed hypoglycaemia																
<65	69	(35.0)	320	165.79	101	(55.2)	623	347.30	4	(2.0)	10	4.95	174	(29.9)	953	165.90
>=65	37	(47.4)	147	196.03	47	(53.4)	246	298.45	2	(2.8)	3	4.30	86	(36.3)	396	174.28
65<= <75	36	(47.4)	146	199.55	46	(54.8)	241	304.27	2	(3.0)	3	4.64	84	(37.2)	390	179.67
>=75	1	(50.0)	1	54.76	1	(25.0)	5	155.29	0				2	(18.2)	6	59.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Hypoglycaemic episodes by classification and age (years) at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA																
<65	166	(84.3)	3306	1712.86	166	(90.7)	4216	2350.30	39	(19.3)	102	50.49	371	(63.7)	7624	1327.24
>=65	74	(94.9)	1524	2032.28	84	(95.5)	2124	2576.87	21	(29.6)	60	85.95	179	(75.5)	3708	1631.90
65<= <75	72	(94.7)	1460	1995.53	80	(95.2)	2070	2613.44	19	(28.8)	57	88.10	171	(75.7)	3587	1652.46
>=75	2	(100.0)	64	3504.65	4	(100.0)	54	1677.17	2	(40.0)	3	58.78	8	(72.7)	121	1192.21
Severe hypoglycaemia																
<65	1	(0.5)	1	0.52	3	(1.6)	3	1.67	0				4	(0.7)	4	0.70
>=65	0				1	(1.1)	3	3.64	0				1	(0.4)	3	1.32
65<= <75	0				1	(1.2)	3	3.79	0				1	(0.4)	3	1.38
>=75	0				0				0				0			
Documented symptomatic hypoglycaemia																
<65	79	(40.1)	465	240.92	96	(52.5)	923	514.55	10	(5.0)	16	7.92	185	(31.8)	1404	244.42
>=65	38	(48.7)	326	434.73	48	(54.5)	452	548.37	6	(8.5)	10	14.33	92	(38.8)	788	346.80
65<= <75	37	(48.7)	323	441.48	47	(56.0)	451	569.40	6	(9.1)	10	15.46	90	(39.8)	784	361.17
>=75	1	(50.0)	3	164.28	1	(25.0)	1	31.06	0				2	(18.2)	4	39.41
Asymptomatic hypoglycaemia																
<65	157	(79.7)	2540	1315.99	148	(80.9)	2966	1653.46	25	(12.4)	70	34.65	330	(56.7)	5576	970.71
>=65	72	(92.3)	1130	1506.87	76	(86.4)	1387	1682.73	18	(25.4)	43	61.60	166	(70.0)	2560	1126.66
65<= <75	70	(92.1)	1069	1461.11	72	(85.7)	1338	1689.27	16	(24.2)	40	61.82	158	(69.9)	2447	1127.28
>=75	2	(100.0)	61	3340.37	4	(100.0)	49	1521.88	2	(40.0)	3	58.78	8	(72.7)	113	1113.39

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Hypoglycaemic episodes by classification and age (years) at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Probable symptomatic hypoglycaemia																
<65	28	(14.2)	72	37.30	20	(10.9)	128	71.36	5	(2.5)	6	2.97	53	(9.1)	206	35.86
>=65	16	(20.5)	34	45.34	10	(11.4)	43	52.17	3	(4.2)	3	4.30	29	(12.2)	80	35.21
65<= <75	16	(21.1)	34	46.47	10	(11.9)	43	54.29	3	(4.5)	3	4.64	29	(12.8)	80	36.85
>=75	0				0				0				0			
Pseudo-hypoglycaemia																
<65	25	(12.7)	228	118.13	32	(17.5)	196	109.26	6	(3.0)	10	4.95	63	(10.8)	434	75.55
>=65	12	(15.4)	34	45.34	19	(21.6)	239	289.96	2	(2.8)	4	5.73	33	(13.9)	277	121.91
65<= <75	12	(15.8)	34	46.47	18	(21.4)	235	296.69	2	(3.0)	4	6.18	32	(14.2)	273	125.77
>=75	0				1	(25.0)	4	124.23	0				1	(9.1)	4	39.41
ADA unclassifiable hypoglycaemia																
<65	0				0				0				0			
>=65	0				0				0				0			
65<= <75	0				0				0				0			
>=75	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

2.7.4.7.1-78 ベースラインの年齢（歳）別の低血糖－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
<65	75				85				160			
>=65	30				20				50			
65<= <75	28				19				47			
>=75	2				1				3			
PYE (years)												
<65	38.80				43.35				82.16			
>=65	15.47				8.91				24.39			
65<= <75	14.44				8.66				23.10			
>=75	1.03				0.25				1.28			
Severe or BG confirmed symptomatic hypoglycaemia												
<65	7	(9.3)	38	97.93	12	(14.1)	33	76.12	19	(11.9)	71	86.42
>=65	8	(26.7)	14	90.47	6	(30.0)	10	112.21	14	(28.0)	24	98.42
65<= <75	8	(28.6)	14	96.96	5	(26.3)	9	103.90	13	(27.7)	23	99.56
>=75	0				1	(100.0)	1	401.37	1	(33.3)	1	77.88
Severe or BG confirmed hypoglycaemia												
<65	20	(26.7)	90	231.94	22	(25.9)	77	177.61	42	(26.3)	167	203.27
>=65	10	(33.3)	34	219.72	10	(50.0)	32	359.08	20	(40.0)	66	270.65
65<= <75	10	(35.7)	34	235.47	9	(47.4)	31	357.86	19	(40.4)	65	281.36
>=75	0				1	(100.0)	1	401.37	1	(33.3)	1	77.88

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Hypoglycaemic episodes by classification and age (years) at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA												
<65	52	(69.3)	457	1177.73	52	(61.2)	507	1169.45	104	(65.0)	964	1173.36
>=65	26	(86.7)	323	2087.33	17	(85.0)	210	2356.45	43	(86.0)	533	2185.68
65<= <75	25	(89.3)	322	2230.01	16	(84.2)	199	2297.24	41	(87.2)	521	2255.22
>=75	1	(50.0)	1	96.63	1	(100.0)	11	4415.11	2	(66.7)	12	934.54
Severe hypoglycaemia												
<65	0				0				0			
>=65	1	(3.3)	1	6.46	0				1	(2.0)	1	4.10
65<= <75	1	(3.6)	1	6.93	0				1	(2.1)	1	4.33
>=75	0				0				0			
Documented symptomatic hypoglycaemia												
<65	22	(29.3)	147	378.83	29	(34.1)	184	424.41	51	(31.9)	331	402.89
>=65	17	(56.7)	64	413.59	13	(65.0)	71	796.71	30	(60.0)	135	553.60
65<= <75	17	(60.7)	64	443.23	12	(63.2)	61	704.18	29	(61.7)	125	541.08
>=75	0				1	(100.0)	10	4013.74	1	(33.3)	10	778.78
Asymptomatic hypoglycaemia												
<65	41	(54.7)	281	724.16	42	(49.4)	308	710.43	83	(51.9)	589	716.92
>=65	23	(76.7)	251	1622.04	14	(70.0)	124	1391.43	37	(74.0)	375	1537.77
65<= <75	22	(78.6)	250	1731.37	13	(68.4)	123	1419.90	35	(74.5)	373	1614.58
>=75	1	(50.0)	1	96.63	1	(100.0)	1	401.37	2	(66.7)	2	155.76

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Hypoglycaemic episodes by classification and age (years) at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Probable symptomatic hypoglycaemia												
<65	8	(10.7)	14	36.08	5	(5.9)	7	16.15	13	(8.1)	21	25.56
>=65	4	(13.3)	5	32.31	0				4	(8.0)	5	20.50
65<= <75	4	(14.3)	5	34.63	0				4	(8.5)	5	21.64
>=75	0				0				0			
Pseudo-hypoglycaemia												
<65	10	(13.3)	15	38.66	5	(5.9)	8	18.45	15	(9.4)	23	28.00
>=65	1	(3.3)	2	12.92	3	(15.0)	15	168.32	4	(8.0)	17	69.71
65<= <75	1	(3.6)	2	13.85	3	(15.8)	15	173.16	4	(8.5)	17	73.59
>=75	0				0				0			
ADA unclassifiable hypoglycaemia												
<65	0				0				0			
>=65	0				0				0			
65<= <75	0				0				0			
>=75	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

2.7.4.7.1-79 ベースラインの腎機能別の低血糖－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
Normal function	24				20				23				67			
Mild impairment	251				251				250				752			
PYE (years)																
Normal function	23.25				18.69				21.69				63.62			
Mild impairment	244.75				243.12				250.15				738.02			
Severe or BG confirmed symptomatic hypoglycaemia																
Normal function	4	(16.7)	15	64.52	4	(20.0)	7	37.46	0				8	(11.9)	22	34.58
Mild impairment	49	(19.5)	120	49.03	76	(30.3)	355	146.02	3	(1.2)	4	1.60	128	(17.0)	479	64.90
Severe or BG confirmed hypoglycaemia																
Normal function	5	(20.8)	27	116.13	9	(45.0)	61	326.45	0				14	(20.9)	88	138.32
Mild impairment	101	(40.2)	440	179.78	139	(55.4)	808	332.34	6	(2.4)	13	5.20	246	(32.7)	1261	170.86
ADA																
Normal function	17	(70.8)	362	1557.00	16	(80.0)	380	2033.63	5	(21.7)	8	36.89	38	(56.7)	750	1178.83
Mild impairment	223	(88.8)	4468	1825.53	234	(93.2)	5960	2451.45	55	(22.0)	154	61.56	512	(68.1)	10582	1433.83

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2; mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]

Hypoglycaemic episodes by classification and renal function at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe hypoglycaemia																
Normal function	1	(4.2)	1	4.30	0				0				1	(1.5)	1	1.57
Mild impairment	0				4	(1.6)	6	2.47	0				4	(0.5)	6	0.81
Documented symptomatic hypoglycaemia																
Normal function	12	(50.0)	109	468.82	7	(35.0)	48	256.88	2	(8.7)	3	13.83	21	(31.3)	160	251.48
Mild impairment	105	(41.8)	682	278.65	137	(54.6)	1327	545.82	14	(5.6)	23	9.19	256	(34.0)	2032	275.33
Asymptomatic hypoglycaemia																
Normal function	16	(66.7)	180	774.20	12	(60.0)	247	1321.86	4	(17.4)	5	23.06	32	(47.8)	432	679.01
Mild impairment	213	(84.9)	3490	1425.94	212	(84.5)	4106	1688.87	39	(15.6)	108	43.17	464	(61.7)	7704	1043.87
Probable symptomatic hypoglycaemia																
Normal function	3	(12.5)	3	12.90	1	(5.0)	21	112.38	0				4	(6.0)	24	37.72
Mild impairment	41	(16.3)	103	42.08	29	(11.6)	150	61.70	8	(3.2)	9	3.60	78	(10.4)	262	35.50
Pseudo-hypoglycaemia																
Normal function	5	(20.8)	69	296.78	4	(20.0)	64	342.51	0				9	(13.4)	133	209.05
Mild impairment	32	(12.7)	193	78.86	47	(18.7)	371	152.60	8	(3.2)	14	5.60	87	(11.6)	578	78.32

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2; mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]

Hypoglycaemic episodes by classification and renal function at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia																
Normal function	0				0				0				0			
Mild impairment	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2; mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]

2.7.4.7.1-80 ベースラインの腎機能別の低血糖－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Normal function	12				12				24			
Mild impairment	93				93				186			
PYE (years)												
Normal function	6.20				6.24				12.43			
Mild impairment	48.08				46.03				94.11			
Severe or BG confirmed symptomatic hypoglycaemia												
Normal function	2	(16.7)	6	96.84	3	(25.0)	18	288.61	5	(20.8)	24	193.04
Mild impairment	13	(14.0)	46	95.67	15	(16.1)	25	54.31	28	(15.1)	71	75.44
Severe or BG confirmed hypoglycaemia												
Normal function	3	(25.0)	8	129.12	5	(41.7)	22	352.74	8	(33.3)	30	241.30
Mild impairment	27	(29.0)	116	241.25	27	(29.0)	87	189.01	54	(29.0)	203	215.70
ADA												
Normal function	6	(50.0)	45	726.30	9	(75.0)	106	1699.58	15	(62.5)	151	1214.55
Mild impairment	72	(77.4)	735	1528.63	60	(64.5)	611	1327.43	132	(71.0)	1346	1430.23

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2;
mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]

Hypoglycaemic episodes by classification and renal function at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe hypoglycaemia												
Normal function	0				0				0			
Mild impairment	1	(1.1)	1	2.08	0				1	(0.5)	1	1.06
Documented symptomatic hypoglycaemia												
Normal function	4	(33.3)	22	355.08	6	(50.0)	73	1170.47	10	(41.7)	95	764.12
Mild impairment	35	(37.6)	189	393.08	36	(38.7)	182	395.41	71	(38.2)	371	394.22
Asymptomatic hypoglycaemia												
Normal function	4	(33.3)	16	258.24	6	(50.0)	26	416.88	10	(41.7)	42	337.82
Mild impairment	60	(64.5)	516	1073.16	50	(53.8)	406	882.06	110	(59.1)	922	979.70
Probable symptomatic hypoglycaemia												
Normal function	3	(25.0)	3	48.42	2	(16.7)	4	64.14	5	(20.8)	7	56.30
Mild impairment	9	(9.7)	16	33.28	3	(3.2)	3	6.52	12	(6.5)	19	20.19
Pseudo-hypoglycaemia												
Normal function	2	(16.7)	4	64.56	1	(8.3)	3	48.10	3	(12.5)	7	56.30
Mild impairment	9	(9.7)	13	27.04	7	(7.5)	20	43.45	16	(8.6)	33	35.07

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2;
mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]

Hypoglycaemic episodes by classification and renal function at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia												
Normal function	0				0				0			
Mild impairment	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2;
mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]

2.7.4.7.1-81 ベースラインの肝機能別の低血糖－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
Normal	226				222				213				661			
Impairment	49				49				60				158			
PYE (years)																
Normal	219.62				213.34				212.03				645.00			
Impairment	48.38				48.47				59.81				156.65			
Severe or BG confirmed symptomatic hypoglycaemia																
Normal	48	(21.2)	125	56.92	67	(30.2)	285	133.59	2	(0.9)	2	0.94	117	(17.7)	412	63.88
Impairment	5	(10.2)	10	20.67	13	(26.5)	77	158.88	1	(1.7)	2	3.34	19	(12.0)	89	56.82
Severe or BG confirmed hypoglycaemia																
Normal	90	(39.8)	403	183.49	125	(56.3)	750	351.55	4	(1.9)	8	3.77	219	(33.1)	1161	180.00
Impairment	16	(32.7)	64	132.30	23	(46.9)	119	245.54	2	(3.3)	5	8.36	41	(25.9)	188	120.02
ADA																
Normal	200	(88.5)	4022	1831.30	208	(93.7)	5537	2595.37	50	(23.5)	120	56.60	458	(69.3)	9679	1500.62
Impairment	40	(81.6)	808	1670.28	42	(85.7)	803	1656.85	10	(16.7)	42	70.23	92	(58.2)	1653	1055.24

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower;
impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]

Hypoglycaemic episodes by classification and hepatic function at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe hypoglycaemia																
Normal	1	(0.4)	1	0.46	3	(1.4)	5	2.34	0				4	(0.6)	6	0.93
Impairment	0				1	(2.0)	1	2.06	0				1	(0.6)	1	0.64
Documented symptomatic hypoglycaemia																
Normal	99	(43.8)	703	320.09	121	(54.5)	1159	543.26	14	(6.6)	19	8.96	234	(35.4)	1881	291.63
Impairment	18	(36.7)	88	181.91	23	(46.9)	216	445.68	2	(3.3)	7	11.70	43	(27.2)	311	198.54
Asymptomatic hypoglycaemia																
Normal	190	(84.1)	3004	1367.79	188	(84.7)	3838	1798.99	35	(16.4)	83	39.14	413	(62.5)	6925	1073.64
Impairment	39	(79.6)	666	1376.74	36	(73.5)	515	1062.61	8	(13.3)	30	50.16	83	(52.5)	1211	773.08
Probable symptomatic hypoglycaemia																
Normal	37	(16.4)	89	40.52	24	(10.8)	129	60.47	7	(3.3)	7	3.30	68	(10.3)	225	34.88
Impairment	7	(14.3)	17	35.14	6	(12.2)	42	86.66	1	(1.7)	2	3.34	14	(8.9)	61	38.94
Pseudo-hypoglycaemia																
Normal	27	(11.9)	225	102.45	42	(18.9)	406	190.31	6	(2.8)	11	5.19	75	(11.3)	642	99.53
Impairment	10	(20.4)	37	76.49	9	(18.4)	29	59.84	2	(3.3)	3	5.02	21	(13.3)	69	44.05

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower;
impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]

Hypoglycaemic episodes by classification and hepatic function at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia																
Normal	0				0				0				0			
Impairment	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower;
impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]

2.7.4.7.1-82 ベースラインの肝機能別の低血糖－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Normal	79				88				167			
Impairment	26				17				43			
PYE (years)												
Normal	40.82				43.70				84.52			
Impairment	13.46				8.56				22.02			
Severe or BG confirmed symptomatic hypoglycaemia												
Normal	11	(13.9)	38	93.09	16	(18.2)	26	59.49	27	(16.2)	64	75.72
Impairment	4	(15.4)	14	104.04	2	(11.8)	17	198.51	6	(14.0)	31	140.78
Severe or BG confirmed hypoglycaemia												
Normal	24	(30.4)	106	259.67	30	(34.1)	92	210.52	54	(32.3)	198	234.26
Impairment	6	(23.1)	18	133.76	2	(11.8)	17	198.51	8	(18.6)	35	158.94
ADA												
Normal	59	(74.7)	658	1611.90	62	(70.5)	624	1427.87	121	(72.5)	1282	1516.75
Impairment	19	(73.1)	122	906.62	7	(41.2)	93	1085.94	26	(60.5)	215	976.36

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower; impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]

Hypoglycaemic episodes by classification and hepatic function at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe hypoglycaemia												
Normal	1	(1.3)	1	2.45	0				1	(0.6)	1	1.18
Impairment	0				0				0			
Documented symptomatic hypoglycaemia												
Normal	30	(38.0)	144	352.76	39	(44.3)	183	418.75	69	(41.3)	327	386.88
Impairment	9	(34.6)	67	497.90	3	(17.6)	72	840.73	12	(27.9)	139	631.23
Asymptomatic hypoglycaemia												
Normal	50	(63.3)	484	1185.65	51	(58.0)	414	947.33	101	(60.5)	898	1062.43
Impairment	14	(53.8)	48	356.70	5	(29.4)	18	210.18	19	(44.2)	66	299.72
Probable symptomatic hypoglycaemia												
Normal	11	(13.9)	17	41.64	4	(4.5)	6	13.73	15	(9.0)	23	27.21
Impairment	1	(3.8)	2	14.86	1	(5.9)	1	11.68	2	(4.7)	3	13.62
Pseudo-hypoglycaemia												
Normal	8	(10.1)	12	29.40	6	(6.8)	21	48.05	14	(8.4)	33	39.04
Impairment	3	(11.5)	5	37.16	2	(11.8)	2	23.35	5	(11.6)	7	31.79

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower; impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]

Hypoglycaemic episodes by classification and hepatic function at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia												
Normal	0				0				0			
Impairment	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower; impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]

2.7.4.7.1-83 前治療の経口糖尿病薬別の低血糖－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
Metformin	47				46				47				140			
Alpha-glucosidase inhibitor	41				40				41				122			
Thiazolidinedione	43				43				42				128			
Sulphonylurea	43				42				42				127			
Sodium-glucose co-transporter 2 inhibitors	61				61				61				183			
Glinide	40				39				40				119			
PYE (years)																
Metformin	46.10				44.82				46.46				137.38			
Alpha-glucosidase inhibitor	38.56				38.39				41.44				118.39			
Thiazolidinedione	42.43				39.90				42.66				125.00			
Sulphonylurea	42.21				39.93				41.39				123.53			
Sodium-glucose co-transporter 2 inhibitors	59.40				60.03				61.09				180.52			
Glinide	39.30				38.73				38.80				116.83			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Hypoglycaemic episodes by classification and pre-trial OAD treatment - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe or BG confirmed symptomatic hypoglycaemia																
Metformin	6	(12.8)	8	17.35	13	(28.3)	47	104.87	0				19	(13.6)	55	40.03
Alpha-glucosidase inhibitor	6	(14.6)	18	46.68	11	(27.5)	45	117.21	0				17	(13.9)	63	53.21
Thiazolidinedione	10	(23.3)	21	49.49	13	(30.2)	77	192.96	0				23	(18.0)	98	78.40
Sulphonylurea	14	(32.6)	52	123.20	19	(45.2)	74	185.32	2	(4.8)	3	7.25	35	(27.6)	129	104.43
Sodium-glucose co-transporter 2 inhibitors	8	(13.1)	13	21.89	11	(18.0)	45	74.96	0				19	(10.4)	58	32.13
Glinide	9	(22.5)	23	58.52	13	(33.3)	74	191.08	1	(2.5)	1	2.58	23	(19.3)	98	83.88
Severe or BG confirmed hypoglycaemia																
Metformin	16	(34.0)	40	86.76	21	(45.7)	76	169.57	0				37	(26.4)	116	84.44
Alpha-glucosidase inhibitor	16	(39.0)	60	155.61	23	(57.5)	147	382.88	0				39	(32.0)	207	174.84
Thiazolidinedione	23	(53.5)	116	273.38	22	(51.2)	140	350.84	1	(2.4)	4	9.38	46	(35.9)	260	208.01
Sulphonylurea	23	(53.5)	137	324.59	29	(69.0)	182	455.78	4	(9.5)	7	16.91	56	(44.1)	326	263.91
Sodium-glucose co-transporter 2 inhibitors	17	(27.9)	59	99.33	31	(50.8)	190	316.49	0				48	(26.2)	249	137.93
Glinide	11	(27.5)	55	139.93	22	(56.4)	134	346.01	1	(2.5)	2	5.16	34	(28.6)	191	163.49

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Hypoglycaemic episodes by classification and pre-trial OAD treatment - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA																
Metformin	41	(87.2)	674	1461.95	43	(93.5)	1066	2378.48	7	(14.9)	11	23.68	91	(65.0)	1751	1274.54
Alpha-glucosidase inhibitor	38	(92.7)	716	1856.98	37	(92.5)	969	2523.91	5	(12.2)	5	12.06	80	(65.6)	1690	1427.45
Thiazolidinedione	40	(93.0)	967	2278.98	39	(90.7)	973	2438.34	10	(23.8)	36	84.39	89	(69.5)	1976	1580.84
Sulphonylurea	35	(81.4)	1074	2544.62	41	(97.6)	1097	2747.20	14	(33.3)	51	123.22	90	(70.9)	2222	1798.81
Sodium-glucose co-transporter 2 inhibitors	50	(82.0)	825	1388.94	53	(86.9)	1399	2330.39	11	(18.0)	30	49.11	114	(62.3)	2254	1248.61
Glinide	36	(90.0)	574	1460.39	37	(94.9)	836	2158.71	13	(32.5)	29	74.75	86	(72.3)	1439	1231.74
Severe hypoglycaemia																
Metformin	0				0				0				0			
Alpha-glucosidase inhibitor	0				1	(2.5)	1	2.60	0				1	(0.8)	1	0.84
Thiazolidinedione	1	(2.3)	1	2.36	1	(2.3)	1	2.51	0				2	(1.6)	2	1.60
Sulphonylurea	0				1	(2.4)	1	2.50	0				1	(0.8)	1	0.81
Sodium-glucose co-transporter 2 inhibitors	0				0				0				0			
Glinide	0				1	(2.6)	3	7.75	0				1	(0.8)	3	2.57

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
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PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Hypoglycaemic episodes by classification and pre-trial OAD treatment - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N	(%)	E R	N	(%)	E R	N	(%)	E R	N	(%)	E R
Documented symptomatic hypoglycaemia												
Metformin	18	(38.3)	95 206.06	24	(52.2)	265 591.27	2	(4.3)	2 4.30	44	(31.4)	362 263.50
Alpha-glucosidase inhibitor	15	(36.6)	109 282.70	17	(42.5)	177 461.02	0			32	(26.2)	286 241.57
Thiazolidinedione	20	(46.5)	94 221.54	23	(53.5)	220 551.32	3	(7.1)	4 9.38	46	(35.9)	318 254.41
Sulphonylurea	17	(39.5)	250 592.32	30	(71.4)	214 535.92	6	(14.3)	14 33.83	53	(41.7)	478 386.96
Sodium-glucose co-transporter 2 inhibitors	24	(39.3)	100 168.36	27	(44.3)	257 428.10	0			51	(27.9)	357 197.76
Glinide	23	(57.5)	143 363.83	23	(59.0)	242 624.89	5	(12.5)	6 15.47	51	(42.9)	391 334.68
Asymptomatic hypoglycaemia												
Metformin	41	(87.2)	516 1119.24	39	(84.8)	524 1169.16	5	(10.6)	8 17.22	85	(60.7)	1048 762.83
Alpha-glucosidase inhibitor	35	(85.4)	479 1242.31	37	(92.5)	756 1969.12	5	(12.2)	5 12.06	77	(63.1)	1240 1047.36
Thiazolidinedione	36	(83.7)	822 1937.25	33	(76.7)	690 1729.14	8	(19.0)	29 67.98	77	(60.2)	1541 1232.83
Sulphonylurea	34	(79.1)	781 1850.42	36	(85.7)	772 1933.31	10	(23.8)	30 72.48	80	(63.0)	1583 1281.51
Sodium-glucose co-transporter 2 inhibitors	50	(82.0)	715 1203.75	47	(77.0)	1091 1817.34	8	(13.1)	24 39.29	105	(57.4)	1830 1013.74
Glinide	33	(82.5)	357 908.29	32	(82.1)	520 1342.74	7	(17.5)	17 43.82	72	(60.5)	894 765.24

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
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PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Hypoglycaemic episodes by classification and pre-trial OAD treatment - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Probable symptomatic hypoglycaemia																
Metformin	6	(12.8)	39	84.59	5	(10.9)	52	116.02	0				11	(7.9)	91	66.24
Alpha-glucosidase inhibitor	9	(22.0)	19	49.28	6	(15.0)	11	28.65	0				15	(12.3)	30	25.34
Thiazolidinedione	8	(18.6)	13	30.64	3	(7.0)	21	52.63	2	(4.8)	2	4.69	13	(10.2)	36	28.80
Sulphonylurea	7	(16.3)	16	37.91	9	(21.4)	59	147.75	2	(4.8)	3	7.25	18	(14.2)	78	63.14
Sodium-glucose co-transporter 2 inhibitors	1	(1.6)	1	1.68	3	(4.9)	13	21.65	1	(1.6)	1	1.64	5	(2.7)	15	8.31
Glinide	13	(32.5)	18	45.80	4	(10.3)	15	38.73	3	(7.5)	3	7.73	20	(16.8)	36	30.81
Pseudo-hypoglycaemia																
Metformin	4	(8.5)	24	52.06	11	(23.9)	225	502.02	1	(2.1)	1	2.15	16	(11.4)	250	181.97
Alpha-glucosidase inhibitor	7	(17.1)	109	282.70	4	(10.0)	24	62.51	0				11	(9.0)	133	112.34
Thiazolidinedione	5	(11.6)	37	87.20	8	(18.6)	41	102.75	1	(2.4)	1	2.34	14	(10.9)	79	63.20
Sulphonylurea	6	(14.0)	27	63.97	7	(16.7)	51	127.72	2	(4.8)	4	9.66	15	(11.8)	82	66.38
Sodium-glucose co-transporter 2 inhibitors	5	(8.2)	9	15.15	10	(16.4)	38	63.30	2	(3.3)	5	8.18	17	(9.3)	52	28.81
Glinide	10	(25.0)	56	142.48	11	(28.2)	56	144.60	2	(5.0)	3	7.73	23	(19.3)	115	98.44

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PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Hypoglycaemic episodes by classification and pre-trial OAD treatment - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia																
Metformin	0				0				0				0			
Alpha-glucosidase inhibitor	0				0				0				0			
Thiazolidinedione	0				0				0				0			
Sulphonylurea	0				0				0				0			
Sodium-glucose co-transporter 2 inhibitors	0				0				0				0			
Glinide	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

2.7.4.7.1-84 前治療の糖尿病治療別の低血糖－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Metformin and basal insulin	46				46				92			
Metformin, basal insulin and one other OAD	20				21				41			
Metformin and pre-mix/ combination insulin	26				25				51			
Metformin, pre-mix/ combination insulin and one other OAD	13				13				26			
PYE (years)												
Metformin and basal insulin	23.85				22.70				46.56			
Metformin, basal insulin and one other OAD	10.34				10.92				21.26			
Metformin and pre-mix/ combination insulin	13.39				11.92				25.31			
Metformin, pre-mix/ combination insulin and one other OAD	6.70				6.72				13.42			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Hypoglycaemic episodes by classification and pre-trial diabetes treatment - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe or BG confirmed symptomatic hypoglycaemia												
Metformin and basal insulin	6	(13.0)	20	83.84	7	(15.2)	9	39.64	13	(14.1)	29	62.29
Metformin, basal insulin and one other OAD	1	(5.0)	1	9.67	3	(14.3)	4	36.63	4	(9.8)	5	23.52
Metformin and pre-mix/ combination insulin	4	(15.4)	21	156.89	6	(24.0)	13	109.05	10	(19.6)	34	134.36
Metformin, pre-mix/ combination insulin and one other OAD	4	(30.8)	10	149.33	2	(15.4)	17	252.82	6	(23.1)	27	201.18
Severe or BG confirmed hypoglycaemia												
Metformin and basal insulin	11	(23.9)	64	268.29	11	(23.9)	28	123.34	22	(23.9)	92	197.61
Metformin, basal insulin and one other OAD	2	(10.0)	8	77.36	3	(14.3)	7	64.11	5	(12.2)	15	70.56
Metformin and pre-mix/ combination insulin	9	(34.6)	31	231.60	12	(48.0)	43	360.72	21	(41.2)	74	292.42
Metformin, pre-mix/ combination insulin and one other OAD	8	(61.5)	21	313.58	6	(46.2)	31	461.02	14	(53.8)	52	387.45

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Hypoglycaemic episodes by classification and pre-trial diabetes treatment - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA												
Metformin and basal insulin	32	(69.6)	329	1379.17	25	(54.3)	214	942.64	57	(62.0)	543	1166.31
Metformin, basal insulin and one other OAD	12	(60.0)	97	938.03	14	(66.7)	55	503.73	26	(63.4)	152	714.98
Metformin and pre-mix/ combination insulin	23	(88.5)	240	1793.00	22	(88.0)	276	2315.32	45	(88.2)	516	2039.05
Metformin, pre-mix/ combination insulin and one other OAD	11	(84.6)	114	1702.31	8	(61.5)	172	2557.94	19	(73.1)	286	2131.00
Severe hypoglycaemia												
Metformin and basal insulin	0				0				0			
Metformin, basal insulin and one other OAD	0				0				0			
Metformin and pre-mix/ combination insulin	1	(3.8)	1	7.47	0				1	(2.0)	1	3.95
Metformin, pre-mix/ combination insulin and one other OAD	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Hypoglycaemic episodes by classification and pre-trial diabetes treatment - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Documented symptomatic hypoglycaemia												
Metformin and basal insulin	17	(37.0)	89	373.09	16	(34.8)	67	295.12	33	(35.9)	156	335.07
Metformin, basal insulin and one other OAD	5	(25.0)	12	116.04	5	(23.8)	20	183.17	10	(24.4)	32	150.52
Metformin and pre-mix/ combination insulin	10	(38.5)	65	485.61	16	(64.0)	98	822.11	26	(51.0)	163	644.12
Metformin, pre-mix/ combination insulin and one other OAD	7	(53.8)	45	671.96	5	(38.5)	70	1041.02	12	(46.2)	115	856.87
Asymptomatic hypoglycaemia												
Metformin and basal insulin	25	(54.3)	229	959.97	20	(43.5)	140	616.68	45	(48.9)	369	792.57
Metformin, basal insulin and one other OAD	10	(50.0)	78	754.29	10	(47.6)	33	302.24	20	(48.8)	111	522.12
Metformin and pre-mix/ combination insulin	20	(76.9)	167	1247.63	18	(72.0)	160	1342.21	38	(74.5)	327	1292.19
Metformin, pre-mix/ combination insulin and one other OAD	9	(69.2)	58	866.09	8	(61.5)	99	1472.30	17	(65.4)	157	1169.81

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Hypoglycaemic episodes by classification and pre-trial diabetes treatment - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Probable symptomatic hypoglycaemia												
Metformin and basal insulin	4	(8.7)	7	29.34	1	(2.2)	1	4.40	5	(5.4)	8	17.18
Metformin, basal insulin and one other OAD	0				1	(4.8)	1	9.16	1	(2.4)	1	4.70
Metformin and pre-mix/ combination insulin	3	(11.5)	4	29.88	2	(8.0)	4	33.56	5	(9.8)	8	31.61
Metformin, pre-mix/ combination insulin and one other OAD	5	(38.5)	8	119.46	1	(7.7)	1	14.87	6	(23.1)	9	67.06
Pseudo-hypoglycaemia												
Metformin and basal insulin	3	(6.5)	4	16.77	3	(6.5)	6	26.43	6	(6.5)	10	21.48
Metformin, basal insulin and one other OAD	4	(20.0)	7	67.69	1	(4.8)	1	9.16	5	(12.2)	8	37.63
Metformin and pre-mix/ combination insulin	2	(7.7)	3	22.41	2	(8.0)	14	117.44	4	(7.8)	17	67.18
Metformin, pre-mix/ combination insulin and one other OAD	2	(15.4)	3	44.80	2	(15.4)	2	29.74	4	(15.4)	5	37.26

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Hypoglycaemic episodes by classification and pre-trial diabetes treatment - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia												
Metformin and basal insulin	0				0				0			
Metformin, basal insulin and one other OAD	0				0				0			
Metformin and pre-mix/ combination insulin	0				0				0			
Metformin, pre-mix/ combination insulin and one other OAD	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

2.7.4.7.1-85 男女別の夜間低血糖－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
Male	194				195				192				581			
Female	81				76				81				238			
PYE (years)																
Male	189.96				188.09				192.61				570.66			
Female	78.04				73.72				79.23				230.99			
Severe or BG confirmed symptomatic hypoglycaemia																
Male	10	(5.2)	13	6.84	14	(7.2)	31	16.48	0				24	(4.1)	44	7.71
Female	3	(3.7)	3	3.84	7	(9.2)	11	14.92	0				10	(4.2)	14	6.06
Severe or BG confirmed hypoglycaemia																
Male	22	(11.3)	45	23.69	33	(16.9)	94	49.98	0				55	(9.5)	139	24.36
Female	5	(6.2)	21	26.91	12	(15.8)	38	51.55	0				17	(7.1)	59	25.54
ADA																
Male	81	(41.8)	392	206.36	103	(52.8)	681	362.07	4	(2.1)	5	2.60	188	(32.4)	1078	188.91
Female	22	(27.2)	137	175.55	33	(43.4)	369	500.55	1	(1.2)	1	1.26	56	(23.5)	507	219.49

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Nocturnal hypoglycaemic episodes by classification and sex - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe hypoglycaemia																
Male	0				0				0				0			
Female	0				0				0				0			
Documented symptomatic hypoglycaemia																
Male	20	(10.3)	36	18.95	36	(18.5)	103	54.76	0				56	(9.6)	139	24.36
Female	10	(12.3)	25	32.03	16	(21.1)	92	124.80	0				26	(10.9)	117	50.65
Asymptomatic hypoglycaemia																
Male	67	(34.5)	329	173.19	83	(42.6)	554	294.54	4	(2.1)	5	2.60	154	(26.5)	888	155.61
Female	16	(19.8)	110	140.95	20	(26.3)	170	230.60	1	(1.2)	1	1.26	37	(15.5)	281	121.65
Probable symptomatic hypoglycaemia																
Male	5	(2.6)	11	5.79	6	(3.1)	10	5.32	0				11	(1.9)	21	3.68
Female	1	(1.2)	1	1.28	1	(1.3)	1	1.36	0				2	(0.8)	2	0.87
Pseudo-hypoglycaemia																
Male	1	(0.5)	16	8.42	7	(3.6)	14	7.44	0				8	(1.4)	30	5.26
Female	1	(1.2)	1	1.28	5	(6.6)	106	143.79	0				6	(2.5)	107	46.32

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Nocturnal hypoglycaemic episodes by classification and sex - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia																
Male	0				0				0				0			
Female	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

2.7.4.7.1-86 男女別の夜間低血糖－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Male	70				63				133			
Female	35				42				77			
PYE (years)												
Male	36.19				31.53				67.73			
Female	18.09				20.73				38.82			
Severe or BG confirmed symptomatic hypoglycaemia												
Male	3	(4.3)	3	8.29	2	(3.2)	2	6.34	5	(3.8)	5	7.38
Female	1	(2.9)	1	5.53	4	(9.5)	6	28.94	5	(6.5)	7	18.03
Severe or BG confirmed hypoglycaemia												
Male	5	(7.1)	10	27.63	5	(7.9)	12	38.05	10	(7.5)	22	32.48
Female	3	(8.6)	16	88.47	5	(11.9)	7	33.77	8	(10.4)	23	59.25
ADA												
Male	19	(27.1)	75	207.23	18	(28.6)	77	244.18	37	(27.8)	152	224.43
Female	9	(25.7)	77	425.74	16	(38.1)	48	231.54	25	(32.5)	125	322.02

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Nocturnal hypoglycaemic episodes by classification and sex - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe hypoglycaemia												
Male	0				0				0			
Female	0				0				0			
Documented symptomatic hypoglycaemia												
Male	9	(12.9)	21	58.02	8	(12.7)	17	53.91	17	(12.8)	38	56.11
Female	4	(11.4)	9	49.76	10	(23.8)	27	130.24	14	(18.2)	36	92.74
Asymptomatic hypoglycaemia												
Male	12	(17.1)	51	140.92	15	(23.8)	58	183.93	27	(20.3)	109	160.94
Female	6	(17.1)	68	375.98	10	(23.8)	16	77.18	16	(20.8)	84	216.40
Probable symptomatic hypoglycaemia												
Male	1	(1.4)	1	2.76	1	(1.6)	1	3.17	2	(1.5)	2	2.95
Female	0				0				0			
Pseudo-hypoglycaemia												
Male	1	(1.4)	2	5.53	1	(1.6)	1	3.17	2	(1.5)	3	4.43
Female	0				1	(2.4)	5	24.12	1	(1.3)	5	12.88

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Nocturnal hypoglycaemic episodes by classification and sex - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia												
Male	0				0				0			
Female	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

2.7.4.7.1-87 ベースラインの BMI（kg/m^2）別の夜間低血糖－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
<25	122				117				118				357			
25<= <30	112				107				109				328			
>=30	41				47				46				134			
PYE (years)																
<25	117.94				111.20				117.32				346.46			
25<= <30	110.64				105.69				109.04				325.37			
>=30	39.42				44.91				45.48				129.82			
Severe or BG confirmed symptomatic hypoglycaemia																
<25	10	(8.2)	13	11.02	14	(12.0)	32	28.78	0				24	(6.7)	45	12.99
25<= <30	3	(2.7)	3	2.71	6	(5.6)	9	8.52	0				9	(2.7)	12	3.69
>=30	0				1	(2.1)	1	2.23	0				1	(0.7)	1	0.77
Severe or BG confirmed hypoglycaemia																
<25	19	(15.6)	46	39.00	24	(20.5)	74	66.54	0				43	(12.0)	120	34.64
25<= <30	8	(7.1)	20	18.08	14	(13.1)	31	29.33	0				22	(6.7)	51	15.67
>=30	0				7	(14.9)	27	60.11	0				7	(5.2)	27	20.80

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
BMI: Body mass index (kg/m^2) at baseline

Nocturnal hypoglycaemic episodes by classification and BMI (kg/m^2) at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA																
<25	55	(45.1)	286	242.51	63	(53.8)	625	562.03	3	(2.5)	4	3.41	121	(33.9)	915	264.10
25<= <30	43	(38.4)	236	213.30	56	(52.3)	296	280.07	1	(0.9)	1	0.92	100	(30.5)	533	163.81
>=30	5	(12.2)	7	17.76	17	(36.2)	129	287.21	1	(2.2)	1	2.20	23	(17.2)	137	105.53
Severe hypoglycaemia																
<25	0				0				0				0			
25<= <30	0				0				0				0			
>=30	0				0				0				0			
Documented symptomatic hypoglycaemia																
<25	21	(17.2)	47	39.85	30	(25.6)	140	125.90	0				51	(14.3)	187	53.97
25<= <30	9	(8.0)	14	12.65	18	(16.8)	51	48.25	0				27	(8.2)	65	19.98
>=30	0				4	(8.5)	4	8.91	0				4	(3.0)	4	3.08
Asymptomatic hypoglycaemia																
<25	46	(37.7)	231	195.87	45	(38.5)	369	331.82	3	(2.5)	4	3.41	94	(26.3)	604	174.34
25<= <30	34	(30.4)	203	183.47	46	(43.0)	235	222.35	1	(0.9)	1	0.92	81	(24.7)	439	134.92
>=30	3	(7.3)	5	12.68	12	(25.5)	120	267.17	1	(2.2)	1	2.20	16	(11.9)	126	97.06

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
BMI: Body mass index (kg/m^2) at baseline

Nocturnal hypoglycaemic episodes by classification and BMI (kg/m^2) at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Probable symptomatic hypoglycaemia																
<25	2	(1.6)	8	6.78	4	(3.4)	8	7.19	0				6	(1.7)	16	4.62
25<= <30	3	(2.7)	3	2.71	3	(2.8)	3	2.84	0				6	(1.8)	6	1.84
>=30	1	(2.4)	1	2.54	0				0				1	(0.7)	1	0.77
Pseudo-hypoglycaemia																
<25	0				6	(5.1)	108	97.12	0				6	(1.7)	108	31.17
25<= <30	1	(0.9)	16	14.46	3	(2.8)	7	6.62	0				4	(1.2)	23	7.07
>=30	1	(2.4)	1	2.54	3	(6.4)	5	11.13	0				4	(3.0)	6	4.62
ADA unclassifiable hypoglycaemia																
<25	0				0				0				0			
25<= <30	0				0				0				0			
>=30	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
BMI: Body mass index (kg/m^2) at baseline

2.7.4.7.1-88 ベースラインの BMI（kg/m^2）別の夜間低血糖－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
<25	26				28				54			
25<= <30	64				53				117			
>=30	15				24				39			
PYE (years)												
<25	13.42				13.74				27.16			
25<= <30	33.06				26.07				59.13			
>=30	7.79				12.46				20.25			
Severe or BG confirmed symptomatic hypoglycaemia												
<25	1	(3.8)	1	7.45	2	(7.1)	2	14.56	3	(5.6)	3	11.05
25<= <30	3	(4.7)	3	9.07	2	(3.8)	4	15.34	5	(4.3)	7	11.84
>=30	0				2	(8.3)	2	16.05	2	(5.1)	2	9.88
Severe or BG confirmed hypoglycaemia												
<25	3	(11.5)	14	104.29	3	(10.7)	3	21.84	6	(11.1)	17	62.59
25<= <30	5	(7.8)	12	36.30	5	(9.4)	14	53.70	10	(8.5)	26	43.97
>=30	0				2	(8.3)	2	16.05	2	(5.1)	2	9.88

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
BMI: Body mass index (kg/m^2) at baseline

Nocturnal hypoglycaemic episodes by classification and BMI (kg/m^2) at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA												
<25	10	(38.5)	53	394.82	9	(32.1)	36	262.09	19	(35.2)	89	327.69
25<= <30	16	(25.0)	96	290.39	21	(39.6)	77	295.33	37	(31.6)	173	292.57
>=30	2	(13.3)	3	38.49	4	(16.7)	12	96.33	6	(15.4)	15	74.07
Severe hypoglycaemia												
<25	0				0				0			
25<= <30	0				0				0			
>=30	0				0				0			
Documented symptomatic hypoglycaemia												
<25	4	(15.4)	6	44.70	6	(21.4)	17	123.76	10	(18.5)	23	84.68
25<= <30	9	(14.1)	24	72.60	9	(17.0)	22	84.38	18	(15.4)	46	77.79
>=30	0				3	(12.5)	5	40.14	3	(7.7)	5	24.69
Asymptomatic hypoglycaemia												
<25	5	(19.2)	46	342.68	6	(21.4)	14	101.92	11	(20.4)	60	220.92
25<= <30	11	(17.2)	70	211.74	16	(30.2)	53	203.28	27	(23.1)	123	208.01
>=30	2	(13.3)	3	38.49	3	(12.5)	7	56.19	5	(12.8)	10	49.38

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
BMI: Body mass index (kg/m^2) at baseline

Nocturnal hypoglycaemic episodes by classification and BMI (kg/m^2) at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Probable symptomatic hypoglycaemia												
<25	1	(3.8)	1	7.45	0				1	(1.9)	1	3.68
25<= <30	0				1	(1.9)	1	3.84	1	(0.9)	1	1.69
>=30	0				0				0			
Pseudo-hypoglycaemia												
<25	0				1	(3.6)	5	36.40	1	(1.9)	5	18.41
25<= <30	1	(1.6)	2	6.05	1	(1.9)	1	3.84	2	(1.7)	3	5.07
>=30	0				0				0			
ADA unclassifiable hypoglycaemia												
<25	0				0				0			
25<= <30	0				0				0			
>=30	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
BMI: Body mass index (kg/m^2) at baseline

2.7.4.7.1-89 ベースラインの年齢（歳）別の夜間低血糖ーSAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
<65	197				183				202				582			
>=65	78				88				71				237			
65<= <75	76				84				66				226			
>=75	2				4				5				11			
PYE (years)																
<65	193.01				179.38				202.03				574.43			
>=65	74.99				82.43				69.80				227.22			
65<= <75	73.16				79.21				64.70				217.07			
>=75	1.83				3.22				5.10				10.15			
Severe or BG confirmed symptomatic hypoglycaemia																
<65	9	(4.6)	12	6.22	14	(7.7)	24	13.38	0				23	(4.0)	36	6.27
>=65	4	(5.1)	4	5.33	7	(8.0)	18	21.84	0				11	(4.6)	22	9.68
65<= <75	4	(5.3)	4	5.47	7	(8.3)	18	22.73	0				11	(4.9)	22	10.13
>=75	0				0				0				0			
Severe or BG confirmed hypoglycaemia																
<65	18	(9.1)	49	25.39	31	(16.9)	85	47.39	0				49	(8.4)	134	23.33
>=65	9	(11.5)	17	22.67	14	(15.9)	47	57.02	0				23	(9.7)	64	28.17
65<= <75	9	(11.8)	17	23.24	14	(16.7)	47	59.34	0				23	(10.2)	64	29.48
>=75	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Nocturnal hypoglycaemic episodes by classification and age (years) at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA																
<65	65	(33.0)	387	200.51	90	(49.2)	534	297.69	3	(1.5)	4	1.98	158	(27.1)	925	161.03
>=65	38	(48.7)	142	189.36	46	(52.3)	516	626.02	2	(2.8)	2	2.87	86	(36.3)	660	290.47
65<= <75	37	(48.7)	137	187.25	45	(53.6)	512	646.42	2	(3.0)	2	3.09	84	(37.2)	651	299.90
>=75	1	(50.0)	5	273.80	1	(25.0)	4	124.23	0				2	(18.2)	9	88.68
Severe hypoglycaemia																
<65	0				0				0				0			
>=65	0				0				0				0			
65<= <75	0				0				0				0			
>=75	0				0				0				0			
Documented symptomatic hypoglycaemia																
<65	16	(8.1)	38	19.69	34	(18.6)	87	48.50	0				50	(8.6)	125	21.76
>=65	14	(17.9)	23	30.67	18	(20.5)	108	131.03	0				32	(13.5)	131	57.65
65<= <75	13	(17.1)	21	28.70	18	(21.4)	108	136.35	0				31	(13.7)	129	59.43
>=75	1	(50.0)	2	109.52	0				0				1	(9.1)	2	19.71
Asymptomatic hypoglycaemia																
<65	55	(27.9)	322	166.83	68	(37.2)	432	240.83	3	(1.5)	4	1.98	126	(21.6)	758	131.96
>=65	28	(35.9)	117	156.02	35	(39.8)	292	354.26	2	(2.8)	2	2.87	65	(27.4)	411	180.88
65<= <75	27	(35.5)	114	155.82	35	(41.7)	292	368.66	2	(3.0)	2	3.09	64	(28.3)	408	187.96
>=75	1	(50.0)	3	164.28	0				0				1	(9.1)	3	29.56

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Nocturnal hypoglycaemic episodes by classification and age (years) at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Probable symptomatic hypoglycaemia																
<65	5	(2.5)	11	5.70	4	(2.2)	4	2.23	0				9	(1.5)	15	2.61
>=65	1	(1.3)	1	1.33	3	(3.4)	7	8.49	0				4	(1.7)	8	3.52
65<= <75	1	(1.3)	1	1.37	3	(3.6)	7	8.84	0				4	(1.8)	8	3.69
>=75	0				0				0				0			
Pseudo-hypoglycaemia																
<65	1	(0.5)	16	8.29	6	(3.3)	11	6.13	0				7	(1.2)	27	4.70
>=65	1	(1.3)	1	1.33	6	(6.8)	109	132.24	0				7	(3.0)	110	48.41
65<= <75	1	(1.3)	1	1.37	5	(6.0)	105	132.57	0				6	(2.7)	106	48.83
>=75	0				1	(25.0)	4	124.23	0				1	(9.1)	4	39.41
ADA unclassifiable hypoglycaemia																
<65	0				0				0				0			
>=65	0				0				0				0			
65<= <75	0				0				0				0			
>=75	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

2.7.4.7.1-90 ベースラインの年齢（歳）別の夜間低血糖ーSAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
<65	75				85				160			
>=65	30				20				50			
65<= <75	28				19				47			
>=75	2				1				3			
PYE (years)												
<65	38.80				43.35				82.16			
>=65	15.47				8.91				24.39			
65<= <75	14.44				8.66				23.10			
>=75	1.03				0.25				1.28			
Severe or BG confirmed symptomatic hypoglycaemia												
<65	3	(4.0)	3	7.73	3	(3.5)	3	6.92	6	(3.8)	6	7.30
>=65	1	(3.3)	1	6.46	3	(15.0)	5	56.11	4	(8.0)	6	24.60
65<= <75	1	(3.6)	1	6.93	3	(15.8)	5	57.72	4	(8.5)	6	25.97
>=75	0				0				0			
Severe or BG confirmed hypoglycaemia												
<65	6	(8.0)	22	56.70	6	(7.1)	13	29.99	12	(7.5)	35	42.60
>=65	2	(6.7)	4	25.85	4	(20.0)	6	67.33	6	(12.0)	10	41.01
65<= <75	2	(7.1)	4	27.70	4	(21.1)	6	69.26	6	(12.8)	10	43.29
>=75	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Nocturnal hypoglycaemic episodes by classification and age (years) at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA												
<65	18	(24.0)	104	268.02	27	(31.8)	91	209.90	45	(28.1)	195	237.35
>=65	10	(33.3)	48	310.19	7	(35.0)	34	381.52	17	(34.0)	82	336.26
65<= <75	10	(35.7)	48	332.42	7	(36.8)	34	392.49	17	(36.2)	82	354.95
>=75	0				0				0			
Severe hypoglycaemia												
<65	0				0				0			
>=65	0				0				0			
65<= <75	0				0				0			
>=75	0				0				0			
Documented symptomatic hypoglycaemia												
<65	8	(10.7)	15	38.66	12	(14.1)	24	55.36	20	(12.5)	39	47.47
>=65	5	(16.7)	15	96.93	6	(30.0)	20	224.42	11	(22.0)	35	143.52
65<= <75	5	(17.9)	15	103.88	6	(31.6)	20	230.88	11	(23.4)	35	151.50
>=75	0				0				0			
Asymptomatic hypoglycaemia												
<65	10	(13.3)	86	221.63	20	(23.5)	65	149.93	30	(18.8)	151	183.79
>=65	8	(26.7)	33	213.26	5	(25.0)	9	100.99	13	(26.0)	42	172.23
65<= <75	8	(28.6)	33	228.54	5	(26.3)	9	103.90	13	(27.7)	42	181.80
>=75	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

Nocturnal hypoglycaemic episodes by classification and age (years) at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Probable symptomatic hypoglycaemia												
<65	1	(1.3)	1	2.58	1	(1.2)	1	2.31	2	(1.3)	2	2.43
>=65	0				0				0			
65<= <75	0				0				0			
>=75	0				0				0			
Pseudo-hypoglycaemia												
<65	1	(1.3)	2	5.15	1	(1.2)	1	2.31	2	(1.3)	3	3.65
>=65	0				1	(5.0)	5	56.11	1	(2.0)	5	20.50
65<= <75	0				1	(5.3)	5	57.72	1	(2.1)	5	21.64
>=75	0				0				0			
ADA unclassifiable hypoglycaemia												
<65	0				0				0			
>=65	0				0				0			
65<= <75	0				0				0			
>=75	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL)

2.7.4.7.1-91 ベースラインの腎機能別の夜間低血糖－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
Normal function	24				20				23				67			
Mild impairment	251				251				250				752			
PYE (years)																
Normal function	23.25				18.69				21.69				63.62			
Mild impairment	244.75				243.12				250.15				738.02			
Severe or BG confirmed symptomatic hypoglycaemia																
Normal function	0				3	(15.0)	3	16.05	0				3	(4.5)	3	4.72
Mild impairment	13	(5.2)	16	6.54	18	(7.2)	39	16.04	0				31	(4.1)	55	7.45
Severe or BG confirmed hypoglycaemia																
Normal function	0				4	(20.0)	5	26.76	0				4	(6.0)	5	7.86
Mild impairment	27	(10.8)	66	26.97	41	(16.3)	127	52.24	0				68	(9.0)	193	26.15
ADA																
Normal function	6	(25.0)	21	90.32	8	(40.0)	24	128.44	1	(4.3)	2	9.22	15	(22.4)	47	73.87
Mild impairment	97	(38.6)	508	207.56	128	(51.0)	1026	422.01	4	(1.6)	4	1.60	229	(30.5)	1538	208.39

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2; mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]

Nocturnal hypoglycaemic episodes by classification and renal function at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe hypoglycaemia																
Normal function	0				0				0				0			
Mild impairment	0				0				0				0			
Documented symptomatic hypoglycaemia																
Normal function	5	(20.8)	9	38.71	4	(20.0)	13	69.57	0				9	(13.4)	22	34.58
Mild impairment	25	(10.0)	52	21.25	48	(19.1)	182	74.86	0				73	(9.7)	234	31.71
Asymptomatic hypoglycaemia																
Normal function	3	(12.5)	12	51.61	5	(25.0)	9	48.16	1	(4.3)	2	9.22	9	(13.4)	23	36.15
Mild impairment	80	(31.9)	427	174.46	98	(39.0)	715	294.09	4	(1.6)	4	1.60	182	(24.2)	1146	155.28
Probable symptomatic hypoglycaemia																
Normal function	0				0				0				0			
Mild impairment	6	(2.4)	12	4.90	7	(2.8)	11	4.52	0				13	(1.7)	23	3.12
Pseudo-hypoglycaemia																
Normal function	0				1	(5.0)	2	10.70	0				1	(1.5)	2	3.14
Mild impairment	2	(0.8)	17	6.95	11	(4.4)	118	48.54	0				13	(1.7)	135	18.29

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2; mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]

Nocturnal hypoglycaemic episodes by classification and renal function at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia																
Normal function	0				0				0				0			
Mild impairment	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2; mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]

2.7.4.7.1-92 ベースラインの腎機能別の夜間低血糖－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Normal function	12				12				24			
Mild impairment	93				93				186			
PYE (years)												
Normal function	6.20				6.24				12.43			
Mild impairment	48.08				46.03				94.11			
Severe or BG confirmed symptomatic hypoglycaemia												
Normal function	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Mild impairment	4	(4.3)	4	8.32	5	(5.4)	7	15.21	9	(4.8)	11	11.69
Severe or BG confirmed hypoglycaemia												
Normal function	0				1	(8.3)	2	32.07	1	(4.2)	2	16.09
Mild impairment	8	(8.6)	26	54.07	9	(9.7)	17	36.93	17	(9.1)	43	45.69
ADA												
Normal function	2	(16.7)	2	32.28	4	(33.3)	16	256.54	6	(25.0)	18	144.78
Mild impairment	26	(28.0)	150	311.97	30	(32.3)	109	236.81	56	(30.1)	259	275.21

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2;
mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]

Nocturnal hypoglycaemic episodes by classification and renal function at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe hypoglycaemia												
Normal function	0				0				0			
Mild impairment	0				0				0			
Documented symptomatic hypoglycaemia												
Normal function	1	(8.3)	1	16.14	2	(16.7)	7	112.24	3	(12.5)	8	64.35
Mild impairment	12	(12.9)	29	60.31	16	(17.2)	37	80.38	28	(15.1)	66	70.13
Asymptomatic hypoglycaemia												
Normal function	0				3	(25.0)	8	128.27	3	(12.5)	8	64.35
Mild impairment	18	(19.4)	119	247.49	22	(23.7)	66	143.39	40	(21.5)	185	196.58
Probable symptomatic hypoglycaemia												
Normal function	1	(8.3)	1	16.14	0				1	(4.2)	1	8.04
Mild impairment	0				1	(1.1)	1	2.17	1	(0.5)	1	1.06
Pseudo-hypoglycaemia												
Normal function	0				1	(8.3)	1	16.03	1	(4.2)	1	8.04
Mild impairment	1	(1.1)	2	4.16	1	(1.1)	5	10.86	2	(1.1)	7	7.44

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2;
mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]

Nocturnal hypoglycaemic episodes by classification and renal function at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia												
Normal function	0				0				0			
Mild impairment	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Renal function: [normal function: eGFR >= 90 mL/min/1.73 m2;
mild impairment: eGFR >= 60 - < 90 mL/min/1.73 m2]

2.7.4.7.1-93 ベースラインの肝機能別の夜間低血糖－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
Normal	226				222				213				661			
Impairment	49				49				60				158			
PYE (years)																
Normal	219.62				213.34				212.03				645.00			
Impairment	48.38				48.47				59.81				156.65			
Severe or BG confirmed symptomatic hypoglycaemia																
Normal	13	(5.8)	16	7.29	17	(7.7)	34	15.94	0				30	(4.5)	50	7.75
Impairment	0				4	(8.2)	8	16.51	0				4	(2.5)	8	5.11
Severe or BG confirmed hypoglycaemia																
Normal	25	(11.1)	61	27.77	38	(17.1)	120	56.25	0				63	(9.5)	181	28.06
Impairment	2	(4.1)	5	10.34	7	(14.3)	12	24.76	0				9	(5.7)	17	10.85
ADA																
Normal	86	(38.1)	444	202.16	114	(51.4)	981	459.83	5	(2.3)	6	2.83	205	(31.0)	1431	221.86
Impairment	17	(34.7)	85	175.71	22	(44.9)	69	142.37	0				39	(24.7)	154	98.31

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower;
impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]

Nocturnal hypoglycaemic episodes by classification and hepatic function at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe hypoglycaemia																
Normal	0				0				0				0			
Impairment	0				0				0				0			
Documented symptomatic hypoglycaemia																
Normal	29	(12.8)	60	27.32	41	(18.5)	173	81.09	0				70	(10.6)	233	36.12
Impairment	1	(2.0)	1	2.07	11	(22.4)	22	45.39	0				12	(7.6)	23	14.68
Asymptomatic hypoglycaemia																
Normal	68	(30.1)	356	162.09	86	(38.7)	680	318.74	5	(2.3)	6	2.83	159	(24.1)	1042	161.55
Impairment	15	(30.6)	83	171.58	17	(34.7)	44	90.79	0				32	(20.3)	127	81.07
Probable symptomatic hypoglycaemia																
Normal	5	(2.2)	11	5.01	7	(3.2)	11	5.16	0				12	(1.8)	22	3.41
Impairment	1	(2.0)	1	2.07	0				0				1	(0.6)	1	0.64
Pseudo-hypoglycaemia																
Normal	2	(0.9)	17	7.74	10	(4.5)	117	54.84	0				12	(1.8)	134	20.78
Impairment	0				2	(4.1)	3	6.19	0				2	(1.3)	3	1.92

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower;
impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]

Nocturnal hypoglycaemic episodes by classification and hepatic function at baseline - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia																
Normal	0				0				0				0			
Impairment	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower;
impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]

2.7.4.7.1-94 ベースラインの肝機能別の夜間低血糖－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Normal	79				88				167			
Impairment	26				17				43			
PYE (years)												
Normal	40.82				43.70				84.52			
Impairment	13.46				8.56				22.02			
Severe or BG confirmed symptomatic hypoglycaemia												
Normal	4	(5.1)	4	9.80	6	(6.8)	8	18.31	10	(6.0)	12	14.20
Impairment	0				0				0			
Severe or BG confirmed hypoglycaemia												
Normal	8	(10.1)	26	63.69	10	(11.4)	19	43.48	18	(10.8)	45	53.24
Impairment	0				0				0			
ADA												
Normal	22	(27.8)	139	340.51	31	(35.2)	113	258.57	53	(31.7)	252	298.14
Impairment	6	(23.1)	13	96.61	3	(17.6)	12	140.12	9	(20.9)	25	113.53

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower; impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]

Nocturnal hypoglycaemic episodes by classification and hepatic function at baseline - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe hypoglycaemia												
Normal	0				0				0			
Impairment	0				0				0			
Documented symptomatic hypoglycaemia												
Normal	10	(12.7)	22	53.89	16	(18.2)	40	91.53	26	(15.6)	62	73.35
Impairment	3	(11.5)	8	59.45	2	(11.8)	4	46.71	5	(11.6)	12	54.49
Asymptomatic hypoglycaemia												
Normal	14	(17.7)	114	279.27	23	(26.1)	66	151.02	37	(22.2)	180	212.96
Impairment	4	(15.4)	5	37.16	2	(11.8)	8	93.41	6	(14.0)	13	59.04
Probable symptomatic hypoglycaemia												
Normal	1	(1.3)	1	2.45	1	(1.1)	1	2.29	2	(1.2)	2	2.37
Impairment	0				0				0			
Pseudo-hypoglycaemia												
Normal	1	(1.3)	2	4.90	2	(2.3)	6	13.73	3	(1.8)	8	9.46
Impairment	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower; impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]

Nocturnal hypoglycaemic episodes by classification and hepatic function at baseline – treatment emergent – trial 4184 – summary – safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia												
Normal	0				0				0			
Impairment	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
Hepatic function: [normal: baseline levels of both transaminases (ALT and AST) are equal to the upper limit of normal range or lower; impairment: Baseline levels of one or both transaminases (ALT and AST) are more than the upper limit of normal range]

2.7.4.7.1-95 前治療の経口糖尿病薬別の夜間低血糖－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects																
Metformin	47				46				47				140			
Alpha-glucosidase inhibitor	41				40				41				122			
Thiazolidinedione	43				43				42				128			
Sulphonylurea	43				42				42				127			
Sodium-glucose co-transporter 2 inhibitors	61				61				61				183			
Glinide	40				39				40				119			
PYE (years)																
Metformin	46.10				44.82				46.46				137.38			
Alpha-glucosidase inhibitor	38.56				38.39				41.44				118.39			
Thiazolidinedione	42.43				39.90				42.66				125.00			
Sulphonylurea	42.21				39.93				41.39				123.53			
Sodium-glucose co-transporter 2 inhibitors	59.40				60.03				61.09				180.52			
Glinide	39.30				38.73				38.80				116.83			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Nocturnal hypoglycaemic episodes by classification and pre-trial OAD treatment - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe or BG confirmed symptomatic hypoglycaemia																
Metformin	2	(4.3)	2	4.34	4	(8.7)	7	15.62	0				6	(4.3)	9	6.55
Alpha-glucosidase inhibitor	1	(2.4)	3	7.78	4	(10.0)	9	23.44	0				5	(4.1)	12	10.14
Thiazolidinedione	1	(2.3)	1	2.36	3	(7.0)	5	12.53	0				4	(3.1)	6	4.80
Sulphonylurea	4	(9.3)	4	9.48	4	(9.5)	13	32.56	0				8	(6.3)	17	13.76
Sodium-glucose co-transporter 2 inhibitors	3	(4.9)	4	6.73	2	(3.3)	2	3.33	0				5	(2.7)	6	3.32
Glinide	2	(5.0)	2	5.09	4	(10.3)	6	15.49	0				6	(5.0)	8	6.85
Severe or BG confirmed hypoglycaemia																
Metformin	5	(10.6)	11	23.86	6	(13.0)	9	20.08	0				11	(7.9)	20	14.56
Alpha-glucosidase inhibitor	3	(7.3)	7	18.15	7	(17.5)	32	83.35	0				10	(8.2)	39	32.94
Thiazolidinedione	7	(16.3)	12	28.28	8	(18.6)	22	55.13	0				15	(11.7)	34	27.20
Sulphonylurea	6	(14.0)	18	42.65	6	(14.3)	20	50.09	0				12	(9.4)	38	30.76
Sodium-glucose co-transporter 2 inhibitors	3	(4.9)	15	25.25	10	(16.4)	32	53.30	0				13	(7.1)	47	26.04
Glinide	3	(7.5)	3	7.63	8	(20.5)	17	43.90	0				11	(9.2)	20	17.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Nocturnal hypoglycaemic episodes by classification and pre-trial OAD treatment - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA																
Metformin	20	(42.6)	129	279.81	21	(45.7)	239	533.26	0				41	(29.3)	368	267.87
Alpha-glucosidase inhibitor	14	(34.1)	78	202.30	17	(42.5)	155	403.72	2	(4.9)	2	4.83	33	(27.0)	235	198.49
Thiazolidinedione	18	(41.9)	100	235.68	24	(55.8)	156	390.94	2	(4.8)	3	7.03	44	(34.4)	259	207.21
Sulphonylurea	18	(41.9)	89	210.87	20	(47.6)	158	395.68	0				38	(29.9)	247	199.96
Sodium-glucose co-transporter 2 inhibitors	18	(29.5)	101	170.04	31	(50.8)	204	339.81	1	(1.6)	1	1.64	50	(27.3)	306	169.51
Glinide	15	(37.5)	32	81.42	23	(59.0)	138	356.34	0				38	(31.9)	170	145.51
Severe hypoglycaemia																
Metformin	0				0				0				0			
Alpha-glucosidase inhibitor	0				0				0				0			
Thiazolidinedione	0				0				0				0			
Sulphonylurea	0				0				0				0			
Sodium-glucose co-transporter 2 inhibitors	0				0				0				0			
Glinide	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Nocturnal hypoglycaemic episodes by classification and pre-trial OAD treatment - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Documented symptomatic hypoglycaemia																
Metformin	6	(12.8)	12	26.03	11	(23.9)	73	162.88	0				17	(12.1)	85	61.87
Alpha-glucosidase inhibitor	3	(7.3)	8	20.75	6	(15.0)	13	33.86	0				9	(7.4)	21	17.74
Thiazolidinedione	3	(7.0)	4	9.43	7	(16.3)	29	72.67	0				10	(7.8)	33	26.40
Sulphonylurea	7	(16.3)	20	47.39	9	(21.4)	26	65.11	0				16	(12.6)	46	37.24
Sodium-glucose co-transporter 2 inhibitors	6	(9.8)	11	18.52	11	(18.0)	36	59.97	0				17	(9.3)	47	26.04
Glinide	5	(12.5)	6	15.27	8	(20.5)	18	46.48	0				13	(10.9)	24	20.54
Asymptomatic hypoglycaemia																
Metformin	16	(34.0)	110	238.60	13	(28.3)	64	142.80	0				29	(20.7)	174	126.65
Alpha-glucosidase inhibitor	12	(29.3)	53	137.46	14	(35.0)	136	354.23	2	(4.9)	2	4.83	28	(23.0)	191	161.33
Thiazolidinedione	14	(32.6)	94	221.54	19	(44.2)	125	313.25	2	(4.8)	3	7.03	35	(27.3)	222	177.60
Sulphonylurea	15	(34.9)	69	163.48	15	(35.7)	125	313.04	0				30	(23.6)	194	157.05
Sodium-glucose co-transporter 2 inhibitors	17	(27.9)	90	151.52	26	(42.6)	164	273.18	1	(1.6)	1	1.64	44	(24.0)	255	141.26
Glinide	9	(22.5)	23	58.52	16	(41.0)	110	284.04	0				25	(21.0)	133	113.84

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Nocturnal hypoglycaemic episodes by classification and pre-trial OAD treatment - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Probable symptomatic hypoglycaemia																
Metformin	1	(2.1)	7	15.18	0				0				1	(0.7)	7	5.10
Alpha-glucosidase inhibitor	1	(2.4)	1	2.59	3	(7.5)	6	15.63	0				4	(3.3)	7	5.91
Thiazolidinedione	1	(2.3)	1	2.36	1	(2.3)	1	2.51	0				2	(1.6)	2	1.60
Sulphonylurea	0				1	(2.4)	2	5.01	0				1	(0.8)	2	1.62
Sodium-glucose co-transporter 2 inhibitors	0				1	(1.6)	1	1.67	0				1	(0.5)	1	0.55
Glinide	3	(7.5)	3	7.63	1	(2.6)	1	2.58	0				4	(3.4)	4	3.42
Pseudo-hypoglycaemia																
Metformin	0				4	(8.7)	102	227.58	0				4	(2.9)	102	74.25
Alpha-glucosidase inhibitor	1	(2.4)	16	41.50	0				0				1	(0.8)	16	13.51
Thiazolidinedione	1	(2.3)	1	2.36	1	(2.3)	1	2.51	0				2	(1.6)	2	1.60
Sulphonylurea	0				2	(4.8)	5	12.52	0				2	(1.6)	5	4.05
Sodium-glucose co-transporter 2 inhibitors	0				1	(1.6)	3	5.00	0				1	(0.5)	3	1.66
Glinide	0				4	(10.3)	9	23.24	0				4	(3.4)	9	7.70

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Nocturnal hypoglycaemic episodes by classification and pre-trial OAD treatment - treatment emergent - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia																
Metformin	0				0				0				0			
Alpha-glucosidase inhibitor	0				0				0				0			
Thiazolidinedione	0				0				0				0			
Sulphonylurea	0				0				0				0			
Sodium-glucose co-transporter 2 inhibitors	0				0				0				0			
Glinide	0				0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

2.7.4.7.1-96 前治療の糖尿病治療別の夜間低血糖－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects												
Metformin and basal insulin	46				46				92			
Metformin, basal insulin and one other OAD	20				21				41			
Metformin and pre-mix/ combination insulin	26				25				51			
Metformin, pre-mix/ combination insulin and one other OAD	13				13				26			
PYE (years)												
Metformin and basal insulin	23.85				22.70				46.56			
Metformin, basal insulin and one other OAD	10.34				10.92				21.26			
Metformin and pre-mix/ combination insulin	13.39				11.92				25.31			
Metformin, pre-mix/ combination insulin and one other OAD	6.70				6.72				13.42			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Nocturnal hypoglycaemic episodes by classification and pre-trial diabetes treatment - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira			IDeg			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Severe or BG confirmed symptomatic hypoglycaemia												
Metformin and basal insulin	1	(2.2)	1	4.19	3	(6.5)	3	13.21	4	(4.3)	4	8.59
Metformin, basal insulin and one other OAD	1	(5.0)	1	9.67	1	(4.8)	1	9.16	2	(4.9)	2	9.41
Metformin and pre-mix/ combination insulin	1	(3.8)	1	7.47	2	(8.0)	4	33.56	3	(5.9)	5	19.76
Metformin, pre-mix/ combination insulin and one other OAD	1	(7.7)	1	14.93	0				1	(3.8)	1	7.45
Severe or BG confirmed hypoglycaemia												
Metformin and basal insulin	4	(8.7)	17	71.26	3	(6.5)	4	17.62	7	(7.6)	21	45.11
Metformin, basal insulin and one other OAD	2	(10.0)	7	67.69	1	(4.8)	1	9.16	3	(7.3)	8	37.63
Metformin and pre-mix/ combination insulin	1	(3.8)	1	7.47	4	(16.0)	6	50.33	5	(9.8)	7	27.66
Metformin, pre-mix/ combination insulin and one other OAD	1	(7.7)	1	14.93	2	(15.4)	8	118.97	3	(11.5)	9	67.06

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Nocturnal hypoglycaemic episodes by classification and pre-trial diabetes treatment - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA												
Metformin and basal insulin	11	(23.9)	73	306.02	12	(26.1)	33	145.36	23	(25.0)	106	227.68
Metformin, basal insulin and one other OAD	6	(30.0)	53	512.53	6	(28.6)	7	64.11	12	(29.3)	60	282.23
Metformin and pre-mix/ combination insulin	7	(26.9)	14	104.59	11	(44.0)	39	327.16	18	(35.3)	53	209.44
Metformin, pre-mix/ combination insulin and one other OAD	4	(30.8)	12	179.19	5	(38.5)	46	684.10	9	(34.6)	58	432.16
Severe hypoglycaemia												
Metformin and basal insulin	0				0				0			
Metformin, basal insulin and one other OAD	0				0				0			
Metformin and pre-mix/ combination insulin	0				0				0			
Metformin, pre-mix/ combination insulin and one other OAD	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Nocturnal hypoglycaemic episodes by classification and pre-trial diabetes treatment - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Documented symptomatic hypoglycaemia												
Metformin and basal insulin	3	(6.5)	5	20.96	8	(17.4)	15	66.07	11	(12.0)	20	42.96
Metformin, basal insulin and one other OAD	3	(15.0)	10	96.70	1	(4.8)	1	9.16	4	(9.8)	11	51.74
Metformin and pre-mix/ combination insulin	4	(15.4)	7	52.30	7	(28.0)	24	201.33	11	(21.6)	31	122.50
Metformin, pre-mix/ combination insulin and one other OAD	3	(23.1)	8	119.46	2	(15.4)	4	59.49	5	(19.2)	12	89.41
Asymptomatic hypoglycaemia												
Metformin and basal insulin	7	(15.2)	67	280.86	8	(17.4)	17	74.88	15	(16.3)	84	180.42
Metformin, basal insulin and one other OAD	4	(20.0)	41	396.49	5	(23.8)	6	54.95	9	(22.0)	47	221.08
Metformin and pre-mix/ combination insulin	4	(15.4)	7	52.30	7	(28.0)	9	75.50	11	(21.6)	16	63.23
Metformin, pre-mix/ combination insulin and one other OAD	3	(23.1)	4	59.73	5	(38.5)	42	624.61	8	(30.8)	46	342.75

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Nocturnal hypoglycaemic episodes by classification and pre-trial diabetes treatment - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Probable symptomatic hypoglycaemia												
Metformin and basal insulin	1	(2.2)	1	4.19	0				1	(1.1)	1	2.15
Metformin, basal insulin and one other OAD	0				0				0			
Metformin and pre-mix/ combination insulin	0				1	(4.0)	1	8.39	1	(2.0)	1	3.95
Metformin, pre-mix/ combination insulin and one other OAD	0				0				0			
Pseudo-hypoglycaemia												
Metformin and basal insulin	0				1	(2.2)	1	4.40	1	(1.1)	1	2.15
Metformin, basal insulin and one other OAD	1	(5.0)	2	19.34	0				1	(2.4)	2	9.41
Metformin and pre-mix/ combination insulin	0				1	(4.0)	5	41.94	1	(2.0)	5	19.76
Metformin, pre-mix/ combination insulin and one other OAD	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

Nocturnal hypoglycaemic episodes by classification and pre-trial diabetes treatment - treatment emergent - trial 4184 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
ADA unclassifiable hypoglycaemia												
Metformin and basal insulin	0				0				0			
Metformin, basal insulin and one other OAD	0				0				0			
Metformin and pre-mix/ combination insulin	0				0				0			
Metformin, pre-mix/ combination insulin and one other OAD	0				0				0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), ADA: American Diabetes Association,
Severe hypoglycaemia: According to the ADA definition of a severe hypoglycaemic episode,
BG confirmed: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),
OAD: Oral anti-diabetic drug

2.7.4.7.1-97 事後調査来院時の抗インスリン抗体価が閾値を超えていた被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	116				46				162			
PYE (years)	115.72				46.01				161.74			
Events	103	(88.8)	429	370.71	39	(84.8)	141	306.44	142	(87.7)	570	352.43
Infections and infestations	72	(62.1)	136	117.52	27	(58.7)	43	93.45	99	(61.1)	179	110.67
Viral upper respiratory tract infection	44	(37.9)	71	61.35	16	(34.8)	24	52.16	60	(37.0)	95	58.74
Influenza	8	(6.9)	8	6.91	3	(6.5)	3	6.52	11	(6.8)	11	6.80
Gastroenteritis	7	(6.0)	7	6.05	2	(4.3)	2	4.35	9	(5.6)	9	5.56
Pharyngitis	6	(5.2)	6	5.18	3	(6.5)	3	6.52	9	(5.6)	9	5.56
Bronchitis	4	(3.4)	6	5.18	2	(4.3)	2	4.35	6	(3.7)	8	4.95
Sinusitis	4	(3.4)	5	4.32	0				4	(2.5)	5	3.09
Cystitis	3	(2.6)	3	2.59	0				3	(1.9)	3	1.85
Herpes zoster	2	(1.7)	2	1.73	1	(2.2)	1	2.17	3	(1.9)	3	1.85
Gingivitis	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Nasopharyngitis	2	(1.7)	5	4.32	0				2	(1.2)	5	3.09
Otitis externa	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Periodontitis	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Purulence	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Tonsillitis	0				2	(4.3)	2	4.35	2	(1.2)	2	1.24
Upper respiratory tract infection	1	(0.9)	1	0.86	1	(2.2)	1	2.17	2	(1.2)	2	1.24
Beta haemolytic streptococcal infection	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Cellulitis	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Conjunctivitis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Dermatitis infected	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Eczema infected	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Enteritis infectious	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Fungal cystitis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Gingival abscess	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62

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	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Helicobacter infection	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Hordeolum	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Oral herpes	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Pneumonia	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Respiratory tract infection	1	(0.9)	2	1.73	0				1	(0.6)	2	1.24
Skin infection	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Tinea pedis	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Ureteritis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Urethritis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Urinary tract infection	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Gastrointestinal disorders	48	(41.4)	96	82.96	12	(26.1)	18	39.12	60	(37.0)	114	70.49
Constipation	14	(12.1)	15	12.96	3	(6.5)	3	6.52	17	(10.5)	18	11.13
Diarrhoea	9	(7.8)	13	11.23	0				9	(5.6)	13	8.04
Gastrooesophageal reflux disease	6	(5.2)	6	5.18	1	(2.2)	1	2.17	7	(4.3)	7	4.33
Abdominal distension	4	(3.4)	4	3.46	1	(2.2)	1	2.17	5	(3.1)	5	3.09
Chronic gastritis	4	(3.4)	4	3.46	1	(2.2)	1	2.17	5	(3.1)	5	3.09
Nausea	5	(4.3)	6	5.18	0				5	(3.1)	6	3.71
Abdominal discomfort	3	(2.6)	4	3.46	1	(2.2)	1	2.17	4	(2.5)	5	3.09
Abdominal pain upper	3	(2.6)	4	3.46	1	(2.2)	1	2.17	4	(2.5)	5	3.09
Dental caries	3	(2.6)	3	2.59	1	(2.2)	1	2.17	4	(2.5)	4	2.47
Colitis	3	(2.6)	3	2.59	0				3	(1.9)	3	1.85
Gastric polyps	2	(1.7)	2	1.73	1	(2.2)	1	2.17	3	(1.9)	3	1.85
Gastritis	2	(1.7)	2	1.73	1	(2.2)	1	2.17	3	(1.9)	3	1.85
Hiatus hernia	1	(0.9)	1	0.86	2	(4.3)	2	4.35	3	(1.9)	3	1.85
Periodontal disease	1	(0.9)	2	1.73	2	(4.3)	2	4.35	3	(1.9)	4	2.47
Stomatitis	3	(2.6)	3	2.59	0				3	(1.9)	3	1.85
Anal fissure	0				2	(4.3)	2	4.35	2	(1.2)	2	1.24
Dyspepsia	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Food poisoning	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Large intestine polyp	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Proctitis	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24

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	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Vomiting	2	(1.7)	4	3.46	0				2	(1.2)	4	2.47
Abdominal pain	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Barrett's oesophagus	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Duodenitis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Enteritis	1	(0.9)	2	1.73	0				1	(0.6)	2	1.24
Enterocolitis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Faeces soft	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Gastric ulcer	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Gastroduodenitis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Haemorrhoids	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Oesophageal polyp	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Oral discomfort	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Parotid gland enlargement	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Musculoskeletal and connective tissue disorders	24	(20.7)	30	25.92	11	(23.9)	13	28.25	35	(21.6)	43	26.59
Arthralgia	3	(2.6)	3	2.59	1	(2.2)	2	4.35	4	(2.5)	5	3.09
Back pain	2	(1.7)	2	1.73	2	(4.3)	2	4.35	4	(2.5)	4	2.47
Myalgia	3	(2.6)	3	2.59	1	(2.2)	1	2.17	4	(2.5)	4	2.47
Periarthritis	2	(1.7)	2	1.73	2	(4.3)	2	4.35	4	(2.5)	4	2.47
Osteoarthritis	1	(0.9)	1	0.86	2	(4.3)	2	4.35	3	(1.9)	3	1.85
Spinal osteoarthritis	3	(2.6)	3	2.59	0				3	(1.9)	3	1.85
Muscle spasms	2	(1.7)	4	3.46	0				2	(1.2)	4	2.47
Pain in extremity	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Tenosynovitis	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Flank pain	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Intervertebral disc protrusion	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Joint contracture	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Joint swelling	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Lumbar spinal stenosis	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Musculoskeletal chest pain	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Musculoskeletal pain	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62

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	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Musculoskeletal stiffness	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Neck pain	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Osteitis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Spinal column stenosis	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Spondylolisthesis	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Eye disorders	23	(19.8)	26	22.47	7	(15.2)	9	19.56	30	(18.5)	35	21.64
Diabetic retinopathy	10	(8.6)	10	8.64	4	(8.7)	6	13.04	14	(8.6)	16	9.89
Dry eye	3	(2.6)	3	2.59	1	(2.2)	1	2.17	4	(2.5)	4	2.47
Conjunctivitis allergic	3	(2.6)	3	2.59	0				3	(1.9)	3	1.85
Macular fibrosis	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Cataract	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Conjunctival haemorrhage	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Diabetic retinal oedema	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Eye inflammation	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Glaucoma	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Ocular discomfort	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Retinal detachment	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Retinal haemorrhage	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Visual impairment	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Vitreous floaters	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Investigations	19	(16.4)	27	23.33	6	(13.0)	10	21.73	25	(15.4)	37	22.88
Weight increased	3	(2.6)	3	2.59	4	(8.7)	4	8.69	7	(4.3)	7	4.33
Blood proinsulin decreased	4	(3.4)	4	3.46	1	(2.2)	1	2.17	5	(3.1)	5	3.09
Free fatty acids decreased	4	(3.4)	5	4.32	1	(2.2)	1	2.17	5	(3.1)	6	3.71
Helicobacter test positive	3	(2.6)	3	2.59	1	(2.2)	1	2.17	4	(2.5)	4	2.47
Insulin C-peptide decreased	2	(1.7)	2	1.73	1	(2.2)	1	2.17	3	(1.9)	3	1.85
Lipase increased	3	(2.6)	5	4.32	0				3	(1.9)	5	3.09
Blood calcitonin increased	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Blood triglycerides increased	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
C-reactive protein increased	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62

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	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Electrocardiogram QT prolonged	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Glomerular filtration rate decreased	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Rheumatoid factor increased	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Urine ketone body present	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Skin and subcutaneous tissue disorders	15	(12.9)	15	12.96	6	(13.0)	6	13.04	21	(13.0)	21	12.98
Eczema	7	(6.0)	7	6.05	0				7	(4.3)	7	4.33
Dermatitis allergic	1	(0.9)	1	0.86	1	(2.2)	1	2.17	2	(1.2)	2	1.24
Dermatitis contact	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Pruritus	1	(0.9)	1	0.86	1	(2.2)	1	2.17	2	(1.2)	2	1.24
Urticaria	1	(0.9)	1	0.86	1	(2.2)	1	2.17	2	(1.2)	2	1.24
Blister	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Dermal cyst	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Hyperkeratosis	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Psoriasis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Rash	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Seborrhoeic dermatitis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Respiratory, thoracic and mediastinal disorders	15	(12.9)	20	17.28	4	(8.7)	5	10.87	19	(11.7)	25	15.46
Rhinitis allergic	4	(3.4)	4	3.46	1	(2.2)	1	2.17	5	(3.1)	5	3.09
Asthma	2	(1.7)	2	1.73	2	(4.3)	2	4.35	4	(2.5)	4	2.47
Sleep apnoea syndrome	2	(1.7)	2	1.73	1	(2.2)	1	2.17	3	(1.9)	3	1.85
Upper respiratory tract inflammation	2	(1.7)	3	2.59	1	(2.2)	1	2.17	3	(1.9)	4	2.47
Cough	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Rhinorrhoea	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Dysphonia	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Oropharyngeal pain	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Productive cough	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62

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	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Respiratory disorder	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Sneezing	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
General disorders and administration site conditions	11	(9.5)	12	10.37	4	(8.7)	4	8.69	15	(9.3)	16	9.89
Injection site reaction	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Administration site mass	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Asthenia	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Feeling abnormal	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Injection site bruising	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Injection site discolouration	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Injection site erythema	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Injection site haemorrhage	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Injection site mass	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Injection site pain	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Injection site pruritus	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Injection site swelling	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Malaise	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Oedema peripheral	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Sense of oppression	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Nervous system disorders	8	(6.9)	10	8.64	6	(13.0)	9	19.56	14	(8.6)	19	11.75
Hypoaesthesia	2	(1.7)	3	2.59	3	(6.5)	3	6.52	5	(3.1)	6	3.71
Headache	2	(1.7)	3	2.59	2	(4.3)	2	4.35	4	(2.5)	5	3.09
Diabetic neuropathy	1	(0.9)	1	0.86	1	(2.2)	1	2.17	2	(1.2)	2	1.24
Carotid arteriosclerosis	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Carotid artery stenosis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Dizziness	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Intercostal neuralgia	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Lumbar radiculopathy	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Somnolence	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62

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	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Injury, poisoning and procedural complications	8	(6.9)	10	8.64	5	(10.9)	6	13.04	13	(8.0)	16	9.89
Contusion	4	(3.4)	4	3.46	2	(4.3)	2	4.35	6	(3.7)	6	3.71
Ligament sprain	1	(0.9)	2	1.73	2	(4.3)	2	4.35	3	(1.9)	4	2.47
Accidental overdose	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Foreign body in eye	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Heat illness	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Muscle strain	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Rib fracture	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Subcutaneous haematoma	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Vascular disorders	8	(6.9)	8	6.91	2	(4.3)	2	4.35	10	(6.2)	10	6.18
Hypertension	5	(4.3)	5	4.32	1	(2.2)	1	2.17	6	(3.7)	6	3.71
Arteriosclerosis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Internal haemorrhage	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Orthostatic hypotension	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Peripheral arterial occlusive disease	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Hepatobiliary disorders	6	(5.2)	7	6.05	3	(6.5)	7	15.21	9	(5.6)	14	8.66
Hepatic steatosis	3	(2.6)	3	2.59	2	(4.3)	2	4.35	5	(3.1)	5	3.09
Gallbladder polyp	1	(0.9)	1	0.86	3	(6.5)	3	6.52	4	(2.5)	4	2.47
Cholelithiasis	1	(0.9)	1	0.86	1	(2.2)	1	2.17	2	(1.2)	2	1.24
Cholecystitis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Chronic hepatitis	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Non-alcoholic fatty liver	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Renal and urinary disorders	5	(4.3)	5	4.32	3	(6.5)	3	6.52	8	(4.9)	8	4.95
Nephrolithiasis	1	(0.9)	1	0.86	3	(6.5)	3	6.52	4	(2.5)	4	2.47
Renal cyst	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Ureterolithiasis	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), MedDRA version 20.0,
Thresholds are 0.6% B/T for insulin degludec specific antibodies and 0.7% B/T for antibodies cross reacting to human insulin.
The thresholds are derived as the 95% percentile taken from the distribution of antibody values in a population of 150 healthy subjects.

Adverse events by system organ class and preferred term - treatment emergent - subjects with anti-insulin antibodies at follow-up visit above threshold - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	(4.3)	5	4.32	1	(2.2)	1	2.17	6	(3.7)	6	3.71
Skin papilloma	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Acrochordon	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Benign neoplasm of bladder	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Gastric cancer stage I	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Thyroid neoplasm	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Psychiatric disorders	5	(4.3)	5	4.32	0				5	(3.1)	5	3.09
Insomnia	5	(4.3)	5	4.32	0				5	(3.1)	5	3.09
Cardiac disorders	2	(1.7)	2	1.73	2	(4.3)	2	4.35	4	(2.5)	4	2.47
Ventricular extrasystoles	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Cardiomegaly	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Myocardial ischaemia	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Endocrine disorders	2	(1.7)	2	1.73	2	(4.3)	2	4.35	4	(2.5)	4	2.47
Thyroid cyst	1	(0.9)	1	0.86	2	(4.3)	2	4.35	3	(1.9)	3	1.85
Thyroid mass	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Ear and labyrinth disorders	3	(2.6)	5	4.32	0				3	(1.9)	5	3.09
Vertigo	2	(1.7)	4	3.46	0				2	(1.2)	4	2.47
Vertigo positional	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Metabolism and nutrition disorders	2	(1.7)	2	1.73	1	(2.2)	1	2.17	3	(1.9)	3	1.85
Dyslipidaemia	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Hyperuricaemia	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Overweight	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Reproductive system and breast disorders	3	(2.6)	3	2.59	0				3	(1.9)	3	1.85

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), MedDRA version 20.0,
Thresholds are 0.6% B/T for insulin degludec specific antibodies and 0.7% B/T for antibodies cross reacting to human insulin.
The thresholds are derived as the 95% percentile taken from the distribution of antibody values in a population of 150 healthy subjects.

Adverse events by system organ class and preferred term - treatment emergent - subjects with anti-insulin antibodies at follow-up visit above threshold - trial 4183 - summary - safety analysis set

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Balanoposthitis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Benign prostatic hyperplasia	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Prostatic calcification	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Blood and lymphatic system disorders	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Anaemia	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Immune system disorders	1	(0.9)	2	1.73	0				1	(0.6)	2	1.24
Allergy to arthropod sting	1	(0.9)	2	1.73	0				1	(0.6)	2	1.24

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), MedDRA version 20.0,
Thresholds are 0.6% B/T for insulin degludec specific antibodies and 0.7% B/T for antibodies cross reacting to human insulin.
The thresholds are derived as the 95% percentile taken from the distribution of antibody values in a population of 150 healthy subjects.

2.7.4.7.1-98 事後調査来院時の抗インスリン抗体価が閾値を超えていた被験者における重篤な有害事象（器官別大分類及び基本語別）－ SAS（4183 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	116				46				162			
PYE (years)	115.72				46.01				161.74			
Events	5	(4.3)	5	4.32	2	(4.3)	3	6.52	7	(4.3)	8	4.95
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(1.7)	2	1.73	0				2	(1.2)	2	1.24
Benign neoplasm of bladder	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Gastric cancer stage I	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Respiratory, thoracic and mediastinal disorders	1	(0.9)	1	0.86	1	(2.2)	1	2.17	2	(1.2)	2	1.24
Sleep apnoea syndrome	1	(0.9)	1	0.86	1	(2.2)	1	2.17	2	(1.2)	2	1.24
Cardiac disorders	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Myocardial ischaemia	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Eye disorders	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Retinal detachment	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Hepatobiliary disorders	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Cholecystitis	1	(0.9)	1	0.86	0				1	(0.6)	1	0.62
Vascular disorders	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62
Peripheral arterial occlusive disease	0				1	(2.2)	1	2.17	1	(0.6)	1	0.62

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days), MedDRA version 20.0,
Thresholds are 0.6% B/T for insulin degludec specific antibodies and 0.7% B/T for antibodies cross reacting to human insulin.
The thresholds are derived as the 95% percentile taken from the distribution of antibody values in a population of 150 healthy subjects.

2.7.4.7.1-99 事後調査来院時に抗リラグルチド抗体が陽性であった被験者における有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira			Lira			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	47				68				115			
PYE (years)	47.42				68.68				116.10			
Events	44	(93.6)	176	371.13	59	(86.8)	244	355.28	103	(89.6)	420	361.75
Infections and infestations	30	(63.8)	56	118.09	38	(55.9)	73	106.29	68	(59.1)	129	111.11
Viral upper respiratory tract infection	16	(34.0)	28	59.04	26	(38.2)	45	65.52	42	(36.5)	73	62.88
Pharyngitis	3	(6.4)	3	6.33	4	(5.9)	4	5.82	7	(6.1)	7	6.03
Gastroenteritis	2	(4.3)	2	4.22	4	(5.9)	4	5.82	6	(5.2)	6	5.17
Periodontitis	2	(4.3)	2	4.22	2	(2.9)	2	2.91	4	(3.5)	4	3.45
Bronchitis	2	(4.3)	2	4.22	1	(1.5)	1	1.46	3	(2.6)	3	2.58
Sinusitis	2	(4.3)	2	4.22	1	(1.5)	3	4.37	3	(2.6)	5	4.31
Dermatitis infected	2	(4.3)	2	4.22	0				2	(1.7)	2	1.72
Influenza	2	(4.3)	2	4.22	0				2	(1.7)	2	1.72
Nasopharyngitis	1	(2.1)	3	6.33	1	(1.5)	1	1.46	2	(1.7)	4	3.45
Cellulitis	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Cystitis	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Enteritis infectious	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Fungal cystitis	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Gastroenteritis norovirus	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Gastroenteritis viral	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Helicobacter infection	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Herpes zoster	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Hordeolum	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Oral herpes	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Otitis externa	0				1	(1.5)	2	2.91	1	(0.9)	2	1.72
Peritonsillitis	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Pulpitis dental	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Purulence	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Respiratory tract infection	1	(2.1)	2	4.22	0				1	(0.9)	2	1.72
Skin infection	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with positive anti-liraglutide antibodies at follow-up visit - trial 4183 - summary - safety analysis set

	IDegLira				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Sycosis barbae	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Tinea pedis	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Tonsillitis	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Upper respiratory tract infection	0				1	(1.5)	2	2.91	1	(0.9)	2	1.72
Gastrointestinal disorders	17	(36.2)	29	61.15	35	(51.5)	74	107.75	52	(45.2)	103	88.72
Constipation	4	(8.5)	4	8.43	9	(13.2)	12	17.47	13	(11.3)	16	13.78
Diarrhoea	4	(8.5)	7	14.76	8	(11.8)	11	16.02	12	(10.4)	18	15.50
Nausea	1	(2.1)	1	2.11	8	(11.8)	14	20.38	9	(7.8)	15	12.92
Dyspepsia	1	(2.1)	1	2.11	7	(10.3)	8	11.65	8	(7.0)	9	7.75
Dental caries	2	(4.3)	2	4.22	3	(4.4)	4	5.82	5	(4.3)	6	5.17
Gastrooesophageal reflux disease	2	(4.3)	2	4.22	3	(4.4)	3	4.37	5	(4.3)	5	4.31
Gastritis	1	(2.1)	1	2.11	3	(4.4)	3	4.37	4	(3.5)	4	3.45
Chronic gastritis	0				3	(4.4)	3	4.37	3	(2.6)	3	2.58
Abdominal discomfort	1	(2.1)	1	2.11	1	(1.5)	1	1.46	2	(1.7)	2	1.72
Abdominal distension	0				2	(2.9)	2	2.91	2	(1.7)	2	1.72
Abdominal pain upper	2	(4.3)	2	4.22	0				2	(1.7)	2	1.72
Gastric polyps	0				2	(2.9)	2	2.91	2	(1.7)	2	1.72
Periodontal disease	0				2	(2.9)	2	2.91	2	(1.7)	2	1.72
Vomiting	0				2	(2.9)	2	2.91	2	(1.7)	2	1.72
Abdominal pain	0				1	(1.5)	2	2.91	1	(0.9)	2	1.72
Barrett's oesophagus	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Colitis	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Duodenitis	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Enterocolitis	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Eructation	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Flatulence	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Haemorrhoids	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Hiatus hernia	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Large intestine polyp	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Melaena	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with positive anti-liraglutide antibodies at follow-up visit - trial 4183 - summary - safety analysis set

	IDegLira				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Parotid gland enlargement	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Proctitis	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Stomatitis	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Musculoskeletal and connective tissue disorders	15	(31.9)	20	42.17	12	(17.6)	15	21.84	27	(23.5)	35	30.15
Back pain	2	(4.3)	2	4.22	3	(4.4)	4	5.82	5	(4.3)	6	5.17
Intervertebral disc protrusion	1	(2.1)	1	2.11	2	(2.9)	2	2.91	3	(2.6)	3	2.58
Periarthritis	1	(2.1)	1	2.11	2	(2.9)	2	2.91	3	(2.6)	3	2.58
Spinal osteoarthritis	3	(6.4)	3	6.33	0				3	(2.6)	3	2.58
Arthralgia	2	(4.3)	2	4.22	0				2	(1.7)	2	1.72
Arthritis	1	(2.1)	1	2.11	1	(1.5)	1	1.46	2	(1.7)	2	1.72
Muscle spasms	1	(2.1)	3	6.33	1	(1.5)	2	2.91	2	(1.7)	5	4.31
Musculoskeletal stiffness	1	(2.1)	1	2.11	1	(1.5)	1	1.46	2	(1.7)	2	1.72
Osteoarthritis	2	(4.3)	2	4.22	0				2	(1.7)	2	1.72
Joint swelling	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Musculoskeletal chest pain	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Musculoskeletal pain	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Myalgia	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Rheumatoid arthritis	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Tenosynovitis	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Trigger finger	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Investigations	7	(14.9)	12	25.30	12	(17.6)	13	18.93	19	(16.5)	25	21.53
Lipase increased	2	(4.3)	3	6.33	6	(8.8)	6	8.74	8	(7.0)	9	7.75
Blood proinsulin decreased	3	(6.4)	3	6.33	0				3	(2.6)	3	2.58
Free fatty acids decreased	3	(6.4)	4	8.43	0				3	(2.6)	4	3.45
Pancreatic enzymes increased	0				2	(2.9)	2	2.91	2	(1.7)	2	1.72
Amylase increased	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Blood creatine phosphokinase increased	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Cardiac murmur	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86

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Adverse events by system organ class and preferred term - treatment emergent - subjects with positive anti-liraglutide antibodies at follow-up visit - trial 4183 - summary - safety analysis set

	IDegLira				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Eosinophil count increased	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Helicobacter test positive	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Insulin C-peptide decreased	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Urine ketone body present	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Skin and subcutaneous tissue disorders	8	(17.0)	8	16.87	9	(13.2)	11	16.02	17	(14.8)	19	16.37
Eczema	3	(6.4)	3	6.33	3	(4.4)	4	5.82	6	(5.2)	7	6.03
Dermatitis contact	1	(2.1)	1	2.11	2	(2.9)	2	2.91	3	(2.6)	3	2.58
Dermal cyst	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Dyshidrotic eczema	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Granuloma annulare	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Pruritus	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Psoriasis	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Scab	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Skin mass	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Solar dermatitis	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Urticaria	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Eye disorders	7	(14.9)	7	14.76	8	(11.8)	12	17.47	15	(13.0)	19	16.37
Diabetic retinopathy	6	(12.8)	6	12.65	2	(2.9)	2	2.91	8	(7.0)	8	6.89
Asthenopia	0				2	(2.9)	2	2.91	2	(1.7)	2	1.72
Glaucoma	0				2	(2.9)	2	2.91	2	(1.7)	2	1.72
Vitreous floaters	1	(2.1)	1	2.11	1	(1.5)	1	1.46	2	(1.7)	2	1.72
Cataract	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Dry eye	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Macular fibrosis	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Retinal detachment	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Retinopathy	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
General disorders and administration site conditions	6	(12.8)	6	12.65	9	(13.2)	11	16.02	15	(13.0)	17	14.64

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with positive anti-liraglutide antibodies at follow-up visit - trial 4183 - summary - safety analysis set

	IDegLira				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Injection site erythema	1	(2.1)	1	2.11	2	(2.9)	2	2.91	3	(2.6)	3	2.58
Injection site reaction	2	(4.3)	2	4.22	1	(1.5)	1	1.46	3	(2.6)	3	2.58
Fatigue	0				2	(2.9)	2	2.91	2	(1.7)	2	1.72
Malaise	1	(2.1)	1	2.11	1	(1.5)	1	1.46	2	(1.7)	2	1.72
Administration site mass	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Fat tissue increased	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Injection site bruising	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Injection site induration	0				1	(1.5)	2	2.91	1	(0.9)	2	1.72
Pain	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Thirst	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Injury, poisoning and procedural complications	6	(12.8)	8	16.87	9	(13.2)	10	14.56	15	(13.0)	18	15.50
Contusion	2	(4.3)	2	4.22	2	(2.9)	2	2.91	4	(3.5)	4	3.45
Ligament sprain	1	(2.1)	2	4.22	2	(2.9)	2	2.91	3	(2.6)	4	3.45
Arthropod sting	0				2	(2.9)	2	2.91	2	(1.7)	2	1.72
Heat illness	1	(2.1)	1	2.11	1	(1.5)	1	1.46	2	(1.7)	2	1.72
Accidental overdose	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Arthropod bite	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Foreign body in eye	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Laceration	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Subcutaneous haematoma	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Suture related complication	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Respiratory, thoracic and mediastinal disorders	7	(14.9)	9	18.98	3	(4.4)	3	4.37	10	(8.7)	12	10.34
Asthma	0				2	(2.9)	2	2.91	2	(1.7)	2	1.72
Rhinitis allergic	1	(2.1)	1	2.11	1	(1.5)	1	1.46	2	(1.7)	2	1.72
Sleep apnoea syndrome	2	(4.3)	2	4.22	0				2	(1.7)	2	1.72
Cough	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Dysphonia	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Productive cough	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Rhinorrhoea	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with positive anti-liraglutide antibodies at follow-up visit - trial 4183 - summary - safety analysis set

	IDegLira				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Sneezing	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Upper respiratory tract inflammation	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Nervous system disorders	2	(4.3)	2	4.22	6	(8.8)	7	10.19	8	(7.0)	9	7.75
Headache	0				3	(4.4)	3	4.37	3	(2.6)	3	2.58
Carotid artery stenosis	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Cervicobrachial syndrome	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Diabetic neuropathy	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Dysgeusia	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Head discomfort	0				1	(1.5)	2	2.91	1	(0.9)	2	1.72
Metabolism and nutrition disorders	2	(4.3)	2	4.22	4	(5.9)	4	5.82	6	(5.2)	6	5.17
Dyslipidaemia	1	(2.1)	1	2.11	1	(1.5)	1	1.46	2	(1.7)	2	1.72
Decreased appetite	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Hypertriglyceridaemia	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Hyperuricaemia	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Hypokalaemia	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Hepatobiliary disorders	1	(2.1)	1	2.11	3	(4.4)	3	4.37	4	(3.5)	4	3.45
Cholelithiasis	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Gallbladder polyp	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Hepatic cyst	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Hepatic steatosis	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(4.3)	2	4.22	2	(2.9)	2	2.91	4	(3.5)	4	3.45
Colon adenoma	0				2	(2.9)	2	2.91	2	(1.7)	2	1.72
Gastric cancer stage I	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Skin papilloma	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86

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Adverse events by system organ class and preferred term - treatment emergent - subjects with positive anti-liraglutide antibodies at follow-up visit - trial 4183 - summary - safety analysis set

	IDegLira				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Endocrine disorders	2	(4.3)	2	4.22	1	(1.5)	1	1.46	3	(2.6)	3	2.58
Hyperthyroidism	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Silent thyroiditis	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Thyroid mass	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Psychiatric disorders	2	(4.3)	2	4.22	1	(1.5)	1	1.46	3	(2.6)	3	2.58
Insomnia	2	(4.3)	2	4.22	0				2	(1.7)	2	1.72
Sleep disorder	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Renal and urinary disorders	2	(4.3)	2	4.22	1	(1.5)	1	1.46	3	(2.6)	3	2.58
Nephrolithiasis	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Renal cyst	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Ureterolithiasis	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Cardiac disorders	0				2	(2.9)	2	2.91	2	(1.7)	2	1.72
Sinus node dysfunction	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Supraventricular extrasystoles	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Ear and labyrinth disorders	2	(4.3)	4	8.43	0				2	(1.7)	4	3.45
Vertigo	2	(4.3)	4	8.43	0				2	(1.7)	4	3.45
Blood and lymphatic system disorders	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Anaemia	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Immune system disorders	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Seasonal allergy	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Reproductive system and breast disorders	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Prostatic calcification	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - subjects with positive anti-liraglutide antibodies at follow-up visit - trial 4183 - summary - safety analysis set

	IDegLira				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Surgical and medical procedures	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Large intestinal polypectomy	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Vascular disorders	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Hypertension	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

2.7.4.7.1-100 事後調査来院時に抗リラグルチド抗体が陽性であった被験者における重篤な有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	47				68				115			
PYE (years)	47.42				68.68				116.10			
Events	2	(4.3)	2	4.22	2	(2.9)	2	2.91	4	(3.5)	4	3.45
Cardiac disorders	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Sinus node dysfunction	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Gastric cancer stage I	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Respiratory, thoracic and mediastinal disorders	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Sleep apnoea syndrome	1	(2.1)	1	2.11	0				1	(0.9)	1	0.86
Surgical and medical procedures	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86
Large intestinal polypectomy	0				1	(1.5)	1	1.46	1	(0.9)	1	0.86

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
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ゾルトファイ配合注フレックスタッチ

2.7.4.7 付録
2. 4183 試験の安全性データ

ノボ ノルディスク ファーマ株式会社

目次

ページ

2.7.4.7.2-1 心血管系事象（器官別大分類及び基本語別）－SAS（4183 試験） 3
2.7.4.7.2-2 膵炎に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験） 6
2.7.4.7.2-3 リパーゼ及びアミラーゼ増加に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験） 7
2.7.4.7.2-4 新生物に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験） 8
2.7.4.7.2-5 甲状腺疾患に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験） 11
2.7.4.7.2-6 カルシトニン増加に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験） 12
2.7.4.7.2-7 腎機能の悪化に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験） 13
2.7.4.7.2-8 アレルギー反応（免疫原性）に関連する可能性がある有害事象（器官別大分類及び基本語別）－SAS（4183 試験） 14
2.7.4.7.2-9 注射部位反応に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験） 16
2.7.4.7.2-10 投薬過誤に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験） 17
2.7.4.7.2-11 高血糖に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験） 18

2.7.4.7 付録 2

2.7.4.7.2-1 心血管系事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira N (%)	IDegLira E	IDegLira R	IDeg N (%)	IDeg E	IDeg R	Lira N (%)	Lira E	Lira R	Total N (%)	Total E	Total R
Number of subjects	275			271			273			819		
PYE (years)	268.00			261.81			271.84			801.65		
Events	16 (5.8)	16	5.97	28 (10.3)	31	11.84	17 (6.2)	17	6.25	61 (7.4)	64	7.98
Cardiac disorders	6 (2.2)	6	2.24	9 (3.3)	9	3.44	11 (4.0)	11	4.05	26 (3.2)	26	3.24
Angina pectoris	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
Ventricular extrasystoles	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
Palpitations	1 (0.4)	1	0.37	1 (0.4)	1	0.38	3 (1.1)	3	1.10	5 (0.6)	5	0.62
Tachycardia	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Acute myocardial infarction	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Atrial fibrillation	0			2 (0.7)	2	0.76	2 (0.7)	2	0.74	4 (0.5)	4	0.50
Atrioventricular block complete	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Atrioventricular block first degree	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Cardiomegaly	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Coronary artery stenosis	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Myocardial ischaemia	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
Sinus arrhythmia	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Sinus node dysfunction	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Supraventricular extrasystoles	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
Supraventricular tachycardia	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

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Treatment emergent: 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.
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Cardiovascular adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
General disorders and administration site conditions	5 (1.8)	5	1.87	10 (3.7)	11	4.20	3 (1.1)	3	1.10	18 (2.2)	19	2.37
Oedema peripheral	4 (1.5)	4	1.49	7 (2.6)	8	3.06	1 (0.4)	1	0.37	12 (1.5)	13	1.62
Peripheral swelling	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Oedema	0			3 (1.1)	3	1.15	2 (0.7)	2	0.74	5 (0.6)	5	0.62
Nervous system disorders	3 (1.1)	3	1.12	5 (1.8)	5	1.91	0			8 (1.0)	8	1.00
Carotid artery stenosis	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Cerebral infarction	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Thalamic infarction	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Carotid arteriosclerosis	0			3 (1.1)	3	1.15	0			3 (0.4)	3	0.37
Loss of consciousness	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Thrombotic cerebral infarction	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Investigations	1 (0.4)	1	0.37	3 (1.1)	4	1.53	1 (0.4)	1	0.37	5 (0.6)	6	0.75
Electrocardiogram QT prolonged	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Blood creatine phosphokinase increased	0			3 (1.1)	4	1.53	1 (0.4)	1	0.37	4 (0.5)	5	0.62
Vascular disorders	1 (0.4)	1	0.37	2 (0.7)	2	0.76	1 (0.4)	1	0.37	4 (0.5)	4	0.50
Orthostatic hypotension	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
Peripheral arterial occlusive disease	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25

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PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
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Cardiovascular adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Skin and subcutaneous tissue disorders	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Chronic pigmented purpura	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

2.7.4.7.2-2 膵炎に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	275			271			273			819		
PYE (years)	268.00			261.81			271.84			801.65		
Events	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
Gastrointestinal disorders	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
Pancreatitis acute	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Autoimmune pancreatitis	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

2.7.4.7.2-3 リパーゼ及びアミラーゼ増加に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira N (%)	E	R	IDeg N (%)	E	R	Lira N (%)	E	R	Total N (%)	E	R
Number of subjects	275			271			273			819		
PYE (years)	268.00			261.81			271.84			801.65		
Events	7 (2.5)	11	4.10	0			18 (6.6)	20	7.36	25 (3.1)	31	3.87
Investigations	6 (2.2)	10	3.73	0			18 (6.6)	20	7.36	24 (2.9)	30	3.74
Lipase increased	6 (2.2)	8	2.99	0			15 (5.5)	15	5.52	21 (2.6)	23	2.87
Amylase increased	2 (0.7)	2	0.75	0			3 (1.1)	3	1.10	5 (0.6)	5	0.62
Pancreatic enzymes increased	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
Metabolism and nutrition disorders	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Hyperlipasaemia	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

2.7.4.7.2-4 新生物に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira N (%)	IDegLira E	IDegLira R	IDeg N (%)	IDeg E	IDeg R	Lira N (%)	Lira E	Lira R	Total N (%)	Total E	Total R
Number of subjects	275			271			273			819		
PYE (years)	268.00			261.81			271.84			801.65		
Events	24 (8.7)	28	10.45	23 (8.5)	31	11.84	26 (9.5)	30	11.04	73 (8.9)	89	11.10
Gastrointestinal disorders	10 (3.6)	11	4.10	7 (2.6)	7	2.67	10 (3.7)	11	4.05	27 (3.3)	29	3.62
Large intestine polyp	6 (2.2)	6	2.24	3 (1.1)	3	1.15	4 (1.5)	4	1.47	13 (1.6)	13	1.62
Barrett's oesophagus	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
Gastric polyps	2 (0.7)	2	0.75	3 (1.1)	3	1.15	5 (1.8)	5	1.84	10 (1.2)	10	1.25
Oesophageal polyp	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Duodenal polyp	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Pancreatic cyst	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (2.2)	6	2.24	6 (2.2)	8	3.06	5 (1.8)	5	1.84	17 (2.1)	19	2.37
Skin papilloma	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
Benign neoplasm of bladder	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Gastric cancer stage I	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Thyroid neoplasm	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Uterine leiomyoma	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Acrochordon	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Adrenal neoplasm	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Basal cell carcinoma	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Benign neoplasm of thyroid gland	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Neoplasm adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Breast cancer	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Colon adenoma	0			0			3 (1.1)	3	1.10	3 (0.4)	3	0.37
Lung adenocarcinoma	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Lung neoplasm malignant	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Metastases to lymph nodes	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Oligodendroglioma	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Renal and urinary disorders	5 (1.8)	5	1.87	2 (0.7)	2	0.76	2 (0.7)	2	0.74	9 (1.1)	9	1.12
Renal cyst	5 (1.8)	5	1.87	2 (0.7)	2	0.76	2 (0.7)	2	0.74	9 (1.1)	9	1.12
Endocrine disorders	2 (0.7)	2	0.75	5 (1.8)	5	1.91	1 (0.4)	1	0.37	8 (1.0)	8	1.00
Thyroid cyst	2 (0.7)	2	0.75	5 (1.8)	5	1.91	1 (0.4)	1	0.37	8 (1.0)	8	1.00
Hepatobiliary disorders	2 (0.7)	2	0.75	6 (2.2)	6	2.29	4 (1.5)	4	1.47	12 (1.5)	12	1.50
Gallbladder polyp	1 (0.4)	1	0.37	5 (1.8)	5	1.91	2 (0.7)	2	0.74	8 (1.0)	8	1.00
Hepatic cyst	1 (0.4)	1	0.37	1 (0.4)	1	0.38	2 (0.7)	2	0.74	4 (0.5)	4	0.50
Reproductive system and breast disorders	1 (0.4)	1	0.37	2 (0.7)	3	1.15	1 (0.4)	2	0.74	4 (0.5)	6	0.75
Ovarian cyst	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
Cervical cyst	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Cervical polyp	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Endometrial hyperplasia	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Skin and subcutaneous tissue disorders	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
Dermal cyst	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Neoplasm adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Infections and infestations	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Infected dermal cyst	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Investigations	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Carbohydrate antigen 125 increased	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Musculoskeletal and connective tissue disorders	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Synovial cyst	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Surgical and medical procedures	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Large intestinal polypectomy	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

2.7.4.7.2-5 甲状腺疾患に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	275			271			273			819		
PYE (years)	268.00			261.81			271.84			801.65		
Events	5 (1.8)	6	2.24	7 (2.6)	9	3.44	4 (1.5)	4	1.47	16 (2.0)	19	2.37
Endocrine disorders	4 (1.5)	4	1.49	6 (2.2)	7	2.67	2 (0.7)	2	0.74	12 (1.5)	13	1.62
Thyroid cyst	2 (0.7)	2	0.75	5 (1.8)	5	1.91	1 (0.4)	1	0.37	8 (1.0)	8	1.00
Silent thyroiditis	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Thyroid mass	1 (0.4)	1	0.37	2 (0.7)	2	0.76	0			3 (0.4)	3	0.37
Hyperthyroidism	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Investigations	1 (0.4)	1	0.37	0			2 (0.7)	2	0.74	3 (0.4)	3	0.37
Blood calcitonin increased	1 (0.4)	1	0.37	0			2 (0.7)	2	0.74	3 (0.4)	3	0.37
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	1	0.37	2 (0.7)	2	0.76	0			3 (0.4)	3	0.37
Thyroid neoplasm	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Benign neoplasm of thyroid gland	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

2.7.4.7.2-6 カルシトニン増加に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	275				271				273				819			
PYE (years)	268.00				261.81				271.84				801.65			
Events	1	(0.4)	1	0.37	0				2	(0.7)	2	0.74	3	(0.4)	3	0.37
Investigations	1	(0.4)	1	0.37	0				2	(0.7)	2	0.74	3	(0.4)	3	0.37
Blood calcitonin increased	1	(0.4)	1	0.37	0				2	(0.7)	2	0.74	3	(0.4)	3	0.37

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

2.7.4.7.2-7 腎機能の悪化に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira N	(%)	E	R	IDeg N	(%)	E	R	Lira N	(%)	E	R	Total N	(%)	E	R
Number of subjects	275				271				273				819			
PYE (years)	268.00				261.81				271.84				801.65			
Events	1	(0.4)	1	0.37	1	(0.4)	1	0.38	0				2	(0.2)	2	0.25
Investigations	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
Glomerular filtration rate decreased	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
Renal and urinary disorders	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
Renal impairment	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

2.7.4.7.2-8 アレルギー反応（免疫原性）に関連する可能性がある有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	275			271			273			819		
PYE (years)	268.00			261.81			271.84			801.65		
Events	32 (11.6)	40	14.93	25 (9.2)	30	11.46	19 (7.0)	23	8.46	76 (9.3)	93	11.60
Skin and subcutaneous tissue disorders	23 (8.4)	26	9.70	19 (7.0)	21	8.02	16 (5.9)	18	6.62	58 (7.1)	65	8.11
Eczema	16 (5.8)	18	6.72	6 (2.2)	6	2.29	9 (3.3)	10	3.68	31 (3.8)	34	4.24
Dermatitis contact	2 (0.7)	2	0.75	1 (0.4)	1	0.38	6 (2.2)	7	2.58	9 (1.1)	10	1.25
Rash	2 (0.7)	2	0.75	3 (1.1)	3	1.15	0			5 (0.6)	5	0.62
Dermatitis allergic	1 (0.4)	1	0.37	2 (0.7)	2	0.76	0			3 (0.4)	3	0.37
Dermatitis atopic	1 (0.4)	1	0.37	2 (0.7)	2	0.76	0			3 (0.4)	3	0.37
Drug eruption	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Urticaria	1 (0.4)	1	0.37	3 (1.1)	4	1.53	0			4 (0.5)	5	0.62
Dermatitis	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
Hand dermatitis	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Swelling face	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Respiratory, thoracic and mediastinal disorders	7 (2.5)	7	2.61	2 (0.7)	2	0.76	3 (1.1)	3	1.10	12 (1.5)	12	1.50
Rhinitis allergic	7 (2.5)	7	2.61	2 (0.7)	2	0.76	2 (0.7)	2	0.74	11 (1.3)	11	1.37
Pharyngeal oedema	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
Eye disorders	4 (1.5)	5	1.87	3 (1.1)	4	1.53	2 (0.7)	2	0.74	9 (1.1)	11	1.37
Conjunctivitis allergic	4 (1.5)	5	1.87	2 (0.7)	2	0.76	2 (0.7)	2	0.74	8 (1.0)	9	1.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Allergic reaction (immunogenicity) adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Blepharitis allergic	0			1 (0.4)	2	0.76	0			1 (0.1)	2	0.25
Infections and infestations	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
Dermatitis infected	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
Congenital, familial and genetic disorders	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Epidermolysis	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Gastrointestinal disorders	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Gingival swelling	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Immune system disorders	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Hypersensitivity	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

2.7.4.7.2-9 注射部位反応に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	275			271			273			819		
PYE (years)	268.00			261.81			271.84			801.65		
Events	9 (3.3)	10	3.73	6 (2.2)	6	2.29	12 (4.4)	13	4.78	27 (3.3)	29	3.62
General disorders and administration site conditions	9 (3.3)	10	3.73	6 (2.2)	6	2.29	12 (4.4)	13	4.78	27 (3.3)	29	3.62
Injection site pruritus	2 (0.7)	2	0.75	0			1 (0.4)	1	0.37	3 (0.4)	3	0.37
Injection site reaction	2 (0.7)	2	0.75	0			2 (0.7)	2	0.74	4 (0.5)	4	0.50
Administration site mass	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Injection site discolouration	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Injection site erythema	1 (0.4)	1	0.37	0			3 (1.1)	3	1.10	4 (0.5)	4	0.50
Injection site haemorrhage	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Injection site pain	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
Injection site swelling	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
Infusion site bruising	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
Injection site bruising	0			2 (0.7)	2	0.76	2 (0.7)	2	0.74	4 (0.5)	4	0.50
Injection site induration	0			1 (0.4)	1	0.38	3 (1.1)	4	1.47	4 (0.5)	5	0.62
Injection site mass	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

2.7.4.7.2-10 投薬過誤に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira N	(%)	E	R	IDeg N	(%)	E	R	Lira N	(%)	E	R	Total N	(%)	E	R
Number of subjects	275				271				273				819			
PYE (years)	268.00				261.81				271.84				801.65			
Events	2	(0.7)	2	0.75	2	(0.7)	2	0.76	3	(1.1)	3	1.10	7	(0.9)	7	0.87
Injury, poisoning and procedural complications	2	(0.7)	2	0.75	2	(0.7)	2	0.76	2	(0.7)	2	0.74	6	(0.7)	6	0.75
Accidental overdose	1	(0.4)	1	0.37	1	(0.4)	1	0.38	1	(0.4)	1	0.37	3	(0.4)	3	0.37
Overdose	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
Incorrect dose administered	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
Wrong drug administered	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
Psychiatric disorders	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
Suicide attempt	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

2.7.4.7.2-11 高血糖に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira N (%)	E	R	IDeg N (%)	E	R	Lira N (%)	E	R	Total N (%)	E	R
Number of subjects	275			271			273			819		
PYE (years)	268.00			261.81			271.84			801.65		
Events	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Investigations	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Urine ketone body present	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

ゾルトファイ配合注フレックスタッチ

2.7.4.7 付録
3. 4184 試験の安全性データ

ノボ ノルディスク ファーマ株式会社

目次

ページ

2.7.4.7.3-1 心血管系事象（器官別大分類及び基本語別）－SAS（4184 試験） 3
2.7.4.7.3-2 膵炎に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 4
2.7.4.7.3-3 リパーゼ及びアミラーゼ増加に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 5
2.7.4.7.3-4 新生物に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 6
2.7.4.7.3-5 甲状腺疾患に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 7
2.7.4.7.3-6 カルシトニン増加に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 8
2.7.4.7.3-7 腎機能の悪化に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 9
2.7.4.7.3-8 アレルギー反応（免疫原性）に関連する可能性がある有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 10
2.7.4.7.3-9 注射部位反応に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 11
2.7.4.7.3-10 投薬過誤に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 12
2.7.4.7.3-11 高血糖に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験） 13

2.7.4.7 付録 3

2.7.4.7.3-1 心血管系事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira N (%)	IDegLira E	IDegLira R	IDeg N (%)	IDeg E	IDeg R	Total N (%)	Total E	Total R
Number of subjects	105			105			210		
PYE (Years)	54.28			52.27			106.54		
Events	7 (6.7)	9	16.58	3 (2.9)	4	7.65	10 (4.8)	13	12.20
Cardiac disorders	2 (1.9)	3	5.53	0			2 (1.0)	3	2.82
Acute myocardial infarction	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
Cardiac failure congestive	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
Supraventricular extrasystoles	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
General disorders and administration site conditions	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82
Oedema peripheral	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82
Investigations	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
Electrocardiogram ST-T segment depression	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
Electrocardiogram T wave inversion	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
Nervous system disorders	1 (1.0)	1	1.84	1 (1.0)	2	3.83	2 (1.0)	3	2.82
Lacunar infarction	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
Loss of consciousness	0			1 (1.0)	2	3.83	1 (0.5)	2	1.88
Renal and urinary disorders	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
Acute kidney injury	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
Vascular disorders	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
Orthostatic hypotension	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

2.7.4.7.3-2 膵炎に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

There is no data for this Table

2.7.4.7.3-3 リパーゼ及びアミラーゼ増加に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira N	(%)	E	R	IDeg N	(%)	E	R	Total N	(%)	E	R
Number of subjects	105				105				210			
PYE (Years)	54.28				52.27				106.54			
Events	2	(1.9)	2	3.68	0				2	(1.0)	2	1.88
Investigations	2	(1.9)	2	3.68	0				2	(1.0)	2	1.88
Lipase increased	2	(1.9)	2	3.68	0				2	(1.0)	2	1.88

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

2.7.4.7.3-4 新生物に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira N	(%)	E	R	IDeg N	(%)	E	R	Total N	(%)	E	R
Number of subjects	105				105				210			
PYE (Years)	54.28				52.27				106.54			
Events	4	(3.8)	6	11.05	4	(3.8)	5	9.57	8	(3.8)	11	10.32
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(1.9)	2	3.68	2	(1.9)	2	3.83	4	(1.9)	4	3.75
Adenocarcinoma	1	(1.0)	1	1.84	0				1	(0.5)	1	0.94
Uterine leiomyoma	1	(1.0)	1	1.84	0				1	(0.5)	1	0.94
Pancreatic carcinoma	0				1	(1.0)	1	1.91	1	(0.5)	1	0.94
Renal cell carcinoma	0				1	(1.0)	1	1.91	1	(0.5)	1	0.94
Renal and urinary disorders	2	(1.9)	2	3.68	1	(1.0)	1	1.91	3	(1.4)	3	2.82
Renal cyst	2	(1.9)	2	3.68	1	(1.0)	1	1.91	3	(1.4)	3	2.82
Gastrointestinal disorders	1	(1.0)	1	1.84	0				1	(0.5)	1	0.94
Large intestine polyp	1	(1.0)	1	1.84	0				1	(0.5)	1	0.94
Infections and infestations	1	(1.0)	1	1.84	0				1	(0.5)	1	0.94
Infected dermal cyst	1	(1.0)	1	1.84	0				1	(0.5)	1	0.94
Reproductive system and breast disorders	0				1	(1.0)	2	3.83	1	(0.5)	2	1.88
Uterine cyst	0				1	(1.0)	2	3.83	1	(0.5)	2	1.88

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

2.7.4.7.3-5 甲状腺疾患に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	105			105			210		
PYE (Years)	54.28			52.27			106.54		
Events	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
Endocrine disorders	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
Thyroid mass	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

2.7.4.7.3-6 カルシトニン増加に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

There is no data for this Table

2.7.4.7.3-7 腎機能の悪化に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira N	(%)	E	R	IDeg N	(%)	E	R	Total N	(%)	E	R
Number of subjects	105				105				210			
PYE (Years)	54.28				52.27				106.54			
Events	1	(1.0)	1	1.84	1	(1.0)	1	1.91	2	(1.0)	2	1.88
Renal and urinary disorders	1	(1.0)	1	1.84	0				1	(0.5)	1	0.94
Acute kidney injury	1	(1.0)	1	1.84	0				1	(0.5)	1	0.94
Investigations	0				1	(1.0)	1	1.91	1	(0.5)	1	0.94
Glomerular filtration rate decreased	0				1	(1.0)	1	1.91	1	(0.5)	1	0.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

2.7.4.7.3-8 アレルギー反応（免疫原性）に関連する可能性がある有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	105			105			210		
PYE (Years)	54.28			52.27			106.54		
Events	2 (1.9)	2	3.68	6 (5.7)	6	11.48	8 (3.8)	8	7.51
Skin and subcutaneous tissue disorders	2 (1.9)	2	3.68	6 (5.7)	6	11.48	8 (3.8)	8	7.51
Eczema	2 (1.9)	2	3.68	4 (3.8)	4	7.65	6 (2.9)	6	5.63
Dermatitis	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
Rash	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

2.7.4.7.3-9 注射部位反応に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira N	(%)	E	R	IDeg N	(%)	E	R	Total N	(%)	E	R
Number of subjects	105				105				210			
PYE (Years)	54.28				52.27				106.54			
Events	1	(1.0)	1	1.84	3	(2.9)	3	5.74	4	(1.9)	4	3.75
General disorders and administration site conditions	1	(1.0)	1	1.84	3	(2.9)	3	5.74	4	(1.9)	4	3.75
Injection site induration	1	(1.0)	1	1.84	0				1	(0.5)	1	0.94
Administration site induration	0				2	(1.9)	2	3.83	2	(1.0)	2	1.88
Injection site discomfort	0				1	(1.0)	1	1.91	1	(0.5)	1	0.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

2.7.4.7.3-10 投薬過誤に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	105			105			210		
PYE (Years)	54.28			52.27			106.54		
Events	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
Injury, poisoning and procedural complications	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
Wrong drug administered	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

2.7.4.7.3-11 高血糖に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

There is no data for this Table

ゾルトファイ配合注フレックスタッチ

2.7.4.7 付録
4. 併合データ及び市販後データ

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表2.7.4.7.4-1 重篤な有害事象の要約－臨床試験の併合データ

SOC/PT	Investigational Medicinal Product	Blinded	Active comparator(s)/ Other active comparator(s)	Placebo	Pre-randomisation
Infections and infestations	**36**	**0**	**35**	**2**	**3**
Abscess	0	0	1	0	0
Appendicitis	2	0	1	0	0
Appendicitis perforated	1	0	0	0	0
Bronchitis	0	0	1	1	0
Cellulitis	1	0	2	0	0
Dacryocystitis	1	0	0	0	0
Dengue fever	0	0	0	1	0
Diverticulitis	1	0	0	0	0
Gastroenteritis	4	0	2	0	0
Gastroenteritis viral	0	0	2	0	0
Infected skin ulcer	0	0	1	0	0
Influenza	1	0	0	0	0
Localised infection	1	0	0	0	1
Lower respiratory tract infection	2	0	2	0	0
Meningitis haemophilus	1	0	0	0	0
Osteomyelitis	2	0	0	0	0
Pneumonia	5	0	6	0	1
Pneumonia haemophilus	1	0	0	0	0
Pneumonia influenzal	0	0	1	0	0
Postoperative wound infection	1	0	1	0	0
Pyelonephritis chronic	2	0	0	0	0
Sepsis	0	0	2	0	0
Septic shock	1	0	0	0	0
Subcutaneous abscess	1	0	0	0	0

Cumulative tabulation of serious adverse events from clinical trials

SOC/PT	Investigational Medicinal Product	Blinded	Active comparator(s)/ Other active comparator(s)	Placebo	Pre-randomisation
Tonsillitis	0	0	1	0	0
Urinary tract infection	2	0	4	0	0
Vestibular neuronitis	1	0	0	0	0
Viral infection	0	0	1	0	0
Anal abscess	1	0	0	0	0
Streptococcal sepsis	0	0	1	0	0
Groin abscess	0	0	1	0	0
Staphylococcal bacteraemia	1	0	0	0	0
Bacterial sepsis	0	0	1	0	0
Urinary tract infection bacterial	0	0	1	0	0
Acute hepatitis B	0	0	0	0	1
Diabetic foot infection	1	0	0	0	0
Perichondritis	0	0	1	0	0
Cholecystitis infective	1	0	1	0	0
Post procedural infection	1	0	0	0	0
Herpes zoster meningitis	0	0	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**18**	**0**	**24**	**0**	**3**
Adenocarcinoma of colon	0	0	1	0	0
Basal cell carcinoma	0	0	2	0	0
Benign hepatic neoplasm	0	0	1	0	0
Benign neoplasm of bladder	1	0	0	0	0
Bladder cancer stage 0, with cancer in situ	1	0	0	0	0
Breast cancer	0	0	3	0	0
Choroid melanoma	0	0	0	0	1

Cumulative tabulation of serious adverse events from clinical trials

SOC/PT	Investigational Medicinal Product	Blinded	Active comparator(s)/ Other active comparator(s)	Placebo	Pre-randomisation
Chronic myeloid leukaemia	1	0	0	0	0
Colon cancer	1	0	0	0	0
Endometrial adenocarcinoma	1	0	1	0	0
Gastric cancer stage I	1	0	0	0	0
Inflammatory carcinoma of breast stage III	1	0	0	0	0
Lung adenocarcinoma	0	0	2	0	0
Malignant melanoma	1	0	0	0	0
Metastases to lymph nodes	0	0	1	0	0
Oesophageal adenocarcinoma	0	0	1	0	0
Pancreatic carcinoma	0	0	1	0	0
Pancreatic carcinoma metastatic	1	0	1	0	1
Pituitary tumour	1	0	0	0	0
Plasmacytoma	1	0	0	0	0
Prostate cancer stage II	1	0	0	0	0
Rectal adenocarcinoma	1	0	0	0	0
Squamous cell carcinoma of skin	0	0	1	0	0
Uterine cancer	0	0	1	0	0
Colon adenoma	1	0	0	0	0
Gastrointestinal stromal tumour	0	0	1	0	0
Lung neoplasm malignant	1	0	1	0	0
Pancreatic carcinoma stage IV	0	0	1	0	0
Pleural mesothelioma malignant	1	0	0	0	0
Prostate cancer	1	0	1	0	1
Adrenal neoplasm	0	0	1	0	0
Renal cell carcinoma	0	0	2	0	0

Cumulative tabulation of serious adverse events from clinical trials

SOC/PT	Investigational Medicinal Product	Blinded	Active comparator(s)/ Other active comparator(s)	Placebo	Pre-randomisation
Invasive ductal breast carcinoma	1	0	1	0	0
Blood and lymphatic system disorders	**1**	**0**	**0**	**1**	**0**
Iron deficiency anaemia	1	0	0	0	0
Thrombocytopenia	0	0	0	1	0
Endocrine disorders	**1**	**0**	**3**	**0**	**0**
Adrenal insufficiency	1	0	0	0	0
Goitre	0	0	1	0	0
Thyroid mass	0	0	2	0	0
Metabolism and nutrition disorders	**10**	**1**	**5**	**0**	**0**
Diabetes mellitus inadequate control	2	1	0	0	0
Gout	0	0	1	0	0
Hyperglycaemia	1	0	3	0	0
Hypoglycaemia	6	0	1	0	0
Obesity	1	0	0	0	0
Psychiatric disorders	**2**	**0**	**4**	**0**	**0**
Anxiety	0	0	1	0	0
Depression	1	0	1	0	0
Suicide attempt	0	0	2	0	0
Major depression	1	0	0	0	0
Nervous system disorders	**22**	**0**	**19**	**0**	**1**
Carpal tunnel syndrome	0	0	1	0	0
Cerebral infarction	1	0	1	0	0
Cerebrovascular accident	1	0	0	0	1
Dizziness	1	0	0	0	0

Cumulative tabulation of serious adverse events from clinical trials

SOC/PT	Investigational Medicinal Product	Blinded	Active comparator(s)/ Other active comparator(s)	Placebo	Pre-randomisation
Facial paralysis	1	0	1	0	0
Guillain-Barre syndrome	0	0	1	0	0
Haemorrhagic stroke	1	0	1	0	0
Hypertensive encephalopathy	1	0	0	0	0
Loss of consciousness	0	0	2	0	0
Migraine	2	0	0	0	0
Sciatica	0	0	2	0	0
Seizure	1	0	1	0	0
Syncope	2	0	0	0	0
Transient ischaemic attack	1	0	1	0	0
Vertebrobasilar insufficiency	2	0	0	0	0
Vertigo CNS origin	0	0	1	0	0
Lacunar infarction	1	0	0	0	0
Progressive multiple sclerosis	0	0	1	0	0
Ischaemic stroke	2	0	1	0	0
Mononeuropathy	0	0	1	0	0
Thalamic infarction	2	0	0	0	0
Hypoglycaemic unconsciousness	3	0	3	0	0
Thrombotic cerebral infarction	0	0	1	0	0
Eye disorders	**4**	**1**	**5**	**0**	**0**
Angle closure glaucoma	0	0	1	0	0
Cataract	0	0	1	0	0
Diplopia	0	0	1	0	0
Retinal detachment	2	0	1	0	0
Visual impairment	0	1	0	0	0

Cumulative tabulation of serious adverse events from clinical trials

SOC/PT	Investigational Medicinal Product	Blinded	Active comparator(s)/ Other active comparator(s)	Placebo	Pre-randomisation
Vitreous haemorrhage	0	0	1	0	0
Necrotising retinitis	1	0	0	0	0
Normal tension glaucoma	1	0	0	0	0
Ear and labyrinth disorders	**1**	**0**	**1**	**0**	**0**
Vertigo	0	0	1	0	0
Vertigo positional	1	0	0	0	0
Cardiac disorders	**47**	**1**	**36**	**1**	**2**
Acute myocardial infarction	7	0	6	0	0
Angina pectoris	5	0	2	0	0
Angina unstable	3	0	3	0	1
Arrhythmia	1	0	1	0	0
Arteriosclerosis coronary artery	1	0	1	0	0
Atrial fibrillation	7	0	2	0	0
Atrial flutter	1	0	0	0	0
Atrioventricular block complete	1	0	1	0	0
Atrioventricular block second degree	0	0	0	1	0
Cardiac arrest	0	0	1	0	0
Cardiac failure	1	0	2	0	0
Cardiac failure acute	1	0	0	0	0
Cardiac failure chronic	1	0	3	0	0
Cardiac failure congestive	2	0	2	0	0
Coronary artery disease	1	1	1	0	0
Coronary artery occlusion	0	0	2	0	0
Coronary artery stenosis	1	0	0	0	0
Myocardial infarction	3	0	2	0	0

Cumulative tabulation of serious adverse events from clinical trials

SOC/PT	Investigational Medicinal Product	Blinded	Active comparator(s)/ Other active comparator(s)	Placebo	Pre-randomisation
Myocardial ischaemia	2	0	1	0	1
Pericarditis	0	0	1	0	0
Supraventricular tachycardia	2	0	1	0	0
Ventricular fibrillation	1	0	0	0	0
Ventricular tachycardia	1	0	0	0	0
Silent myocardial infarction	0	0	1	0	0
Acute coronary syndrome	1	0	2	0	0
Hypertensive cardiomyopathy	1	0	0	0	0
Cardiac disorder	1	0	0	0	0
Coronary artery dilatation	1	0	0	0	0
Sinus node dysfunction	1	0	1	0	0
Vascular disorders	**14**	**0**	**5**	**0**	**0**
Aortic stenosis	1	0	0	0	0
Circulatory collapse	1	0	0	0	0
Embolism arterial	0	0	1	0	0
Hypertension	1	0	0	0	0
Hypertensive crisis	0	0	1	0	0
Hypotension	2	0	0	0	0
Varicose vein	0	0	1	0	0
Vasoconstriction	0	0	1	0	0
Peripheral arterial occlusive disease	5	0	1	0	0
Peripheral artery stenosis	1	0	0	0	0
Peripheral artery thrombosis	3	0	0	0	0
Respiratory, thoracic and mediastinal disorders	**5**	**0**	**16**	**0**	**1**

Cumulative tabulation of serious adverse events from clinical trials

SOC/PT	Investigational Medicinal Product	Blinded	Active comparator(s)/ Other active comparator(s)	Placebo	Pre-randomisation
Asthma	0	0	2	0	0
Bronchitis chronic	0	0	1	0	0
Chronic obstructive pulmonary disease	2	0	5	0	1
Dyspnoea	0	0	1	0	0
Interstitial lung disease	0	0	1	0	0
Lung consolidation	0	0	1	0	0
Pleural effusion	0	0	1	0	0
Pleural thickening	1	0	0	0	0
Pulmonary hypertension	0	0	0	0	0
Pulmonary oedema	0	0	1	0	0
Respiratory distress	0	0	1	0	0
Sleep apnoea syndrome	1	0	2	0	0
Lung perforation	1	0	0	0	0
Gastrointestinal disorders	**21**	**0**	**18**	**1**	**1**
Abdominal pain	1	0	2	0	0
Anal fistula	0	0	1	0	0
Colitis	1	0	0	0	0
Colitis ischaemic	1	0	0	0	0
Diarrhoea	1	0	0	0	0
Enteritis	1	0	0	0	0
Gastritis	1	0	2	0	0
Gastrooesophageal reflux disease	2	0	2	0	0
Gastrointestinal haemorrhage	1	0	0	0	0
Impaired gastric emptying	0	0	0	1	0
Irritable bowel syndrome	1	0	0	0	0

Cumulative tabulation of serious adverse events from clinical trials

SOC/PT	Investigational Medicinal Product	Blinded	Active comparator(s)/ Other active comparator(s)	Placebo	Pre-randomisation
Nausea	1	0	1	0	0
Pancreatitis	0	0	1	0	0
Pancreatitis acute	3	0	3	0	0
Small intestinal obstruction	2	0	0	0	0
Umbilical hernia	1	0	2	0	0
Vomiting	1	0	2	0	0
Gastroduodenitis	1	0	0	0	0
Large intestine polyp	1	0	0	0	0
Varices oesophageal	0	0	1	0	0
Salivary gland mass	0	0	0	0	1
Autoimmune pancreatitis	0	0	1	0	0
Functional gastrointestinal disorder	1	0	0	0	0
Hepatobiliary disorders	**14**	**0**	**14**	**0**	**1**
Biliary colic	2	0	1	0	0
Cholecystitis	2	0	1	0	0
Cholecystitis acute	6	0	4	0	0
Cholelithiasis	3	0	7	0	1
Hepatic cyst	1	0	0	0	0
Jaundice cholestatic	0	0	1	0	0
Skin and subcutaneous tissue disorders	**1**	**0**	**2**	**0**	**0**
Stevens-Johnson syndrome	0	0	1	0	0
Diabetic foot	1	0	1	0	0
Musculoskeletal and connective tissue disorders	**11**	**1**	**13**	**0**	**0**

Cumulative tabulation of serious adverse events from clinical trials

SOC/PT	Investigational Medicinal Product	Blinded	Active comparator(s)/ Other active comparator(s)	Placebo	Pre-randomisation
Arthralgia	1	0	1	0	0
Lumbar spinal stenosis	1	0	0	0	0
Musculoskeletal pain	2	0	0	0	0
Osteoarthritis	2	0	7	0	0
Rheumatoid arthritis	1	0	0	0	0
Rotator cuff syndrome	0	1	0	0	0
Spinal osteoarthritis	0	0	1	0	0
Tendonitis	0	0	1	0	0
Pseudarthrosis	0	0	1	0	0
Intervertebral disc protrusion	2	0	1	0	0
Musculoskeletal chest pain	0	0	1	0	0
Spinal pain	2	0	0	0	0
Renal and urinary disorders	**12**	**0**	**10**	**0**	**0**
Haematuria	1	0	1	0	0
Nephrolithiasis	4	0	1	0	0
Proteinuria	0	0	1	0	0
Renal colic	1	0	1	0	0
Renal cyst	1	0	0	0	0
Renal failure	2	0	1	0	0
Stag horn calculus	1	0	0	0	0
Renal impairment	0	0	1	0	0
Chronic kidney disease	0	0	1	0	0
Acute kidney injury	2	0	3	0	0
Pregnancy, puerperium and perinatal conditions	**4**	**0**	**2**	**0**	**0**
Abortion spontaneous	1	0	2	0	0

Cumulative tabulation of serious adverse events from clinical trials

SOC/PT	Investigational Medicinal Product	Blinded	Active comparator(s)/ Other active comparator(s)	Placebo	Pre-randomisation
Pre-eclampsia	1	0	0	0	0
Premature baby	1	0	0	0	0
Imminent abortion	1	0	0	0	0
Reproductive system and breast disorders	**4**	**0**	**6**	**0**	**2**
Benign prostatic hyperplasia	1	0	1	0	1
Cervical dysplasia	0	0	0	0	1
Dysfunctional uterine bleeding	1	0	0	0	0
Endometrial hyperplasia	0	0	1	0	0
Metrorrhagia	1	0	1	0	0
Spermatocele	0	0	1	0	0
Uterine prolapse	0	0	1	0	0
Vaginal haemorrhage	0	0	1	0	0
Postmenopausal haemorrhage	1	0	0	0	0
General disorders and administration site conditions	**11**	**0**	**2**	**0**	**2**
Chest pain	4	0	0	0	0
Chills	0	0	1	0	0
Death	1	0	0	0	0
Mass	1	0	0	0	0
Pyrexia	2	0	0	0	0
Non-cardiac chest pain	3	0	1	0	2
Investigations	**6**	**0**	**4**	**0**	**0**
Amylase increased	1	0	0	0	0
Blood glucose increased	1	0	1	0	0
Blood potassium increased	1	0	0	0	0

Cumulative tabulation of serious adverse events from clinical trials

SOC/PT	Investigational Medicinal Product	Blinded	Active comparator(s)/ Other active comparator(s)	Placebo	Pre-randomisation
Chest X-ray abnormal	1	0	0	0	0
Electrocardiogram abnormal	0	0	1	0	0
Lipase increased	1	0	0	0	0
Foetal heart rate abnormal	0	0	1	0	0
Cardiovascular evaluation	1	0	0	0	0
Metabolic function test	0	0	1	0	0
Injury, poisoning and procedural complications	**28**	**1**	**16**	**1**	**1**
Acetabulum fracture	0	0	1	0	0
Chemical poisoning	0	0	0	0	1
Fall	6	0	3	0	0
Femoral neck fracture	1	0	1	0	0
Femur fracture	0	1	0	0	0
Fibula fracture	2	0	0	0	0
Foot fracture	1	0	3	0	0
Gun shot wound	2	0	0	0	0
Hip fracture	1	0	0	0	0
Humerus fracture	1	0	2	0	0
Ilium fracture	0	0	1	0	0
Rib fracture	1	0	0	0	0
Road traffic accident	3	0	2	0	0
Spinal compression fracture	1	0	0	0	0
Spinal fracture	1	0	0	0	0
Stab wound	1	0	0	1	0
Tibia fracture	1	0	0	0	0
Wrong drug administered	0	0	1	0	0

Cumulative tabulation of serious adverse events from clinical trials

SOC/PT	Investigational Medicinal Product	Blinded	Active comparator(s)/ Other active comparator(s)	Placebo	Pre-randomisation
Thoracic vertebral fracture	1	0	0	0	0
Post procedural haemorrhage	0	0	1	0	0
Nerve injury	1	0	0	0	0
Respiratory fume inhalation disorder	0	0	1	0	0
Craniocerebral injury	1	0	0	0	0
Postoperative respiratory failure	1	0	0	0	0
Meniscus injury	2	0	0	0	0
Surgical and medical procedures	**11**	**0**	**13**	**0**	**0**
Coronary artery bypass	2	0	1	0	0
Spinal decompression	0	0	1	0	0
Thrombectomy	1	0	0	0	0
Tympanoplasty	2	0	0	0	0
Coronary revascularisation	3	0	3	0	0
Hip surgery	1	0	0	0	0
Coronary arterial stent insertion	1	0	2	0	0
Lesion excision	0	0	1	0	0
Cardiac ablation	1	0	1	0	0
Varicose vein operation	0	0	1	0	0
Percutaneous coronary intervention	0	0	2	0	0
Large intestinal polypectomy	0	0	1	0	0
Product issues	**2**	**0**	**0**	**0**	**0**
Device failure	2	0	0	0	0
Total	**286**	**5**	**253**	**6**	**17**

Cumulative tabulation of serious adverse events from clinical trials

Report generation criteria

Report based on Argus insight Frozen case series **20180403_Cumulative_AllProducts** created on **03-Apr-2018 08:00:46**
Product alias(es): **Insulin degludec liraglutide B5 , Insulin degludec liraglutide FlexPen , Insulin degludec liraglutide PDS290 , Insulin degludec liraglutide Penfill , Insulin degludec liraglutide V2**
Project ID(s): **Not Selected**
Trial ID(s): **[NN9068-3697,NN9068-3851,NN9068-3871,NN9068-3912,NN9068-3951,NN9068-3952,NN9068-4026,NN9068-4056,NN9068-4119,NN9068-4139,NN9068-4148,NN9068-4166,NN9068-4183,NN9068-4184,NN9068-4185,NN9068-4228,NN9068-4229]**
Include only trials where product is primary IMP : **Yes**
Reporting period date range : **01-Jan-1900** through **31-Mar-2018**
Comparator of interest : **Not Provided**
Pre-randomised events included : **Yes**
Report generated on **05-Apr-2018 07:04:34**
MedDRA Version : **20.1**
SOC : System organ class
PT : Preferred term

表2.7.4.7.4-2 すべての副作用の要約－海外市販後データ

SOC/PT	Spontaneous, including competent authorities (worldwide) and literature					Non-interventional post-marketing sources and reports from other solicited sources	
	Serious		Non-Serious		Total	Serious	
	Period	Cumulative	Period	Cumulative	All Cumulative	Period	Cumulative
Infections and infestations	**1**	**4**	**4**	**8**	**12**	**0**	**0**
Cellulitis	0	1	0	0	1	0	0
Fungal infection	0	0	2	3	3	0	0
Influenza	0	0	1	1	1	0	0
Lower respiratory tract infection	0	1	0	0	1	0	0
Nasopharyngitis	0	0	1	1	1	0	0
Pneumonia	1	2	0	0	2	0	0
Urinary tract infection	0	0	0	2	2	0	0
Bacterial infection	0	0	0	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5**	**12**	**0**	**0**	**12**	**0**	**0**
Adenocarcinoma gastric	0	1	0	0	1	0	0
Cholangiocarcinoma	1	1	0	0	1	0	0
Gastrointestinal carcinoma	0	1	0	0	1	0	0
Pancreatic carcinoma	1	3	0	0	3	0	0
Pancreatic carcinoma metastatic	0	2	0	0	2	0	0
Small cell lung cancer	0	1	0	0	1	0	0
Lung neoplasm malignant	2	2	0	0	2	0	0
Malignant peritoneal neoplasm	1	1	0	0	1	0	0
Blood and lymphatic system disorders	**0**	**2**	**0**	**1**	**3**	**0**	**0**
Eosinophilia	0	0	0	1	1	0	0
Neutropenia	0	1	0	0	1	0	0
Spleen disorder	0	1	0	0	1	0	0
Immune system disorders	**0**	**0**	**2**	**6**	**6**	**0**	**0**
Hypersensitivity	0	0	2	6	6	0	0
Endocrine disorders	**0**	**2**	**0**	**0**	**2**	**0**	**0**

Number of Adverse Reactions by Preferred Term from Post-Marketing Sources - Xultophy

SOC/PT	Spontaneous, including competent authorities (worldwide) and literature					Non-interventional post-marketing sources and reports from other solicited sources	
	Serious		Non-Serious		Total	Serious	
	Period	Cumulative	Period	Cumulative	All Cumulative	Period	Cumulative
Hypothyroidism	0	1	0	0	1	0	0
Autoimmune thyroiditis	0	1	0	0	1	0	0
Metabolism and nutrition disorders	**3**	**18**	**15**	**47**	**65**	**0**	**0**
Dehydration	0	1	0	0	1	0	0
Diabetes mellitus inadequate control	0	0	3	10	10	0	0
Diabetic ketoacidosis	0	2	0	0	2	0	0
Gout	0	0	0	1	1	0	0
Hypercholesterolaemia	0	1	0	0	1	0	0
Hyperglycaemia	0	0	3	8	8	0	0
Hyperkalaemia	0	1	0	0	1	0	0
Hyperphosphataemia	0	1	0	0	1	0	0
Hypoglycaemia	2	8	6	12	20	0	0
Increased appetite	0	0	0	1	1	0	0
Insulin resistance	0	0	0	1	1	0	0
Metabolic acidosis	0	1	0	0	1	0	0
Obesity	1	1	0	0	1	0	0
Fluid intake reduced	0	1	0	0	1	0	0
Feeding disorder	0	0	1	1	1	0	0
Decreased appetite	0	0	2	13	13	0	0
Type 1 diabetes mellitus	0	1	0	0	1	0	0
Psychiatric disorders	**0**	**1**	**2**	**10**	**11**	**0**	**0**
Anger	0	0	1	1	1	0	0
Delirium	0	1	0	0	1	0	0
Depressed mood	0	0	0	1	1	0	0
Depression	0	0	1	1	1	0	0

Number of Adverse Reactions by Preferred Term from Post-Marketing Sources - Xultophy

SOC/PT	Spontaneous, including competent authorities (worldwide) and literature					Non-interventional post-marketing sources and reports from other solicited sources	
	Serious		Non-Serious		Total	Serious	
	Period	Cumulative	Period	Cumulative	All Cumulative	Period	Cumulative
Hallucination	0	0	0	1	1	0	0
Insomnia	0	0	0	2	2	0	0
Nightmare	0	0	0	1	1	0	0
Panic attack	0	0	0	1	1	0	0
Sleep disorder	0	0	0	2	2	0	0
Nervous system disorders	**1**	**5**	**12**	**42**	**47**	**0**	**0**
Aphasia	0	1	0	0	1	0	0
Burning sensation	0	0	0	1	1	0	0
Dizziness	0	1	5	14	15	0	0
Dysgeusia	0	0	1	1	1	0	0
Guillain-Barre syndrome	0	1	0	0	1	0	0
Headache	0	0	2	11	11	0	0
Hypoaesthesia	0	0	2	4	4	0	0
Hypoglycaemic coma	1	1	0	0	1	0	0
Neuropathy peripheral	0	0	0	1	1	0	0
Paraesthesia	0	0	1	3	3	0	0
Somnolence	0	0	1	2	2	0	0
Syncope	0	1	0	0	1	0	0
Tremor	0	0	0	2	2	0	0
Visual field defect	0	0	0	1	1	0	0
Balance disorder	0	0	0	2	2	0	0
Eye disorders	**2**	**3**	**2**	**10**	**13**	**0**	**0**
Dry eye	0	0	0	1	1	0	0
Eye haemorrhage	0	1	0	0	1	0	0
Eye irritation	0	0	0	1	1	0	0

Number of Adverse Reactions by Preferred Term from Post-Marketing Sources - Xultophy

SOC/PT	Spontaneous, including competent authorities (worldwide) and literature					Non-interventional post-marketing sources and reports from other solicited sources	
	Serious		Non-Serious		Total	Serious	
	Period	Cumulative	Period	Cumulative	All Cumulative	Period	Cumulative
Eye swelling	0	0	0	1	1	0	0
Eyelid oedema	0	0	1	2	2	0	0
Retinopathy	2	2	0	0	2	0	0
Vision blurred	0	0	1	4	4	0	0
Visual impairment	0	0	0	1	1	0	0
Ear and labyrinth disorders	**0**	**0**	**4**	**6**	**6**	**0**	**0**
Tinnitus	0	0	2	3	3	0	0
Vertigo	0	0	2	3	3	0	0
Cardiac disorders	**1**	**7**	**0**	**3**	**10**	**0**	**0**
Cardiac failure	0	1	0	0	1	0	0
Cardiac failure congestive	1	1	0	0	1	0	0
Myocardial infarction	0	3	0	0	3	0	0
Palpitations	0	0	0	2	2	0	0
Sinus bradycardia	0	1	0	0	1	0	0
Tachycardia	0	0	0	1	1	0	0
Cardiopulmonary failure	0	1	0	0	1	0	0
Vascular disorders	**0**	**2**	**2**	**3**	**5**	**0**	**0**
Flushing	0	0	0	1	1	0	0
Hypertension	0	1	0	0	1	0	0
Hypotension	0	1	0	0	1	0	0
Lymphoedema	0	0	1	1	1	0	0
Hot flush	0	0	1	1	1	0	0
Respiratory, thoracic and mediastinal disorders	**1**	**2**	**3**	**6**	**8**	**0**	**0**
Chronic obstructive pulmonary disease	0	1	0	0	1	0	0

Number of Adverse Reactions by Preferred Term from Post-Marketing Sources - Xultophy

SOC/PT	Spontaneous, including competent authorities (worldwide) and literature					Non-interventional post-marketing sources and reports from other solicited sources	
	Serious		Non-Serious		Total	Serious	
	Period	Cumulative	Period	Cumulative	All Cumulative	Period	Cumulative
Cough	0	0	0	1	1	0	0
Dyspnoea	1	1	0	2	3	0	0
Respiratory disorder	0	0	1	1	1	0	0
Rhinorrhoea	0	0	1	1	1	0	0
Oropharyngeal pain	0	0	1	1	1	0	0
Gastrointestinal disorders	**21**	**38**	**56**	**188**	**226**	**0**	**0**
Abdominal discomfort	0	0	1	4	4	0	0
Abdominal distension	0	0	3	7	7	0	0
Abdominal pain	2	3	6	14	17	0	0
Abdominal pain lower	0	0	0	1	1	0	0
Abdominal pain upper	0	1	3	10	11	0	0
Breath odour	1	1	0	1	2	0	0
Constipation	0	0	1	6	6	0	0
Diarrhoea	0	2	9	23	25	0	0
Diverticulum	0	1	0	0	1	0	0
Dyspepsia	0	0	2	8	8	0	0
Dysphagia	0	0	0	1	1	0	0
Eructation	0	0	2	6	6	0	0
Flatulence	0	0	2	7	7	0	0
Gastritis	0	0	0	2	2	0	0
Gastrooesophageal reflux disease	0	1	2	5	6	0	0
Gastrointestinal disorder	0	0	1	2	2	0	0
Leukoplakia oral	1	1	0	0	1	0	0
Lip oedema	1	1	0	0	1	0	0
Lip swelling	0	0	1	1	1	0	0

Number of Adverse Reactions by Preferred Term from Post-Marketing Sources - Xultophy

SOC/PT	Spontaneous, including competent authorities (worldwide) and literature					Non-interventional post-marketing sources and reports from other solicited sources	
	Serious		Non-Serious		Total	Serious	
	Period	Cumulative	Period	Cumulative	All Cumulative	Period	Cumulative
Nausea	2	3	13	57	60	0	0
Oral discomfort	0	0	1	1	1	0	0
Pancreatic pseudocyst	0	1	0	0	1	0	0
Pancreatitis	8	10	0	0	10	0	0
Pancreatitis acute	2	6	0	0	6	0	0
Pancreatitis chronic	0	1	0	0	1	0	0
Pancreatitis necrotising	1	1	0	0	1	0	0
Retching	0	0	0	1	1	0	0
Tongue oedema	1	1	0	0	1	0	0
Tooth disorder	0	0	0	1	1	0	0
Vomiting	2	3	8	23	26	0	0
Neurogenic bowel	0	0	0	1	1	0	0
Small intestinal haemorrhage	0	1	0	0	1	0	0
Faecalith	0	0	0	1	1	0	0
Hypoaesthesia oral	0	0	1	2	2	0	0
Mouth swelling	0	0	0	1	1	0	0
Anal incontinence	0	0	0	2	2	0	0
Hepatobiliary disorders	**2**	**5**	**1**	**2**	**7**	**0**	**0**
Biliary colic	0	0	0	1	1	0	0
Cholelithiasis	1	2	0	0	2	0	0
Hepatitis acute	0	1	0	0	1	0	0
Jaundice	1	2	0	0	2	0	0
Liver disorder	0	0	1	1	1	0	0
Skin and subcutaneous tissue disorders	**2**	**2**	**20**	**66**	**68**	**0**	**0**
Acne	0	0	0	1	1	0	0

Number of Adverse Reactions by Preferred Term from Post-Marketing Sources - Xultophy

SOC/PT	Spontaneous, including competent authorities (worldwide) and literature					Non-interventional post-marketing sources and reports from other solicited sources	
	Serious		Non-Serious		Total	Serious	
	Period	Cumulative	Period	Cumulative	All Cumulative	Period	Cumulative
Alopecia	0	0	1	1	1	0	0
Blister	0	0	0	2	2	0	0
Dermatitis allergic	0	0	0	1	1	0	0
Dry skin	0	0	0	1	1	0	0
Erythema	0	0	2	5	5	0	0
Fixed eruption	0	0	0	1	1	0	0
Hyperhidrosis	0	0	1	6	6	0	0
Petechiae	0	0	1	2	2	0	0
Pruritus	1	1	5	12	13	0	0
Rash	0	0	0	6	6	0	0
Rash erythematous	0	0	0	1	1	0	0
Rash generalised	0	0	0	2	2	0	0
Rash macular	0	0	0	1	1	0	0
Rash maculo-papular	1	1	0	0	1	0	0
Rash papular	0	0	0	1	1	0	0
Rash pruritic	0	0	1	3	3	0	0
Skin discolouration	0	0	0	1	1	0	0
Skin exfoliation	0	0	0	1	1	0	0
Skin reaction	0	0	2	2	2	0	0
Swelling face	0	0	0	4	4	0	0
Urticaria	0	0	3	5	5	0	0
Vascular purpura	0	0	1	1	1	0	0
Lipodystrophy acquired	0	0	1	1	1	0	0
Pruritus generalised	0	0	2	4	4	0	0
Skin mass	0	0	0	1	1	0	0

Number of Adverse Reactions by Preferred Term from Post-Marketing Sources - Xultophy

SOC/PT	Spontaneous, including competent authorities (worldwide) and literature					Non-interventional post-marketing sources and reports from other solicited sources	
	Serious		Non-Serious		Total	Serious	
	Period	Cumulative	Period	Cumulative	All Cumulative	Period	Cumulative
Musculoskeletal and connective tissue disorders	**2**	**2**	**2**	**13**	**15**	**0**	**0**
Arthralgia	0	0	1	3	3	0	0
Back pain	0	0	0	1	1	0	0
Joint stiffness	0	0	0	1	1	0	0
Joint swelling	0	0	0	1	1	0	0
Muscle atrophy	0	0	0	1	1	0	0
Muscle spasms	0	0	1	1	1	0	0
Muscular weakness	1	1	0	1	2	0	0
Pain in extremity	0	0	0	3	3	0	0
Pathological fracture	1	1	0	0	1	0	0
Muscle tightness	0	0	0	1	1	0	0
Renal and urinary disorders	**4**	**7**	**2**	**4**	**11**	**1**	**1**
Dysuria	0	0	0	1	1	0	0
Pollakiuria	0	0	0	1	1	0	0
Renal disorder	0	0	1	1	1	0	0
Renal failure	0	0	0	0	0	1	1
Renal tubular necrosis	1	1	0	0	1	0	0
Urinary incontinence	0	0	1	1	1	0	0
Tubulointerstitial nephritis	1	1	0	0	1	0	0
Acute kidney injury	2	5	0	0	5	0	0
Reproductive system and breast disorders	**0**	**0**	**3**	**4**	**4**	**0**	**0**
Breast pain	0	0	1	1	1	0	0
Penile pain	0	0	1	1	1	0	0
Erectile dysfunction	0	0	1	1	1	0	0

Number of Adverse Reactions by Preferred Term from Post-Marketing Sources - Xultophy

SOC/PT	Spontaneous, including competent authorities (worldwide) and literature					Non-interventional post-marketing sources and reports from other solicited sources	
	Serious		Non-Serious		Total	Serious	
	Period	Cumulative	Period	Cumulative	All Cumulative	Period	Cumulative
Vulvovaginal swelling	0	0	0	1	1	0	0
General disorders and administration site conditions	**0**	**1**	**33**	**112**	**113**	**0**	**0**
Asthenia	0	0	1	4	4	0	0
Chest discomfort	0	0	0	2	2	0	0
Chest pain	0	0	1	1	1	0	0
Chills	0	0	0	2	2	0	0
Condition aggravated	0	0	1	1	1	0	0
Discomfort	0	0	0	1	1	0	0
Drug effect decreased	0	0	0	1	1	0	0
Drug ineffective	0	0	2	7	7	0	0
Face oedema	0	0	0	1	1	0	0
Fatigue	0	0	0	3	3	0	0
Feeling abnormal	0	0	3	5	5	0	0
Feeling hot	0	0	0	1	1	0	0
Gait disturbance	0	0	1	2	2	0	0
Hangover	0	0	1	1	1	0	0
Hunger	0	0	0	1	1	0	0
Injection site bruising	0	0	0	2	2	0	0
Injection site erythema	0	0	3	11	11	0	0
Injection site haemorrhage	0	0	1	3	3	0	0
Injection site hypersensitivity	0	0	0	1	1	0	0
Injection site mass	0	0	2	3	3	0	0
Injection site pain	0	0	2	5	5	0	0
Injection site pruritus	0	0	5	13	13	0	0
Injection site rash	0	0	1	3	3	0	0

Number of Adverse Reactions by Preferred Term from Post-Marketing Sources - Xultophy

SOC/PT	Spontaneous, including competent authorities (worldwide) and literature					Non-interventional post-marketing sources and reports from other solicited sources	
	Serious		Non-Serious		Total	Serious	
	Period	Cumulative	Period	Cumulative	All Cumulative	Period	Cumulative
Injection site urticaria	0	0	0	1	1	0	0
Malaise	0	1	4	11	12	0	0
Mucosal dryness	0	0	0	1	1	0	0
Oedema peripheral	0	0	0	6	6	0	0
Pyrexia	0	0	1	1	1	0	0
Swelling	0	0	0	1	1	0	0
Peripheral swelling	0	0	1	5	5	0	0
Idiosyncratic drug reaction	0	0	0	1	1	0	0
Injection site discolouration	0	0	0	2	2	0	0
Injection site discomfort	0	0	1	1	1	0	0
Adverse event	0	0	2	2	2	0	0
Inflammation	0	0	0	1	1	0	0
Drug intolerance	0	0	0	1	1	0	0
Injection site papule	0	0	0	1	1	0	0
Injection site eczema	0	0	0	1	1	0	0
No adverse event	0	0	0	2	2	0	0
Investigations	**6**	**10**	**62**	**147**	**157**	**0**	**0**
Alanine aminotransferase increased	1	1	0	0	1	0	0
Blood creatinine increased	1	1	0	0	1	0	0
Blood glucose abnormal	0	0	3	7	7	0	0
Blood glucose decreased	0	0	5	10	10	0	0
Blood glucose increased	1	3	27	65	68	0	0
Blood pressure abnormal	1	1	0	0	1	0	0
Blood pressure decreased	0	0	1	1	1	0	0
Blood pressure increased	0	0	1	3	3	0	0

Number of Adverse Reactions by Preferred Term from Post-Marketing Sources - Xultophy

SOC/PT	Spontaneous, including competent authorities (worldwide) and literature					Non-interventional post-marketing sources and reports from other solicited sources	
	Serious		Non-Serious		Total	Serious	
	Period	Cumulative	Period	Cumulative	All Cumulative	Period	Cumulative
Blood triglycerides increased	0	0	0	1	1	0	0
Glycosylated haemoglobin decreased	0	0	1	1	1	0	0
Glycosylated haemoglobin increased	0	0	9	16	16	0	0
Heart rate increased	0	0	1	4	4	0	0
Lipase increased	0	2	1	1	3	0	0
Liver function test abnormal	0	0	0	1	1	0	0
Weight decreased	1	1	8	16	17	0	0
Weight increased	0	0	3	13	13	0	0
Blood glucose fluctuation	1	1	1	4	5	0	0
Weight abnormal	0	0	0	1	1	0	0
Insulin-like growth factor decreased	0	0	0	1	1	0	0
Hepatic enzyme increased	0	0	1	2	2	0	0
Injury, poisoning and procedural complications	**1**	**4**	**51**	**175**	**179**	**0**	**0**
Accidental overdose	0	0	1	2	2	0	0
Fall	0	0	0	1	1	0	0
Inappropriate schedule of drug administration	0	0	0	4	4	0	0
Intentional overdose	0	0	1	4	4	0	0
Overdose	0	1	0	5	6	0	0
Wrong drug administered	0	0	0	1	1	0	0
Contusion	0	0	0	1	1	0	0
Prescribed overdose	0	0	1	3	3	0	0
Off label use	0	0	31	104	104	0	0

Number of Adverse Reactions by Preferred Term from Post-Marketing Sources - Xultophy

SOC/PT	Spontaneous, including competent authorities (worldwide) and literature					Non-interventional post-marketing sources and reports from other solicited sources	
	Serious		Non-Serious		Total	Serious	
	Period	Cumulative	Period	Cumulative	All Cumulative	Period	Cumulative
Underdose	0	0	2	2	2	0	0
Abdominal injury	0	1	0	0	1	0	0
Drug prescribing error	0	0	1	6	6	0	0
Incorrect route of drug administration	0	0	1	1	1	0	0
Incorrect drug administration duration	0	0	2	3	3	0	0
Drug dispensing error	0	0	0	2	2	0	0
Incorrect dose administered	0	0	1	5	5	0	0
Extra dose administered	0	0	2	3	3	0	0
Incorrect dose administered by device	0	0	0	1	1	0	0
Product label confusion	0	0	0	1	1	0	0
Toxicity to various agents	0	1	0	0	1	0	0
Intercepted drug prescribing error	0	0	1	1	1	0	0
Exposure during pregnancy	0	0	0	1	1	0	0
Lack of injection site rotation	0	0	1	1	1	0	0
Drug titration error	0	0	0	3	3	0	0
Expired product administered	0	0	0	1	1	0	0
Intentional product misuse	0	0	0	1	1	0	0
Drug dose titration not performed	0	0	1	3	3	0	0
Intentional product use issue	0	0	1	1	1	0	0
Product use issue	0	0	0	3	3	0	0
Product use in unapproved indication	0	0	0	2	2	0	0
Wrong technique in product usage process	0	0	3	4	4	0	0

Number of Adverse Reactions by Preferred Term from Post-Marketing Sources - Xultophy

SOC/PT	Spontaneous, including competent authorities (worldwide) and literature					Non-interventional post-marketing sources and reports from other solicited sources	
	Serious		Non-Serious		Total	Serious	
	Period	Cumulative	Period	Cumulative	All Cumulative	Period	Cumulative
Wrong technique in device usage process	0	0	0	1	1	0	0
Contraindicated product administered	0	0	0	1	1	0	0
Product storage error	1	1	1	3	4	0	0
Surgical and medical procedures	**1**	**2**	**0**	**0**	**2**	**0**	**1**
Hospitalisation	0	0	0	0	0	0	1
Intervertebral disc operation	1	1	0	0	1	0	0
Therapy change	0	1	0	0	1	0	0
Social circumstances	**0**	**0**	**1**	**1**	**1**	**0**	**0**
Treatment noncompliance	0	0	1	1	1	0	0
Product issues	**0**	**0**	**8**	**16**	**16**	**0**	**0**
Device breakage	0	0	1	1	1	0	0
Device leakage	0	0	2	3	3	0	0
Device failure	0	0	0	1	1	0	0
Device malfunction	0	0	1	2	2	0	0
Product odour abnormal	0	0	1	2	2	0	0
Product quality issue	0	0	1	3	3	0	0
Device issue	0	0	1	2	2	0	0
Device defective	0	0	1	1	1	0	0
Product supply issue	0	0	0	1	1	0	0
Total	**53**	**129**	**285**	**870**	**999**	**1**	**2**

Note: The table includes all AEs reported from spontaneous sources and SARs from non-interventional studies.

Number of Adverse Reactions by Preferred Term from Post-Marketing Sources - Xultophy

Report Generation Criteria

Report based on Argus Insight Frozen Case Series **20180403_Cumulative_AllProducts**
Product abbreviation(s): **IDEGL**
Product alias(es): **Insulin degludec liraglutide B5 , Insulin degludec liraglutide FlexPen , Insulin degludec liraglutide PDS290 , Insulin degludec liraglutide Penfill , Insulin degludec liraglutide V2**
Country: **All**
Reporting period date range: **01-Oct-2017** through **31-Mar-2018**
Split tables per indication: **No**
Report generated on **05-Apr-2018 07:04:32**
MedDRA version: **20.1**
SOC: system organ class
PT: preferred term

ゾルトファイ配合注フレックスタッチ

2.7.4.7 付録
5. 4183 試験及び 4184 試験における過量投与及び急性胆石症に関連する有害事象

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目次

ページ

2.7.4.7.5-1 過量投与に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....3

2.7.4.7.5-2 過量投与に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....3

2.7.4.7.5-3 胆石症に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験）.....4

2.7.4.7.5-4 胆石症に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験）.....4

2.7.4.7.5-5 過量投与及び胆石症に関連する有害事象の検索に用いた用語.....5

2.7.4.7 付録 5

2.7.4.7.5-1 過量投与に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	275				271				273				819			
PYE (years)	268.00				261.81				271.84				801.65			
Events	2	(0.7)	2	0.75	1	(0.4)	1	0.38	2	(0.7)	2	0.74	5	(0.6)	5	0.62
Injury, poisoning and procedural complications	2	(0.7)	2	0.75	1	(0.4)	1	0.38	1	(0.4)	1	0.37	4	(0.5)	4	0.50
Accidental overdose	1	(0.4)	1	0.37	1	(0.4)	1	0.38	1	(0.4)	1	0.37	3	(0.4)	3	0.37
Overdose	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
Psychiatric disorders	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
Suicide attempt	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

nn9068/nn9068-exploratory/lsueot011_20180717_er
17JUL2018:14:00:14 - t_sum_oae_soc_4183.sas/t_sum_oae_soc_4183.txt

2.7.4.7.5-2 過量投与に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

There is no data for this Table

nn9068/nn9068-exploratory/lsueot011_20180717_er
17JUL2018:14:00:24 - t_sum_oae_soc_4184.sas/t_sum_oae_soc_4184.txt

2.7.4.7.5-3 胆石症に関連する有害事象（器官別大分類及び基本語別）－SAS（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	275				271				273				819			
PYE (years)	268.00				261.81				271.84				801.65			
Events	3	(1.1)	4	1.49	3	(1.1)	3	1.15	3	(1.1)	4	1.47	9	(1.1)	11	1.37
Hepatobiliary disorders	3	(1.1)	4	1.49	3	(1.1)	3	1.15	3	(1.1)	4	1.47	9	(1.1)	11	1.37
Cholelithiasis	3	(1.1)	3	1.12	3	(1.1)	3	1.15	3	(1.1)	3	1.10	9	(1.1)	9	1.12
Cholecystitis	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
Cholecystitis acute	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

nn9068/nn9068-exploratory/lsueot011_20180717_er
17JUL2018:13:57:07 - t_sum_gae_soc_4183.sas/t_sum_gae_soc_4183.txt

2.7.4.7.5-4 胆石症に関連する有害事象（器官別大分類及び基本語別）－SAS（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	105				105				210			
PYE (years)	54.28				52.27				106.54			
Events	0				2	(1.9)	2	3.83	2	(1.0)	2	1.88
Hepatobiliary disorders	0				2	(1.9)	2	3.83	2	(1.0)	2	1.88
Cholecystitis acute	0				1	(1.0)	1	1.91	1	(0.5)	1	0.94
Cholelithiasis	0				1	(1.0)	1	1.91	1	(0.5)	1	0.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events,
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100),
PYE: Patient years of exposure (1 PYE = 365.25 days),
MedDRA version 20.0

nn9068/nn9068-exploratory/lsueot011_20180717_er
17JUL2018:13:57:16 - t_sum_gae_soc_4184.sas/t_sum_gae_soc_4184.txt

2.7.4.7.5-5 過量投与及び胆石症に関連する有害事象の検索に用いた用語

Adverse Event Class	Preferred Term
Gallstone disease	AIDS cholangiopathy
	Abnormal faeces
	Ampulla of Vater stenosis
	Bile culture positive
	Bile duct necrosis
	Bile duct obstruction
	Bile duct pressure increased
	Bile duct stenosis
	Bile duct stenosis traumatic
	Bile duct stent insertion
	Bile duct stent removal
	Bile duct stone
	Bile output abnormal
	Bile output decreased
	Bile output increased
	Biliary abscess
	Biliary anastomosis
	Biliary anastomosis complication
	Biliary ascites
	Biliary cast syndrome
	Biliary cirrhosis
	Biliary cirrhosis primary
	Biliary colic
	Biliary dilatation
	Biliary dyskinesia
	Biliary dyspepsia
	Biliary fibrosis
	Biliary fistula
	Biliary fistula repair
	Biliary ischaemia
	Biliary sepsis
	Biliary sphincterotomy
	Biliary tract dilation procedure

Terms used for search for adverse events of gallstone disease and overdose

Adverse Event Class	Preferred Term
Gallstone disease	Biliary tract disorder
	Biliary tract infection
	Biliary tract operation
	Bilirubin conjugated abnormal
	Bilirubin conjugated increased
	Bilirubin excretion disorder
	Bilirubin urine present
	Bilirubinuria
	Biloma
	Biloma rupture
	Biopsy bile duct abnormal
	Biopsy gallbladder abnormal
	Blood alkaline phosphatase abnormal
	Blood alkaline phosphatase increased
	Blood bilirubin abnormal
	Blood bilirubin increased
	Blood bilirubin unconjugated increased
	Cholangiectasis acquired
	Cholangiogram abnormal
	Cholangiolitis
	Cholangiostomy
	Cholangitis
	Cholangitis acute
	Cholangitis chronic
	Cholangitis infective
	Cholangitis sclerosing
	Cholecystectomy
	Cholecystitis
	Cholecystitis acute
	Cholecystitis chronic
	Cholecystitis infective
	Cholecystocholangitis
	Cholecystoenterostomy

MedDRA version 20.0

Terms used for search for adverse events of gallstone disease and overdose

Adverse Event Class	Preferred Term
Gallstone disease	Cholecystogram intravenous abnormal
	Cholecystogram oral abnormal
	Cholecystostomy
	Choledochectomy
	Choledochoenterostomy
	Choledocholithotomy
	Choledochostomy
	Choledochotomy
	Cholelithiasis
	Cholelithiasis migration
	Cholelithiasis obstructive
	Cholelithotomy
	Cholelithotripsy
	Cholestasis
	Cholestasis of pregnancy
	Deficiency of bile secretion
	Dilatation intrahepatic duct acquired
	Emphysematous cholecystitis
	Endoscopic retrograde cholangiopancreatography abnormal
	Endoscopy biliary tract abnormal
	Faeces pale
	Gallbladder abscess
	Gallbladder cholesterolosis
	Gallbladder disorder
	Gallbladder empyema
	Gallbladder enlargement
	Gallbladder fibrosis
	Gallbladder fistula
	Gallbladder fistula repair
	Gallbladder injury
	Gallbladder mucocoele
	Gallbladder necrosis
	Gallbladder non-functioning

MedDRA version 20.0

Terms used for search for adverse events of gallstone disease and overdose

Adverse Event Class	Preferred Term
Gallstone disease	Gallbladder obstruction
	Gallbladder oedema
	Gallbladder operation
	Gallbladder pain
	Gallbladder palpable
	Gallbladder perforation
	Gallbladder varices
	Gallbladder volvulus
	Gallstone ileus
	Haemobilia
	Hepatitis cholestatic
	Hepatobiliary disease
	Hepatobiliary infection
	Hepatolithectomy
	Hydrocholecystis
	Hyperbilirubinaemia
	Hyperplastic cholecystopathy
	Jaundice
	Jaundice cholestatic
	Jaundice extrahepatic obstructive
	Lemmel's syndrome
	Limy bile syndrome
	Pancreatobiliary sphincterotomy
	Parenteral nutrition associated liver disease
	Perforation bile duct
	Porcelain gallbladder
	Post cholecystectomy syndrome
	Post procedural bile leak
	Reynold's syndrome
	Sphincter of Oddi dysfunction
	Ultrasound biliary tract abnormal
	Urine bilirubin increased
	Urobilinogen urine decreased

MedDRA version 20.0

Terms used for search for adverse events of gallstone disease and overdose

Adverse Event Class	Preferred Term
Gallstone disease	Vanishing bile duct syndrome
	X-ray hepatobiliary abnormal
Overdose	Accidental overdose
	Completed suicide
	Intentional overdose
	Overdose
	Prescribed overdose
	Radiation overdose
	Suicide attempt

ゾルトファイ配合注フレックスタッチ

2.7.5 参考文献

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2.7.5　参考文献

参考文献は、Module 2.5、Module 2.7.1、Module 2.7.2、Module 2.7.3 及び Module 2.7.4 の参考文献の項にそれぞれ示した。

ゾルトファイ配合注フレックスタッチ

2.7.6 個々の試験のまとめ

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目次

	Page
目次	2
2.7.6.1 NN9068-3632	3
2.7.6.2 NN9068-3871	9
2.7.6.3 NN9068-4026	14
2.7.6.4 NN9068-4183	18
2.7.6.5 NN9068-4184	90
2.7.6.6 NN9068-3697	124
2.7.6.7 NN9068-3697-extension	134
2.7.6.8 NN9068-3912	145
2.7.6.9 NN9068-3851	154
2.7.6.10 NN9068-3951	162
2.7.6.11 NN9068-3952	171
2.7.6.12 NN9068-4119	178
2.7.6.13 NN9068-4056	186
2.7.6.14 NN9068-4185	194
2.7.6.15 NN9068-4229	203
2.7.6.16 NN2211-3925	214

2.7.6.1 NN9068-3632

2.7.6.1.1 臨床試験概要

Trial Registration ID-number： NCT00983021	EudraCT number（欧州のみ）：2009-011269-95
治験の標題： 健康被験者を対象とした NN9068 の安全性、忍容性、薬物動態及び薬力学的作用を NN1250 及び NN2211 と比較検討する試験	
治験責任医師名： Dr. [redacted]	
治験実施施設： [redacted] Germany	
公表文献（引用文献）： 本治験総括報告書作成時点でなし	
治験期間： 開始日：2009 年 9 月 1 日 終了日：2009 年 12 月 21 日	**開発のフェーズ**： 第 1 相
目的： 主要目的： • インスリン デグルデク／リラグルチド（IDegLira）の安全性及び忍容性を、リラグルチド及びインスリン デグルデク（IDeg）の同時分割注射（以下、リラグルチド+IDeg同時分割注射）、リラグルチド単剤注射及びIDegの単剤注射と比較検討する。 主な副次的目的： • リラグルチド及びIDegの$AUC_{0-\infty,SD}$を指標として、IDegLiraと、それに対応するリラグルチド+IDeg同時分割注射との相対的バイオアベイラビリティを検討する。 • リラグルチド及びIDegの$AUC_{0-\infty,SD}$を指標として、IDegLiraと、それに対応するリラグルチド単剤注射及びIDeg単剤注射との相対的バイオアベイラビリティを検討する。 その他の副次的目的： • 薬物動態特性について、IDegLiraとリラグルチド+IDeg同時分割注射との間、ならびにIDegLiraとリラグルチド単剤注射及びIDeg単剤注射との間で比較検討する。 • グルコースクランプ施行下での薬力学的作用〔グルコース注入速度（GIR）〕について、IDegLiraとリラグルチド+IDeg同時分割注射との間、ならびにIDegLiraとリラグルチド単剤注射及びIDeg単剤注射との間で探索的検討を行う。	
治験方法： 本試験は、健康男性被験者を対象とした、1 施設、単回投与、無作為割り付け、二重盲検、ダブルダミー、4 期クロスオーバー試験であり、グルコースクランプ施行下で、リラグルチド+IDeg 同時分割注射、IDeg＋プラセボ（IDeg 単剤注射）及びリラグルチド＋プラセボ（リラグルチド単剤注射）を対照として、IDeg 及びリラグルチドの配合剤（IDegLira）の単回投与時の安全性及び忍容性について検討した。また、本試験では、IDegLira とリラグルチド+IDeg 同時分割注射との間、ならびに IDegLira とそれに対応する IDeg 単剤注射及びリラグルチド単剤注射との相対的バイオアベイラビリティを検討するよう計画された。 本試験は 6 回の来院により構成された〔適格性を評価するスクリーニング来院（来院 1、初回投与前 2～28 日）、24 時間グルコースクランプを実施する 4 回の院内投与来院（来院 2～5、各来院の間隔は 7～15 日）及び投与後 96 時間まで追加の採血を行う来院〕。安全性評価のための事後調査来院（来院 6、最終投与後 4～14 日）は、すべての被験者が最終投与後の来院 5 で実施した（治験実施計画書で許容されてい	

た）。当該来院では凝固パラメータ及び抗体の採血も行った。すべての被験者は各投与来院日に計 4 回の治験薬の投与〔IDegLira＋プラセボ、IDeg＋プラセボ、リラグルチド＋プラセボ、リラグルチド+IDeg 同時分割注射を無作為割り付けされた順序でそれぞれ実施〕を受けた。各投与来院日に 2 種類の製剤を投与した。
計画及び解析された被験者数： 本試験では計 46 例の被験者がスクリーニングを受けた。無作為割り付けされた 24 例を安全性解析対象集団（SAS）及び最大の解析対象集団（FAS）に含めた。24 例すべての被験者が試験を完了した。
診断及び主要な組入れ基準： 年齢 18 歳以上 55 歳以下の男性健康被験者。BMI（kg/m^2）が 18.0 以上 27.0 以下の被験者。体重 60 kg 以上 90 kg 以下の被験者。空腹時血糖値が 6.1 mmol/L（110 mg/dL）以下の被験者。
被験薬、用量及び投与方法、ロット番号： • NN9068（IDegLira）：IDeg 17単位=100 nmol（600 nmol/mL）＋リラグルチド0.6 mg=160 nmol（960 nmol/mL）、ペン型注入器（ペンフィル®、3 mL）として提供された。ロット番号：XLDP015 • NN2211（リラグルチド）：リラグルチド0.6 mg=160 nmol（960 nmol/mL）、ペン型注入器（ペンフィル®、3 mL）として提供された。ロット番号：VQ503 16 • NN1250（IDeg）：IDeg 17単位=100 nmol（600 nmol/mL）、ペン型注入器（ペンフィル®、3 mL）として提供された。ロット番号：VCQ00 13 すべての治験薬は皮下投与した。
投与期間： 治験薬は 4 つの投与日にそれぞれ投与した。
対照薬、用量及び投与方法、ロット番号： プラセボ、ペン型注入器（ペンフィル®、3 mL）として提供され、皮下投与した。ロット番号：XLDPOO6
評価基準：**有効性** <u>薬物動態及び薬力学的作用</u> • 投与後72時間のリラグルチド濃度－時間推移曲線 • 投与後96時間のIDeg濃度－時間推移曲線 • 投与後24時間のGIR
評価基準：**安全性** プライマリーエンドポイントは以下の安全性及び忍容性であった： • 有害事象 • 注射部位の局所忍容性 • グルコースクランプ後の低血糖〔米国糖尿病学会（ADA）の分類による低血糖及びノボ ノルディスク社（NN）の定義による重大でない低血糖〕 • 臨床検査項目（安全性評価のための血糖値、血液学的検査、血液生化学的検査、尿検査、カルシトニン） • 臨床パラメータ（バイタルサイン、心電図、身体所見） その他の安全性エンドポイント〔来院 2（投与前）及び来院 5（最終投与後）に評価〕は以下のとおりであった： • IDeg特異抗体 • リラグルチド特異抗体

統計手法：

安全性エンドポイントの統計手法

安全性エンドポイントについては投与法ごとに要約した。正式な統計的仮説検定は計画／実施しなかった。

- 試験期間中に発現したすべての有害事象について、投与法別、重症度別、治験薬との因果関係別にMedical Dictionary for Regulatory Activities（MedDRA）の器官別大分類及び基本語ごとに要約した。
- 試験期間中の注射部位反応については一覧表を作成した。
- 試験期間中の低血糖は、ADA及びNNの分類を用いて投与法別及びカテゴリー別に要約した。
- すべての臨床検査項目、バイタルサイン及び心電図は、投与法別及び来院別に要約した。さらに、凝固パラメータについてのみ、来院1から来院5までの変化量も要約した。相当数のカルシトニン検体が定量下限値（LLOQ）未満であることが予想され、LLOQ未満の検体はLLOQ/2として取り扱った。カルシトニンは以下のカテゴリーを用いて要約した：
  - LLOQ未満
  - LLOQ超、基準範囲の上限（UNR）以下
  - UNR超、1.5×UNR以下
  - 1.5×UNR超

薬物動態エンドポイントの統計手法

薬物動態エンドポイントは、IDegLira＋プラセボ、IDeg＋プラセボ、リラグルチド＋プラセボ、リラグルチド+IDeg 同時分割注射における、投与後 72 時間のリラグルチド濃度－時間推移曲線及び投与後 96 時間 IDeg 濃度－時間推移曲線から算出した。

主な薬物動態のセカンダリーエンドポイント

- $AUC_{lira,\ 0\text{-}\infty,\ SD}$：投与後0（投与時点）～無限大時間におけるリラグルチド濃度推移曲線下面積
- $AUC_{IDeg,\ 0\text{-}\infty,\ SD}$：投与後0（投与時点）～無限大時間におけるIDeg濃度推移曲線下面積

その他の薬物動態のセカンダリーエンドポイント

- $C_{max,\ lira,\ SD}$：最高血中リラグルチド濃度
- $C_{max,\ IDeg,\ SD}$：最高血中IDeg濃度
- $AUC_{lira,\ 0\text{-}24h,\ SD}$：投与後0（投与時点）～24時間におけるリラグルチド濃度推移曲線下面積
- $AUC_{IDeg,\ 0\text{-}24h,\ SD}$：投与後0（投与時点）～24時間におけるIDeg濃度推移曲線下面積
- $AUC_{lira,\ 0\text{-}72h,\ SD}$：投与後0（投与時点）～72時間におけるリラグルチド濃度推移曲線下面積
- $AUC_{IDeg,\ 0\text{-}96h,\ SD}$：投与後0（投与時点）～96時間におけるIDeg濃度推移曲線下面積
- $t_{max,\ lira,\ SD}$：最高血中リラグルチド濃度到達時間
- $t_{max,\ IDeg,\ SD}$：最高血中IDeg濃度到達時間
- $t_{½,\ lira,\ SD}$：リラグルチドの終末相の半減期
- $t_{½,\ IDeg,\ SD}$：IDegの終末相の半減期
- $\lambda_{z,\ lira,\ SD}$：リラグルチドの終末相の消失速度定数
- $\lambda_{z,\ IDeg,\ SD}$：IDegの終末相の消失速度定数
- $CL/F_{lira,\ SD}$：リラグルチド皮下投与後の見かけのクリアランス
- $CL/F_{IDeg,\ SD}$：IDeg皮下投与後の見かけのクリアランス
- $V_z/F_{lira,\ SD}$：終末相の速度定数を用いたリラグルチドの見かけの分布容積
- $V_z/F_{IDeg,\ SD}$：終末相の速度定数を用いたIDegの見かけの分布容積
- $MRT_{lira,\ SD}$：リラグルチドの平均滞留時間
- $MRT_{IDeg,\ SD}$：IDegの平均滞留時間

薬物動態エンドポイントの解析

薬物動態エンドポイントについて、リラグルチド及び IDeg の濃度－時間推移データはノンコンパートメントモデルを用いて算出した。投与法の変数は 3 水準とした（IDegLira、リラグルチド+IDeg 同時分割注射、及び IDeg 単剤注射又はリラグルチド単剤注射）。$AUC_{lira,\ 0\text{-}\infty,\ SD}$、$AUC_{IDeg,0\text{-}\infty,\ SD}$、$C_{max,\ lira,\ SD}$及び$C_{max,\ IDeg,\ SD}$は対数変換し、投与法及び時期を固定効果、被験者を変量効果とし、誤差項に正規性を仮定した正

規線形混合モデルを用いて解析した。投与法間の差の推定値をもとのスケールに逆変換し、投与法間の比を95%信頼区間とともに示した。さらに、$AUC_{0-\infty,SD}$及び$C_{max,SD}$については、IDeg及びリラグルチドのいずれも、投与法間の比の推定値を90%信頼区間とともに示した。

リラグルチドの薬物動態エンドポイントについて、以下の投与法間の比を推定した：

- IDegLiraの一部として投与した時のリラグルチドと、リラグルチド単剤注射時のリラグルチド
- IDegLiraの一部として投与した時のリラグルチドと、リラグルチド+IDeg同時分割注射時のリラグルチド
- リラグルチド+IDeg同時分割注射時のリラグルチドと、リラグルチド単剤注射時のリラグルチド

IDegの薬物動態エンドポイントについて、以下の投与法間の比を推定した：

- IDegLiraの一部として投与した時のIDegと、IDeg単剤注射時のIDeg
- IDegLiraの一部として投与した時のIDegと、リラグルチド+IDeg同時分割注射時のIDeg
- リラグルチド+IDeg同時分割注射時のIDegと、IDeg単剤注射時のIDeg

IDegLiraの一部として投与した時とリラグルチド単剤注射時における、$AUC_{lira,\ 0-\infty,\ SD}$及び$C_{max,lira,\ 0-\infty,\ SD}$の比較は、リラグルチドの薬物動態エンドポイントにおいて主に興味のある比較であった。また、IDegLiraの一部として投与した時とIDeg単剤注射時における$AUC_{IDeg,\ 0-\infty,\ SD}$及び$C_{max,IDeg,\ 0-\infty,\ SD}$の比較は、IDegの薬物動態エンドポイントにおいて主に興味のある比較であった。その他のIDeg及びリラグルチドの薬物動態エンドポイントは記述統計量を用いて評価した。

<u>薬力学的作用エンドポイントの統計手法</u>

IDegLira、リラグルチド及びIDegの薬力学的作用エンドポイント（投与後0～24時間の評価）：

- GIR_{max},：最大GIR
- $tGIR_{max}$,：GIR_{max}到達時間
- $AUC_{GIR,\ 0-24h,\ SD}$：投与後0～24時間におけるGIR推移曲線下面積

薬力学的作用エンドポイントの解析

薬力学的作用エンドポイントの$AUC_{GIR,0-24,SD}$はスムージングされたGIR推移曲線から算出し、投与法及び時期を固定効果、被験者を変量効果として含めた共分散分析（ANCOVA）モデルを用いて解析した。4つの投与法間に差がないという仮説を検定した。IDegLiraについて、以下の投与法間の比を推定した：

- IDegLiraと、リラグルチド単剤注射
- IDegLiraと、IDeg単剤注射
- IDegLiraと、リラグルチド+IDeg同時分割注射

同様の解析を$GIR_{max,SD}$について行った。$GIR_{max,SD}$到達時間（$tGIR_{max,SD}$）は記述統計量を用いて評価した。グルコースクランプ施行下における血糖値及びC-ペプチドを、記述統計量を用いて要約した。

被験者背景：

計46例の健康男性被験者がスクリーニングを受け、そのうち24例が無作為割り付けされて試験期間中に治験薬の投与を受けた。24例すべての被験者が試験を完了した。無作為割り付けされたすべての被験者において、スクリーニング（来院1）時の平均年齢は36歳（範囲：22～55歳）、平均体重は79.6 kg（範囲：63.4～90.0 kg）、平均BMI（kg/m^2）は24.7（範囲：20.3～26.9）であった。3例の被験者でスクリーニング時に合併症が報告された（高コレステロール血症、高脂血症、僧帽弁閉鎖不全症）。

有効性の結果：

- リラグルチド+IDeg同時分割注射時に対する、IDegLiraの一部として投与した時の、IDegの相対的バイオアベイラビリティ（AUCの比の推定値）は0.98（95%信頼区間：[0.94; 1.03]）であった。
- リラグルチド+IDeg同時分割注射時に対する、IDegLiraの一部として投与した時の、リラグルチドの相対的バイオアベイラビリティ（AUCの比の推定値）は0.89（95%信頼区間：[0.82: 0.98]）であった。
- IDeg単剤注射時に対する、IDegLiraの一部として投与した時の、IDegの相対的バイオアベイラビリティ（AUCの比の推定値）は、1.03（95%信頼区間：[0.98;1.07]）であった。
- リラグルチド単剤注射時に対する、IDegLiraの一部として投与した時の、リラグルチドの相対的バイオアベイラビリティ（AUCの比の推定値）は、0.89（95%信頼区間：[0.81; 0.97]）であった。

- $AUC_{0-\infty,IDeg,SD}$及び$C_{max,IDeg,SD}$は、IDegLiraの一部として投与した時のIDegとIDeg単剤注射時のIDegで同様であった。
- $AUC_{0-\infty,lira,SD}$及び$C_{max,lira,SD}$は、リラグルチド単剤注射時のリラグルチドと比較して、IDegLiraの一部として投与した時のリラグルチドで、統計的に有意に小さかった〔$AUC_{0-\infty,lira,SD}$の比の推定値：0.89（p=0.011）、$C_{max,lira,SD}$の比の推定値：0.77（p=0.0006）〕。
- $GIR_{max,0-24,SD}$及び$AUC_{GIR,0-24,SD}$は、IDeg単剤注射時と比較して、リラグルチドが投与される時（IDegLira、リラグルチド単剤注射、リラグルチド+IDeg同時分割注射）で大きかった。

安全性の結果：

- 試験期間中、計36件の有害事象が報告された。リラグルチド及びIDegの同時分割注射では、他の投与法と比較し、有害事象を報告した被験者がわずかに多かった。最も高頻度に報告された有害事象は頭痛（21件）及び嘔吐（3件）であった。有害事象の大部分は軽度（25件）であった。

すべての有害事象の概要、ならびに治験薬との因果関係が「あり」又は「可能性あり」と判定された有害事象の器官別大分類及び基本語ごとの要約を以下に示す：

治験薬投与下で発現した有害事象の要約 - SAS

	IDeg/Lira		Liraglutide		IDeg		Liraglutide + IDeg	
	N (%)	E	N (%)	E	N (%)	E	N (%)	E
Safety Analysis Set	24		24		24		24	
Adverse Events	6 (25.0)	7	6 (25.0)	7	6 (25.0)	9	11 (45.8)	13
Serious Adverse Events	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Severity								
Mild	4 (16.7)	4	4 (16.7)	5	4 (16.7)	7	8 (33.3)	9
Moderate	3 (12.5)	3	2 (8.3)	2	2 (8.3)	2	4 (16.7)	4
Relation to Treatment								
Possible	5 (20.8)	5	4 (16.7)	4	3 (12.5)	4	6 (25.0)	8
Unlikely	2 (8.3)	2	3 (12.5)	3	4 (16.7)	5	5 (20.8)	5
Adverse Events Withdrawals	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

IDeg: insulin degludec; IDeg/Lira: insulin degludec/liraglutide; N: Number of subjects with adverse events, %: Proportion of subjects having adverse events; E: Number of adverse events

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、治験薬投与下で発現した有害事象 - 器官別大分類及び基本語別 - SAS

	IDeg/Lira			Liraglutide			IDeg			Liraglutide + IDeg		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	24			24			24			24		
Adverse Events	5	(20.8)	5	4	(16.7)	4	3	(12.5)	4	6	(25.0)	8
Nervous System Disorders	5	(20.8)	5	3	(12.5)	3	3	(12.5)	3	6	(25.0)	6
Headache	5	(20.8)	5	3	(12.5)	3	3	(12.5)	3	6	(25.0)	6
Gastrointestinal Disorders							1	(4.2)	1	2	(8.3)	2
Nausea							1	(4.2)	1			
Vomiting										2	(8.3)	2
Investigations				1	(4.2)	1						
Body Temperature Increased				1	(4.2)	1						

IDeg: insulin degludec; IDeg/Lira: insulin degludec/liraglutide; N: Number of subjects with adverse events. %: Proportion of subjects having adverse events; E: Number of adverse events

- 死亡、重篤な有害事象又は中止に至った有害事象は報告されなかった。
- IDeg+リラグルチドの同時分割注射を受けた1例の被験者において、IDegの注射部位で1件の血腫が報告された。
- 試験期間中、ADA分類に基づく症候性低血糖は報告されなかった。NNの定義（血糖値が3.1 mmol/L以下）に基づく重大でない低血糖は2件報告された。
- リラグルチド特異抗体が陽性である検体は来院2又は来院5で認められなかった。来院2から来院5までのIDeg特異抗体価又は交叉抗体価に変化は認められなかった。
- バイタルサイン、心電図、身体所見又は臨床検査所見について、投与法間で違いは認められなかった。

全体の結論：

- 試験期間中、IDegLiraの安全性又は忍容性上の懸念は認められなかった。
- 有害事象の大部分は軽度であり、重篤な有害事象又は中止に至った有害事象は報告されなかった。
- IDegのバイオアベイラビリティは、IDegLiraの一部としてIDegを投与した時と、リラグルチド又はプラセボと同時にIDegを投与した時との間で変化はみられなかった。
- リラグルチドのバイオアベイラビリティは、IDeg又はプラセボと同時にリラグルチドを投与した時と比較して、IDegLiraの一部としてリラグルチドを投与した時で小さくなった。
- IDegLiraの薬力学的作用について、IDegとリラグルチドの効果は、相乗効果ではなく相加効果であると考えられた。

本試験は、ヘルシンキ宣言の精神（2008 年）及び ICH-GCP（1996 年）を遵守して実施された。

ここに提示する結果は、2010 年 7 月 30 日の時点での臨床データベースに基づいている。

2.7.6.2 NN9068-3871

2.7.6.2.1 臨床試験概要

Trial Registration ID-number： NTC01319240	UTN：U1111-1119-2417 EudraCT number：2010-021190-36
治験の標題： 健康被験者を対象としたインスリン デグルデク／リラグルチド（A3）の薬物動態、安全性及び忍容性をインスリン デグルデク及びリラグルチドと比較検討する試験	
治験責任医師名： [redacted] Dr Med, [redacted]	
治験実施施設： 以下の 1 施設において実施された： [redacted] Germany	
公表文献（引用文献）： 本治験総括報告書作成時点でなし	
治験期間： 開始日：2011 年 3 月 18 日 終了日：2011 年 5 月 27 日	**開発のフェーズ**： 第 1 相

目的：

主要目的：

- インスリン デグルデク（IDeg）とリラグルチドのバイオアベイラビリティについて、インスリン デグルデク／リラグルチド（IDegLira）（A3）として投与した場合と、インスリン デグルデク（IDeg）及びリラグルチドを別々に投与した場合との間で比較検討する。

副次的目的：

- 薬物動態特性について、IDegLira（A3）と、IDeg及びリラグルチドを別々に投与した場合との間で比較検討する。
- 安全性及び忍容性について、IDegLira（A3）と、IDeg及びリラグルチドを別々に投与した場合との間で比較検討する。

治験方法：

本試験は、健康男性被験者を対象とした、IDegLira（A3）単回投与後の薬物動態、安全性及び忍容性を検討する、1 施設、単回投与、無作為割り付け、二重盲検、3 期クロスオーバー試験であった。また、本試験では、IDegLira（A3）として投与した場合と、IDeg 及びリラグルチドを別々に投与した場合との間で、IDeg とリラグルチドの相対的バイオアベイラビリティを検討するよう計画された。低血糖の発現を防ぐため、治験薬投与後 24 時間にわたりグルコース注入を行った。

本試験は、各健康男性被験者が実施する 5 回の来院から構成された〔スクリーニング来院（来院 1、初回投与前 2～28 日）、3 回の院内投与来院（来院 2～4）及び事後調査来院（来院 5、最終投与後 7～14 日）〕。

被験者は、6 通りの投与順序〔IDegLira（A3）、IDeg 及びリラグルチドの投与順序〕のうちの 1 つに無作為に割り付けられた。

3 回の各投与来院（来院 2～4）で薬物動態、安全性及び忍容性を評価した。

被験者は治験薬投与後 36 時間（治験責任医師により必要と判断された場合にはさらに長時間）治験実施施設に滞在した。治験薬投与後 24 時間はグルコース注入のため被験者を Biostator に接続した。その後、治験薬投与後 120 時間に採血を行うため被験者は再来院した。来院 2～4 の投与と投与の間に 7～15 日間の wash-out 期間を設けた。

各被験者の試験期間は 23～72 日であった〔2～28 日間のスクリーニング来院、各 4 日間 3 回の院内投与来

院及び最終投与後 7～14 日の安全性評価のための事後調査来院（来院 5）〕。
計画及び解析された被験者数： 本試験では 31 例の被験者がスクリーニングを受けた。無作為割り付けされた 24 例を安全性解析対象集団（SAS）及び最大の解析対象集団（FAS）に含めた。23 例の被験者が試験を完了した。
診断及び主要な組入れ基準： 年齢 18 歳以上 55 歳以下の男性健康被験者。Body Mass Index（BMI）（kg/m^2）が 20.0 以上 27.0 以下の被験者。体重 75 kg 以上 90 kg 以下の被験者。空腹時血糖値が 6.1 mmol/L（110 mg/dL）未満の被験者。
被験薬、用量及び投与方法、ロット番号： IDegLira（IDeg 17単位＋リラグルチド1.0 mg）。ロット番号：YLDP014 IDeg 17単位。ロット番号：XCQ0044 リラグルチド 1.0 mg。ロット番号：YQ50698 すべての治験薬はペン型注入器（ペンフィル®、3 mL）で皮下投与した。
投与期間： 治験薬は 3 回の各投与日に単回投与した。
評価基準：**薬物動態** IDeg とリラグルチドのバイオアベイラビリティについて、IDegLira として投与した場合と、IDeg 及びリラグルチドを別々に投与した場合との間で検討した。 IDeg 及びリラグルチドの薬物動態を評価した。 IDegLira、IDeg 及びリラグルチドの投与を受けた被験者における薬物動態エンドポイントは、投与後 72 時間のリラグルチド濃度－時間推移曲線及び投与後 120 時間の IDeg 濃度－時間推移曲線から算出した。
評価基準：**安全性** 試験期間中に記録した安全性評価は、有害事象、身体所見、併用薬、バイタルサイン、心電図、局所忍容性評価、グルコース注入及び血糖値測定、低血糖ならびに臨床検査の安全性評価項目であった。
統計手法： 以下の 2 つの解析対象集団を定義した： 安全性解析対象集団（SAS）：治験薬を少なくとも 1 回投与されたすべての被験者を含めた。SAS に含まれる被験者は as treated の評価に寄与した。 最大の解析対象集団（FAS）：無作為割り付けされたすべての被験者を含めた。例外的に、被験者を除外することがある。その場合、除外する正当な理由を示し文書化することとした。被験者は as treated の評価に寄与した。 薬物動態エンドポイントの解析は FAS に基づいて行った。安全性エンドポイントの解析は SAS に基づいて行った。 <u>プライマリーエンドポイント</u> 主要目的は、$AUC_{IDeg,\ 0\text{-}\infty,\ SD}$ 及び $AUC_{lira,\ 0\text{-}\infty,\ SD}$ を指標として、IDeg とリラグルチドのバイオアベイラビリティについて、IDegLira（A3）として投与した場合と、IDeg 及びリラグルチドを別々に投与した場合との間で比較検討することであった。 $AUC_{IDeg,\ 0\text{-}\infty,\ SD}$ は、IDegLira（A3）の一部として投与した場合と、IDeg を単独で投与した場合について、モデルによらない標準的なノンコンパートメント法を用い、投与後 120 時間の IDeg 濃度－時間推移曲線から算出した。同様に、$AUC_{lira,\ 0\text{-}\infty,\ SD}$ は、IDegLira（A3）として投与した場合とリラグルチドを単独で投与した場合について、モデルによらない標準的なノンコンパートメント法を用い、投与後 72 時間のリラグルチド濃度－時間推移曲線から算出した。 $AUC_{IDeg,\ 0\text{-}\infty,\ SD}$ 及び $AUC_{lira,\ 0\text{-}\infty,\ SD}$ は、対数変換値に基づく正規線形モデルを用いて解析した。本モデルは製剤、時期及び被験者を固定効果として含めた。製剤間の差の推定値をもとのスケールに逆変換し、製剤間の比を 90%信頼区間とともに示した。 IDeg の薬物動態エンドポイントについては、IDegLira（A3）の一部として投与した場合と、IDeg を投与

した場合の、製剤間の比を推定した。
リラグルチドの薬物動態エンドポイントについては、IDegLira（A3）の一部として投与した場合と、リラグルチドを投与した場合の、製剤間の比を推定した。
セカンダリーエンドポイント
薬物動態のセカンダリーエンドポイント
IDeg における薬物動態のセカンダリーエンドポイント（$AUC_{IDeg, 0\text{-}120h, SD}$、$C_{max, IDeg, SD}$、$t_{max, IDeg, SD}$、$t_{½, IDeg, SD}$、$CL/F_{IDeg}$、$MRT_{IDeg}$）は、IDegLira（A3）及び IDeg の投与後 120 時間の IDeg 濃度－時間推移曲線から算出した。
リラグルチドにおける薬物動態のセカンダリーエンドポイント（$AUC_{Lira, 0\text{-}72h, SD}$、$C_{max, Lira, SD}$、$t_{max, Lira, SD}$、$t_{½, Lira, SD}$、$CL/F_{Lira}$、$MRT_{Lira}$）は、IDegLira（A3）及びリラグルチドの投与後 72 時間のリラグルチド濃度－時間推移曲線から算出した。
IDeg 及びリラグルチドの濃度－時間推移のデータは、ノンコンパートメントモデルを用いて解析した。解析には投与後の実際の測定時間を用いた。
$AUC_{IDeg, 0\text{-}120h, SD}$及び$AUC_{lira, 0\text{-}72h, SD}$は台形法を用いて算出した。
$C_{max, IDeg, SD}$及び$C_{max, lira, SD}$はすべての利用可能な血中濃度の最大値、$t_{max, IDeg, SD}$及び$t_{max, lira, SD}$は対応する血中濃度到達時間からそれぞれ算出した。
$\lambda_{z, IDeg}$及び$\lambda_{z, lira}$は、IDeg 及びリラグルチドの濃度－時間推移曲線の終末相において対数線形回帰を用いてそれぞれ推定した。終末相の半減期である$t_{½, IDeg}$及び$t_{½, lira}$は、$t_{½, IDeg}=\log 2/\lambda_{z, IDeg}$及び$t_{½, lira}=\log 2/\lambda_{z, lira}$としてそれぞれ算出した。
CL/F_{IDeg}及びCL/F_{lira}は、投与量/$AUC_{IDeg, 0\text{-}\infty, SD}$及び投与量/$AUC_{lira, 0\text{-}\infty, SD}$としてそれぞれ算出した。
MRT_{IDeg}（平均滞留時間）は$AUMC_{IDeg\ 0\text{-}\infty, SD}/AUC_{IDeg, 0\text{-}\infty, SD}$として算出した。この分子は$AUMC_{IDeg, 0\text{-}t, SD}+AUMC_{IDeg, t\text{-}\infty, SD}$として算出される、濃度の 1 次モーメント推移曲線下面積である。$AUMC_{IDeg, 0\text{-}t, SD}$は以下のとおり算出している：

$$\frac{1}{2}\sum_{i=2}^{n}(t_i - t_{i-1})\cdot(t_i C_i + t_{i-1}C_{i-1})。$$

また、$AUMC_{IDeg, t\text{-}\infty, SD}$は$\hat{C}(t)\cdot t/\lambda_z + \hat{C}(t)/\lambda_z^2$として算出し、ここでの$\hat{C}(t)$は、対数変換後の IDeg 曲線の線形部から予測される、時間 t（測定可能であった最終時点）における血中濃度である。同様に、MRT_{lira}も$AUMC_{lira\ 0\text{-}\infty, SD}/AUC_{lira, 0\text{-}\infty, SD}$として算出した。
すべての薬物動態エンドポイントは記述統計量を用いて製剤ごとに要約した。さらに、すべての薬物動態エンドポイントについて、一覧表を作成した。一覧表には、最終測定時点から無限大時間における AUC の外挿部分の割合（$AUC_{\%Extrap, IDeg}$及び$AUC_{\%Extrap, lira}$）を含めた。
薬物動態プロファイルの個々及び平均の曲線を製剤ごとにプロットした。薬物動態プロファイルについては、線形及び対数線形のスケールを用いた。個々のプロファイルには、終末相の速度定数（λ_z）の推定に用いた観測値を図示した。
統計解析の結果の提示には最小二乗平均を含めた。統計解析した薬物動態エンドポイントについて、製剤間の差（又は比）の推定値を両側信頼区間とともに示した。エンドポイントを対数変換した場合には、製剤間の差の推定値及び信頼区間をもとのスケールに逆変換し、製剤間の比と信頼区間を示した。また、データが非正規性を場合にはノンパラメトリック法又はロバスト法を適用した。
$C_{max, IDeg, SD}$及び$C_{max, lira, SD}$は、対数変換値に基づく正規線形モデルを用いて解析した。本モデルには、製剤、時期及び被験者を固定効果として含めた。製剤間の差の推定値をもとのスケールに逆変換し、90%信頼区間とともに比として示した。
IDeg の薬物動態エンドポイントについては、IDegLira（A3）の一部として投与した場合と、IDeg を投与した場合の、製剤間の比を推定した。
リラグルチドの薬物動態エンドポイントについては、IDegLira（A3）の一部として投与した場合と、IDeg を投与した場合の、製剤間の比を推定した。

その他の IDeg 及びリラグルチドの薬物動態エンドポイントは記述統計量を示した。

安全性のセカンダリーエンドポイント

すべての安全性エンドポイントは製剤ごとに要約して一覧表を作成した。安全性エンドポイントのすべての図表及び一覧表に SAS を用いた。正式な統計的仮説検定は実施せず、欠測値を補完する手法も適用しなかった。

事後解析

薬物動態解析として、IDegLira 投与後に IDeg 濃度が顕著に高かった 1 例の被験者（被験者 13）を除いた感度分析を行った。

さらに、顕著に大きい値／外れ値〔定量下限値（LLOQ）を下回る特定の値〕を除いた感度分析も行った。

被験者 15 は投与前の値が IDeg の LLOQ を超えていたため、当該プロファイルにおいて、全ての投与後の値から投与前値を引いて感度分析を行った。

被験者背景：

24 例の白人健康男性が本試験に登録された。スクリーニング（来院 1）時の平均年齢は 38 歳（範囲：25～53 歳）、平均身長は 180.7 cm（範囲：171.0～191.0 cm）、平均体重は 82.6 kg（範囲：75.4～89.8 kg）、平均 BMI は 25.3 kg/m^2（範囲：22.7～27.0 kg/m^2）であった。2 例の被験者でスクリーニング時に合併症が報告された（両被験者ともにジルベール症候群）。

薬物動態の結果：

- IDegの投与に対する、IDegLiraの一部として投与した場合の、IDegの相対的バイオアベイラビリティ（$AUC_{0-\infty}$比）の推定値は1.11（90%信頼区間：[1.06; 1.16]）であった。
- リラグルチドの投与に対する、IDegLiraの一部として投与した場合の、リラグルチドの相対的バイオアベイラビリティ（$AUC_{0-\infty}$比）の推定値は0.86（90%信頼区間：[0.79; 0.94]）であった。
- $C_{max,IDeg,SD}$は、IDegLiraの一部として投与した場合とIDegの投与との間で同様であった〔製剤間の比：1.03（90%信頼区間：[0.93; 1.13]）〕。
- $C_{max,lira,SD}$は、リラグルチドの投与と比較して、IDegLiraの一部として投与した場合で低かった〔製剤間の比：0.76（90%信頼区間：[0.66; 0.88]）〕。

安全性の結果：

- 試験期間中に21件の有害事象が報告された。最も高頻度に報告された有害事象は頭痛（10件）及び嘔吐（4件）であった。有害事象の大部分（12件）は軽度であった。
- 死亡、特に注目すべき医学的事象、重篤な有害事象又は試験の中止に至った有害事象は報告されなかった。
- 試験期間中に報告されたADA分類に基づく低血糖は、無症候性低血糖のみであった。ノボ ノルディスク社の分類に基づく重大でない低血糖はリラグルチドによる投与を受けた被験者で1件認められた。
- 臨床的に問題となる所見は認められず、バイタルサイン、身体所見、心電図又は臨床検査項目について、製剤間で違いはみられなかった。
- 注射部位反応が認められた被験者はいなかった。

表 1：治験薬投与下で発現したすべての有害事象の要約 - SAS

	insulin degludec/ liraglutide(A3)		insulin degludec		liraglutide	
	N (%)	E	N (%)	E	N (%)	E
Subjects	23		24		24	
All Adverse Events	4 (17.4)	5	6 (25.0)	7	8 (33.3)	9
SAE	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Deaths	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Non-serious AEs	4 (17.4)	5	6 (25.0)	7	8 (33.3)	9
MESI	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
AEs by Severity						
Mild	4 (17.4)	4	4 (16.7)	4	4 (16.7)	4
Moderate	1 (4.3)	1	3 (12.5)	3	4 (16.7)	5
AEs by Relationship						
Probable	1 (4.3)	1	1 (4.2)	1	1 (4.2)	1
Possible	2 (8.7)	2	4 (16.7)	4	6 (25.0)	7
Unlikely	1 (4.3)	2	2 (8.3)	2	1 (4.2)	1
AEs leading to Withdrawal	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

N: Number of subjects with adverse events
%: Proportion of subjects having adverse events
E: Number of adverse events

全体の結論：

- IDegのバイオアベイラビリティは、IDegLiraの一部として投与した場合とIDegを投与した場合で同様であった。
- リラグルチドのバイオアベイラビリティは、リラグルチドを投与した場合と比較して、IDegLiraの一部として投与した場合に減少した。
- IDegの$AUC_{0-\infty,SD}$及び$C_{max,SD}$は、IDegLiraの一部として投与した場合とIDegを投与した場合で同様であった。一方、リラグルチドの$AUC_{0-\infty,SD}$及び$C_{max,SD}$は、リラグルチドの投与と比較して、IDegLiraの一部として投与した場合に低かった。
- 試験期間中、IDegLiraの安全性又は忍容性上の懸念は認められなかった。

本試験は、ヘルシンキ宣言の精神（2008）及びICH-GCP（1996）を遵守して実施された。

ここに提示する結果は、2011年9月30日の時点での臨床データベースに基づいている。

2.7.6.3 NN9068-4026

2.7.6.3.1 臨床試験概要

Trial Registration ID-number： NCT01916174	UTN：U1111-1137-3809 EudraCT number：2012-005468-93
治験の標題： 健康被験者を対象としたインスリン デグルデク／リラグルチドの 2 製剤（B5 及び V2）の生物学的同等性試験	
治験責任医師名： Dr. med. [redacted]	
治験実施施設： [redacted] Germany	
公表文献（引用文献）： 本治験総括報告書作成時点でなし	
治験期間： 開始日：2013 年 8 月 5 日 終了日：2013 年 11 月 4 日	**開発のフェーズ**： 第 1 相
Cut-off date： ここに提示する結果は、2014 年 1 月 3 日の時点での臨床データベースに基づいている。	
目的： 主要目的： • インスリン デグルデク／リラグルチド（IDegLira）の2製剤（B5及びV2）の生物学的同等性を検討する。 副次的目的： • インスリン デグルデク（IDeg）及びリラグルチドについて、IDegLiraの2製剤（B5及びV2）の薬物動態特性を比較検討する。 • IDegLiraの2製剤（B5及びV2）単回投与後の安全性及び忍容性を評価する。	
治験方法： 本試験は、健康被験者を対象とした、1 施設、無作為割り付け、二重盲検、単回投与、2 期クロスオーバー試験であった。本試験では IDegLira（B5 及び V2）の生物学的同等性の比較ならびに IDegLira の 2 製剤単回投与後の薬物動態、安全性及び忍容性の検討が計画された。 本試験期間は 4 回の来院により構成された〔スクリーニング来院（来院 1、初回投与前 2～28 日）、2 回の投与来院（来院 2～3、2 回の投与来院間に 7～15 日間の wash-out 期間を設けた）及び 1 回の事後調査来院（来院 4）〕。各被験者は、来院 2 において、2 つの投与順序（来院間隔を設けた 2 回の投与来院で、B5 の後に V2 を単回投与、又はその逆の順序の単回投与）のいずれかに無作為に割り付けられた。被験者は、2 回の投与来院に、治験薬投与後 24 時間（治験責任医師により必要と判断された場合にはさらに長時間）治験実施施設に滞在することとした。低血糖の発現を防ぐため、治験薬投与後 24 時間にわたりグルコース注入を行った。IDeg 濃度―時間推移プロファイルは投与後 120 時間、リラグルチド濃度―時間推移プロファイルは投与後 72 時間のものとした。	
計画及び解析された被験者数： 計 50 例の健康被験者の無作為割り付けが計画された。計 64 例がスクリーニングを受け、50 例（男性：32 例、女性：18 例）が無作為割り付けされ治験薬の投与を受けた。計 48 例の被験者が試験を完了した。	

診断及び主要な組入れ基準：

年齢 18 歳以上 55 歳以下の健康被験者（男女）。Body Mass Index（BMI）（kg/m^2）が 18.5 以上 27.0 以下の被験者。体重 60 kg 以上 90 kg 以下の被験者。空腹時血糖値が 6.1 mmol/L 未満の被験者。

主な除外基準は、妊娠した被験者又は避妊法が不適切であった被験者（女性）、スクリーニング前 3 ヵ月以内に 500 mL を超えて血液又は血漿献血を行った被験者、癌の既往を有する又は併発している被験者、治験責任医師が本試験の結果に影響を及ぼす可能性があると判断した、臨床的に問題となる心血管系、呼吸器系、代謝系、腎及び肝、消化器系、内分泌系（糖尿病を含む）、血液系、皮膚系、生殖器系、神経系、精神系の疾患又はその他の臨床的に問題となる疾患を有する被験者、薬物乱用又はアルコール乱用があり、スクリーニング前 2 週間以内に何らかの医薬品（パラセタモール、アセチルサリチル酸、避妊薬及びビタミン剤を除く）を使用した被験者とした。

被験薬、用量及び投与方法、ロット番号：

本試験では IDegLira の 2 製剤を用いた。

Trial Product	Dose	Batch Number
Insulin degludec/liraglutide B5	17 Dose steps (17 units IDeg and 0.61 mg liraglutide)	BW56288
Insulin degludec/liraglutide V2	17 Dose steps (17 units IDeg and 0.61 mg liraglutide)	CW58106

すべての治験薬はノボペン® 4 を使用してカートリッジ（ペンフィル®、3 mL）で皮下投与した。

投与期間：

治験薬は 2 回の各投与日にいずれかの治験薬を単回注射した。

評価基準：薬物動態

薬物動態の評価基準は、IDegLira 投与後の血清中 IDeg 濃度及び血漿中リラグルチド濃度であった。

薬物動態エンドポイントは、投与後 120 時間の IDeg 濃度－時間推移曲線及び投与後 72 時間のリラグルチド濃度－時間推移曲線から算出した。

評価基準：安全性

安全性の評価基準は、有害事象、身体所見、バイタルサイン、局所忍容性評価、血糖値、低血糖、臨床検査、体重及び BMI であった。

統計手法：

検出力の算出

過去の試験（NN9068-3632）のデータを用いて見積もった結果、IDegLira（B5）と IDegLira（V2）との間の比を 1 と仮定した場合、生物学的同等性を示す検出力を 90%に保持するために必要な完了例は 45 例であった。

解析対象集団

50 例すべての被験者を最大の解析対象集団（FAS）及び安全性解析対象集団（SAS）に含めた。薬物動態エンドポイントの解析は FAS に、安全性エンドポイントの解析は SAS に基づき行った。試験を中止した 2 例の被験者は、いずれかの投与来院で評価困難なデータがあったため、薬物動態エンドポイントの解析に部分的に寄与した。

プライマリーエンドポイント

本試験において IDeg 及びリラグルチドの個々の濃度推移プロファイルより算出される 4 つの co-primary エンドポイント：$AUC_{IDeg,0\text{-}tz,SD}$、$C_{max,IDeg,SD}$、$AUC_{Lira,0\text{-}tz,SD}$ 及び $C_{max,Lira,SD}$

これらのエンドポイントは分散分析（ANOVA）を用いて解析した。不等分散性を考慮し、対数変換した値を用いた。各エンドポイントの統計モデルには、製剤、時期、投与順序及び投与順序内の被験者を固定効果として含めた。プライマリーエンドポイントについて同等性を検定するために、2 製剤間の比を推定し、比の 90%信頼区間を算出した。

4 つの co-primary エンドポイントのすべてにおいて 2 製剤間の比の 90%信頼区間が 0.80～1.25 の範囲に完全に含まれた場合、生物学的同等性が示されることとした。
実薬投与量で調整した co-primary エンドポイントの解析を繰り返し行った。盲検解除前に主解析と同様の方法及びモデルを用いて感度分析を行うことを決定した。感度分析では、誤って無作為割り付けされた被験者と、盲検下レビューで study group により妥当でないと判断されたデータポイントを除外した。
セカンダリーエンドポイント
IDeg 及びリラグルチドの個々の濃度プロファイルより算出される薬物動態の主なセカンダリーエンドポイント：$AUC_{IDeg,0-\infty,SD}$、$t_{max,IDeg,SD}$、MRT_{IDeg}、$AUC_{Lira,0-\infty,SD}$、$t_{max,Lira,SD}$ 及び MRT_{Lira}。
$AUC_{IDeg,0-\infty,SD}$ 及び $AUC_{Lira,0-\infty,SD}$ についてはプライマリーエンドポイントと同様の方法を用いて解析したが、その他のすべてのセカンダリーエンドポイントは、記述統計量を用いて IDegLira の 2 製剤間で比較した。
薬物動態に関する追加のセカンダリーエンドポイント
盲検解除前に治験実施計画書に記載されているエンドポイントに加えて算出することが決定されたセカンダリーエンドポイント：外挿した AUC の割合及び外挿した AUC が 20%を超えている被験者数
安全性に関するエンドポイント
治験薬投与下で発現した有害事象、注射部位反応及び治験薬投与下で発現した低血糖の発現件数、ならびに臨床検査項目、バイタルサイン、身体所見、体重、BMI 及び空腹時血糖の変化（量）は、記述統計量を用いて評価した。

被験者背景：
50 例の健康被験者（男性：32 例、女性：18 例）が無作為割り付けされた。被験者の人種は、白人 47 例、黒人又はアフリカ系アメリカ人 1 例及び非インド系アジア人 2 例であった。被験者の平均年齢は 38.9 歳（範囲：18～53 歳）、平均 BMI は 24.0 kg/m^2（範囲：19.5～27.7 kg/m^2）であった。

薬物動態の結果：
- 4つのco-primaryエンドポイントのいずれにおいても、製剤間の比〔IDegLira（V2）/IDegLira（B5）〕の90%信頼区間が0.80～1.25の範囲に完全に含まれたため、IDegLira（V2）及びIDegLira（B5）の生物学的同等性が示された。IDegの製剤間の比は、$AUC_{IDeg,0-tz,SD}$で0.95（90%信頼区間：[0.91 ; 0.98]）、$C_{max,IDeg,SD}$で0.87（90%信頼区間：[0.80 ; 0.94]）であった。リラグルチドの製剤間の比は、$AUC_{Lira,0-tz,SD}$で1.01（90%信頼区間：[0.98 ; 1.04]）、$C_{max,Lira,SD}$で1.00（90%信頼区間：[0.94 ; 1.06]）であった。
- 実投与量で調整した感度分析においても、生物学的同等性が支持される結論に至った。
- セカンダリーエンドポイントについて、IDegLiraの2製剤間に大きな違いはなかった。

安全性の結果：
- 23例において、計47件の有害事象が報告され、最も高頻度に報告された有害事象は頭痛（21件）、嘔吐（7件）及び悪心（6件）であった。重度の有害事象は認められず、すべての被験者が回復した。
- 重篤な有害事象、特に注目すべき医学的事象又は試験の中止に至った有害事象は報告されなかった。
- 注射部位反応は報告されなかった。
- スクリーニング来院から事後調査来院の間に、バイタルサイン、身体所見又は臨床検査項目について、臨床的に問題となる変化は認められなかった。
- 1件の確定低血糖が報告された。報告されたすべての低血糖は、クランプ施行下又はクランプ装置からの切断後1時間以内に発現した。重大な低血糖の報告はなかった。また、夜間低血糖の報告もなかった。

全体の結論： • 4つのco-primaryプライマリーエンドポイントについて、製剤間の比の90%信頼区間が0.80～1.25の範囲に完全に含まれたため、IDegLira（V2）及びIDegLira（B5）の生物学的同等性が示された。 • 薬力学的作用に関するエンドポイントは、IDegLira（B5）とIDegLira（V2）との間で概ね同様であった。 • 本試験において安全性上の懸念は認められなかった。IDegLira（B5）及びIDegLira（V2）の安全性プロファイルは同程度であった。
本試験は、ヘルシンキ宣言の精神、ICH-GCP 及び FDA 21 CFR.312.120 を遵守して実施された。

2.7.6.4 NN9068-4183

2.7.6.4.1 臨床試験概要

治験依頼者名： Novo Nordisk A/S, Novo Allé, 2880 Bagsværd, Denmark	
有効成分名： インスリン デグルデク／リラグルチド（IDegLira）	
治験 ID： NN9068-4183	
Trial Registration ID-number： NCT02607306	UTN：U1111-1170-1332 Japanese registration number：JapicCTI-153089
治験の標題： DUAL™ I Japan‐日本人 2 型糖尿病患者を対象とした、インスリン デグルデク／リラグルチド、インスリン デグルデク及びリラグルチドの有効性及び安全性の比較検討	
治験責任医師名： 71 名の治験責任医師（治験実施施設ごとに 1 名）が任命された。以下の治験責任医師が「治験総括報告書への署名責任を有する医師（signatory investigator）」に任命された： Dr [redacted]	
治験実施施設： 日本国内 71 施設で本試験を実施し、被験者のスクリーニング及び無作為割り付けを行った。	
公表文献（引用文献）： 本治験総括報告書作成時点での公表文献はなし	
治験期間： 開始日：2015 年 11 月 18 日 終了日：2017 年 12 月 22 日	**開発のフェーズ**： 第 3a 相
Cut-off date： ここに提示する結果は、2018 年 2 月 8 日時点での臨床データベースに基づいている。	
報告書作成日： 2018 年 6 月 8 日	
目的： 主要目的： • 日本人2型糖尿病患者を対象として、経口糖尿病薬単剤の併用下でのインスリン デグルデク／リラグルチド（IDegLira）の血糖コントロールにおける有効性を検証する。これは、投与後52週における血糖コントロールについて、IDegLiraのリラグルチドに対する優越性及びインスリン デグルデク（IDeg）に対する非劣性を示すことで行う。 副次的目的： • ベースラインから投与後52週までの体重の変化量、低血糖の発現件数及び血糖コントロールについて、IDegLiraのIDegに対する優越性を検証する。 • 投与後52週におけるIDegLira、IDeg及びリラグルチドの全般的な有効性及び安全性を比較検討する。 薬物動態の目的： • 母集団薬物動態解析を用いて、52週間のIDegLiraと各有効成分単剤（個別投与）の臨床用量での薬物動	

態を比較する。また、事前に規定した共変量の血漿中IDegLira濃度への影響を検討する。

治験方法：

本試験は、経口糖尿病薬単剤〔以下 6 種類：メトホルミン、α-グルコシダーゼ阻害薬（α-GI）、チアゾリジン薬（TZD）、スルホニルウレア薬（SU）、ナトリウム - グルコース共輸送体 2（SGLT-2）阻害薬又はグリニド薬のいずれか〕による治療で十分な血糖コントロールが得られていない日本人 2 型糖尿病患者を対象とした、52 週間、多施設共同、無作為割り付け、3 群並行、非盲検試験であった。HbA1c が 7.0%以上、11.0%以下を「十分な血糖コントロールが得られていない」とした。被験者は、前治療の経口糖尿病薬の併用下（用量の変更は行わない）で、IDegLira、IDeg 又はリラグルチドをそれぞれ 1 日 1 回投与する群に、1：1：1 の割合で無作為に割り付けられた。無作為割り付け被験者数の約 50%が HbA1c 8.3%超となるように組み入れた。

計画及び解析された被験者数：

計画された被験者数（各群に 1：1：1 の割合で無作為割り付け）は 807 例であった。

	IDegLira N (%)	IDeg N (%)	Lira N (%)	Total N (%)
Screened				986
Screening failures				167
Randomised	275 (100.0)	271 (100.0)	273 (100.0)	819 100.0)
Exposed	275 (100.0)	271 (100.0)	273 (100.0)	819 100.0)
Withdrawn at/after randomisation	21 (7.6)	23 (8.5)	10 (3.7)	54 6.6)
Adverse event	8 (2.9)	6 (2.2)	6 (2.2)	20 2.4)
Protocol Violation	4 (1.5)	2 (0.7)	1 (0.4)	7 0.9)
Included in the trial in violation of the inclusion and/or exclusion criteria	2 (0.7)	1 (0.4)	0	3 0.4)
Change of any systemic treatment interfering with glucose metabolism	2 (0.7)	1 (0.4)	1 (0.4)	4 0.5)
Lack of efficacy	0	1 (0.4)	1 (0.4)	2 0.2)
Withdrawal by subject	8 (2.9)	10 (3.7)	2 (0.7)	20 2.4)
Other	1 (0.4)	4 (1.5)	0	5 0.6)
Completed	254 (92.4)	248 (91.5)	263 (96.3)	765 93.4)
Full analysis set (FAS)	275 (100.0)	271 (100.0)	273 (100.0)	819 100.0)
Per protocol analysis set (PP)	270 (98.2)	265 (97.8)	271 (99.3)	806 98.4)
Safety analysis set (SAS)	275 (100.0)	271 (100.0)	273 (100.0)	819 100.0)

N: Number of subjects, %: Percentage of randomised subjects

診断及び主要な組入れ基準：

主な選択基準：

- 性別不問、年齢20歳以上（同意取得時点）の日本人被験者。
- 2型糖尿病患者と診断され（臨床診断に基づく）、スクリーニング前の罹病期間が6ヵ月以上の被験者。
- HbA1c 7.0%以上、11.0%以下（中央検査機関の測定）の被験者。被験者のHbA1cの中央値が8.3%となることを目標とし、HbA1c 8.3%超の被験者の割合が無作為割り付け予定被験者数の約50%となった場合は、残りの割り付けられる被験者のHbA1cはすべて8.3%以下でなければならない。また、HbA1c 8.3%以下の被験者の割合が無作為割り付け予定被験者数の約50%となった場合は、残りの割り付けられる被験者のHbA1cはすべて8.3%超でなければならない。
- BMI（kg/m^2）が20以上の被験者。
- スクリーニングの60日以上前から、国内で承認されている用法・用量に従った経口糖尿病薬単剤（メトホルミン、α-GI、TZD、SU、SGLT-2阻害薬又はグリニド）による安定した治療（薬剤及び投与量に

変更がない）を受けている被験者。

主な除外基準：

- インスリン治療歴がある被験者（ただし、妊娠糖尿病を含む併発疾患のための短期間のインスリン投与は可とする）。
- スクリーニング前60日以内に、選択基準に示した薬剤以外の糖尿病治療薬及び肥満治療薬の投与を受けた被験者。
- 体重又は糖代謝に影響を及ぼすと考えられる併用薬剤の使用開始又は変更（14日以上の使用）が予測される被験者。
- 肝機能障害（アラニンアミノトランスフェラーゼ又はアスパラギン酸アミノトランスフェラーゼが基準範囲上限の2.5倍以上）を有する被験者。
- 腎機能障害（CKD-EPI式によるeGFRが60 mL/min/1.73 m^2未満）を有する被験者。
- スクリーニング時のカルシトニン濃度が50 ng/L以上である被験者。
- 急性又は慢性膵炎の既往歴を有する被験者。
- 本人又は家族が、甲状腺髄様癌又は多発性内分泌腫瘍症候群2型の既往歴を有する被験者。
- 心不全（NYHA分類クラスIII及びIV）を有する被験者。

被験薬、用量及び投与方法、ロット番号：

IDegLira（Xultophy®）

1 mL あたり IDeg 100 単位とリラグルチド 3.6 mg の固定比率の配合剤、ペン型注入器（PDS290、3 mL）と一体化したプレフィルド製剤として提供された。大腿部、上腕部（三角筋部）又は腹〕に皮下注射した。IDegLira の推奨開始用量は 10 用量ステップ（IDeg 10 単位／リラグルチド 0.36 mg）とした。最高用量の 50 用量ステップ（IDeg 50 単位／リラグルチド 1.8 mg）まで、朝食前血糖値 4.0～5.0 mmol/L（72～90 mg/dL）を目標として、事前に規定した投与量調節アルゴリズムに従い、1 週間に 2 回投与量調節を行った。IDegLira は前治療の経口糖尿病薬（用量の変更は行わない）と併用して投与した。ロット番号：FP50665、FP51981、GP51818、EP51277 及び GP51377。

投与期間：

試験期間は約 55 週間〔2 週間のスクリーニング期間、52 週間の投与期間、最終投与来院（来院 54）の 7 日後の事後調査来院（来院 55）〕であった。事後調査来院の目的は、抗体検査の検体採取及び投与終了後 1 週間に発現した有害事象の情報収集であった。

対照薬、用量及び投与方法、ロット番号：

IDeg（トレシーバ®）

1 mL あたり 100 単位、ペン型注入器（PDS290、3 mL）と一体化したプレフィルド製剤として提供された。大腿部、上腕部（三角筋部）又は腹〕に皮下注射した。IDeg の推奨開始用量は 10 単位とした。朝食前血糖値 4.0～5.0 mmol/L（72～90 mg/dL）を目標として、事前に規定した投与量調節アルゴリズムに従い、1 週間に 2 回投与量調節を行った。IDeg は前治療の経口糖尿病薬（用量の変更は行わない）と併用して投与した。最高用量は設定しなかった。ロット番号：FP51117、FP52470、FP52512、FP51299 及び EP51161。

リラグルチド（ビクトーザ®）

1 mL あたり 6.0 mg、ペン型注入器（フレックスペン®、3 mL）と一体化したプレフィルド製剤として提供された。大腿部、上腕部（三角筋部）又は腹〕に皮下注射した。リラグルチドの投与は 0.3 mg／日から開始し、その後は最高用量の 1.8 mg／日まで 1 週間ごとに 0.3 mg ずつ漸増した。規定した用量漸増期間（6 週間）は、最大で 7 日間の延長が可能であった。その後の用量維持期間中はリラグルチドの用量は 1.8 mg／日から変更しないこととしたが、投与終了までに合計 7 日以下であれば減量を可とした。リラグルチドは前治療の経口糖尿病薬（用量の変更は行わない）と併用して投与した。ロット番号：EP50143、FP50923 及び GP52108。

評価基準：**有効性**

プライマリーエンドポイント

- HbA1cのベースラインから投与後52週までの変化量

有効性に関する検証的セカンダリーエンドポイント

以下の検証的セカンダリーエンドポイントについて、IDegLira の IDeg に対する優越性を検証した。これらの検証的セカンダリーエンドポイントに関して、全体の第 1 種の過誤確率を 5%に制御するため、階層的検定手順を用いた。

- 体重のベースラインから投与後52週までの変化量
- 52週間の重大な又は血糖値確定低血糖の発現件数
- HbA1cのベースラインから投与後52週までの変化量

有効性に関する補足的セカンダリーエンドポイント

- 投与後52週におけるインスリン投与量
- 投与後52週におけるレスポンダー（はい／いいえ）：
  - HbA1cが7.0%未満
  - HbA1cが7.0%未満で、体重のベースラインからの変化量が0以下
  - HbA1cが7.0%未満で、投与期間の最後の12週間に重大な又は血糖値確定症候性低血糖の発現がない
  - HbA1cが7.0%未満で、体重のベースラインからの変化量が0以下、かつ投与期間の最後の12週間に重大な又は血糖値確定症候性低血糖の発現がない
  - HbA1cが6.5%以下
  - HbA1cが6.5%以下で、体重のベースラインからの変化量が0以下
  - HbA1cが6.5%以下で、投与期間の最後の12週間に重大な又は血糖値確定症候性低血糖の発現がない
  - HbA1cが6.5%以下で、体重のベースラインからの変化量が0以下、投与期間の最後の12週間に重大な又は血糖値確定症候性低血糖の発現がない
- 以下の項目のベースラインから投与後52週までの変化量：
  - 空腹時血糖値
  - ウエスト周囲径
  - 血圧（収縮期及び拡張期）
  - 9点血糖値プロファイル（血糖自己測定）
    - 9点血糖値プロファイル（各測定点）
    - 9点血糖値プロファイルの平均
    - 食後血糖増加量（朝食、昼食及び夕食の前から各食後90分までの増加量に基づく）の平均。すべての食事による増加量の平均は、すべての利用可能な増加量の平均として計算される。
- 投与後52週における空腹時脂質プロファイル〔総コレステロール、低比重リポタンパク質（LDL）コレステロール、高比重リポタンパク質（HDL）コレステロール、超低比重リポタンパク質（VLDL）コレステロール、中性脂肪及び遊離脂肪酸〕
- 投与後52週における空腹時C-ペプチド、空腹時インスリン、空腹時グルカゴン及びプロインスリン

評価基準：安全性

- 52週間の有害事象の発現件数
- 52週間の重大な又は血糖値確定症候性低血糖の発現件数
- 52週間の重大な又は血糖値確定症候性夜間低血糖の発現件数
- 52週間のADAの低血糖分類による低血糖の発現件数
- 抗薬物抗体〔抗IDeg抗体（IDeg特異抗体及びヒトインスリンとの交叉抗体）、抗リラグルチド抗体（GLP-1との交叉抗体及び中和作用）〕
- 以下の臨床評価におけるベースラインから投与後52週までの変化：
  - 身体検査
  - 眼底検査又は眼底写真
  - 心電図
  - 脈拍

- 以下の臨床検査におけるベースラインから投与後52週までの変化：
  - 血液生化学的検査（アミラーゼ及びリパーゼを含む）
  - 血液学的検査
  - カルシトニン

統計手法：

被験者数の設定

- 被験者数は、優越性及び非劣性のいずれの検定でも、有意水準2.5%の片側検定及び1.0%の標準偏差を仮定した、t-統計量を用いて決定された。治療間差の平均は、非劣性では-0.1%、優越性では-0.3%と仮定した。被験者数の設定には、非劣性の評価にPer-Protocol（PP）解析対象集団（85%と仮定）、優越性の評価に最大の解析対象集団（FAS）を用いた。これらの仮定に基づくと、807例の被験者数により、98.9%の非劣性の検出力及び93.5%の優越性の検出力を示し、主要目的を同時に満たすための検出力は98.9% × 93.5% = 92.5%である。

解析対象集団

- FAS：無作為割り付けされたすべての被験者を含めた。例外的な場合には被験者を除外することが可能であった。その場合、除外する正当な理由を示して文書化することとした。FASにおける統計的な評価はITT（intention to treat）の原則に従い、被験者はas randomisedの評価に寄与した。
- PP解析対象集団：FASに含まれる被験者のうち以下の基準を満たすすべての被験者を含めた。
  - いずれの選択基準にも違反していない
  - いずれの除外基準も満たしていない
  - スクリーニング又は無作為割り付け時に非欠測のHbA1c測定値がある
  - 12週間の曝露後に少なくとも1つの非欠測のHbA1c測定値がある。
  - 少なくとも12週の曝露がある

  PP解析対象集団に含まれる被験者はas treatedの評価に寄与した。
- 安全性解析対象集団（SAS）：治験薬又は対照薬を少なくとも1回投与されたすべての被験者を含めた。SASに含まれる被験者はas treatedの評価に寄与した。
- 完了例の解析対象集団（CAS）：無作為割り付けされて試験を完了したすべての被験者を含めた。CASに含まれる被験者はas randomisedの評価に寄与した。

統計解析

プライマリーエンドポイントである HbA1c のベースラインから投与後 52 週までの変化量は、共分散分析（ANCOVA）モデルを用いて解析した。本試験の主要目的は、日本人 2 型糖尿病患者を対象として、経口糖尿病薬単剤の併用下での IDegLira の血糖コントロールにおける有効性を検証することであった。この検証は、HbA1c ベースラインから投与後 52 週までの変化量の差について、IDegLira と IDeg の比較では 0.3%の非劣性マージン、IDegLira とリラグルチドの比較では 0.0%の優越性マージンと比較することで行った。主要目的は、FAS を対象として、IDegLira の IDeg に対する非劣性及びリラグルチドに対する優越性の両方が検証された場合に限り満たされることとした。検証的セカンダリーエンドポイントである体重のベースラインから投与後 52 週までの変化量は、ANCOVA モデルを用いて解析した。検証的セカンダリーエンドポイントである 52 週間の重大な又は血糖値確定低血糖の発現件数は、負の二項分布回帰モデルを用いて解析した。HbA1c のベースラインから投与後 52 週までの変化量についての IDegLira の IDeg に対する優越性は、主要解析で得られた群差の推定値を用いて評価した。検証的セカンダリーエンドポイントに関して IDegLira の IDeg に対する優越性の検定を行うにあたり、第 1 種の過誤確率を 5%に制御するため、階層的検定手順を用いた。投与後 52 週における経時測定データの欠測値は last observation carried forward（LOCF）法を用いて補完した。

被験者背景：

- 人口統計学的特性及びベースライン特性

	IDegLira N (%)	IDeg N (%)	Lira N (%)	Total N (%)
Number of subjects	275	271	273	819
Age group				
N	275 (100.0)	271 (100.0)	273 (100.0)	819 (100.0)
18<= to <40 years	16 (5.8)	11 (4.1)	11 (4.0)	38 (4.6)
40<= to <65 years	181 (65.8)	172 (63.5)	191 (70.0)	544 (66.4)
65<= to <75 years	76 (27.6)	84 (31.0)	66 (24.2)	226 (27.6)
Elderly (75<= years)	2 (0.7)	4 (1.5)	5 (1.8)	11 (1.3)
Age group (EudraCT)				
N	275 (100.0)	271 (100.0)	273 (100.0)	819 (100.0)
18<= to <65 years	197 (71.6)	183 (67.5)	202 (74.0)	582 (71.1)
65<= to <85 years	78 (28.4)	88 (32.5)	71 (26.0)	237 (28.9)
85<= years	0	0	0	0
Sex				
N	275 (100.0)	271 (100.0)	273 (100.0)	819 (100.0)
Female	81 (29.5)	76 (28.0)	81 (29.7)	238 (29.1)
Male	194 (70.5)	195 (72.0)	192 (70.3)	581 (70.9)
Race				
N	275 (100.0)	271 (100.0)	273 (100.0)	819 (100.0)
Asian	275 (100.0)	271 (100.0)	273 (100.0)	819 (100.0)
Smoker status				
N	275 (100.0)	271 (100.0)	273 (100.0)	819 (100.0)
Current smoker	78 (28.4)	78 (28.8)	74 (27.1)	230 (28.1)
Never smoked	102 (37.1)	105 (38.7)	108 (39.6)	315 (38.5)
Previous smoker	95 (34.5)	88 (32.5)	91 (33.3)	274 (33.5)

N: Number of subjects, %: Percentage of subjects
EduraCT: European union drug regulating authorities clinical trials.

- ベースライン及び糖尿病特性

	IDegLira	IDeg	Lira	Total
Number of subjects	275	271	273	819
Age (years)				
N	275	271	273	819
Mean (SD)	56.9 (10.2)	57.8 (9.9)	56.8 (10.1)	57.2 (10.1)
Median	57.0	59.0	57.0	57.0
Min ; Max	29 ; 81	22 ; 80	25 ; 79	22 ; 81
Height (m)				
N	275	271	273	819
Mean (SD)	1.6 (0.1)	1.7 (0.1)	1.6 (0.1)	1.6 (0.1)
Median	1.7	1.7	1.7	1.7
Min ; Max	1.4 ; 1.8	1.4 ; 1.9	1.4 ; 1.9	1.4 ; 1.9
Body weight (kg)				
N	275	271	273	819
Mean (SD)	70.7 (12.4)	72.6 (14.5)	72.2 (15.0)	71.8 (14.0)
Median	68.7	70.5	70.4	69.8
Min ; Max	44.1 ; 113.3	44.8 ; 161.8	42.3 ; 142.4	42.3 ; 161.8
BMI (kg/m^2)				
N	275	271	273	819
Mean (SD)	26.1 (3.7)	26.6 (4.8)	26.5 (4.5)	26.4 (4.4)
Median	25.5	25.5	25.8	25.6
Min ; Max	19.9 ; 36.8	19.6 ; 56.0	19.8 ; 45.5	19.6 ; 56.0
Duration of diabetes (years)				
N	275	271	273	819
Mean (SD)	9.16 (6.17)	9.67 (5.97)	9.41 (5.92)	9.41 (6.02)
Median	8.05	8.73	8.43	8.46
Min ; Max	0.57 ; 45.35	0.54 ; 30.69	0.79 ; 33.91	0.54 ; 45.35
HbA1c (%)				
N	275	271	273	819
Mean (SD)	8.52 (1.12)	8.53 (1.05)	8.32 (0.99)	8.45 (1.06)
Median	8.30	8.30	8.00	8.20
Min ; Max	6.80 ; 11.20	6.90 ; 11.40	6.70 ; 11.40	6.70 ; 11.40
Fasting plasma glucose (mg/dL)				
N	275	271	272	818
Mean (SD)	178.68 (42.99)	179.94 (42.25)	175.40 (39.79)	178.01 (41.70)
Median	170.00	173.00	168.00	170.00
Min ; Max	92.00 ; 318.00	99.00 ; 307.00	92.00 ; 347.00	92.00 ; 347.00
eGFR (mL/min/1.73m^2)				
N	275	271	273	819
Mean (SD)	77.66 (8.79)	76.47 (8.98)	77.79 (8.21)	77.31 (8.68)
Median	77.00	76.00	78.00	77.00
Min ; Max	60.00 ; 100.00	60.00 ; 111.00	60.00 ; 101.00	60.00 ; 111.00

N: Number of subjects, SD: Standard deviation, BMI: Body mass index,
HbA1c: Haemoglobin A1c, eGFR: estimated glomerular filtration rate
Baseline refers to week 0 except for height and eGFR, these were taken at screening.
The duration of diabetes is calculated as the time from date of diagnosis to the randomisation date.
eGFR was calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.

有効性の結果：

経口糖尿病薬単剤との併用下の IDegLira、IDeg 又はリラグルチドによる 52 週間の治療について、以下の結

論を得た。

HbA1c

- HbA1cは、IDegLira群で8.52%から6.10%へ、IDeg群で8.53%から6.73%へ、リラグルチド群で8.32%から6.52%へと低下した。
- HbA1cのベースラインから投与後52週までの変化量について、IDegに対するIDegLiraの非劣性及び優越性が示された。群差（IDegLira群－IDeg群）の推定値は、非劣性及び優越性のいずれの検定においても、-0.63%（95%信頼区間：[-0.75; -0.52]、p<0.0001）であった。
- HbA1cのベースラインから投与後52週までの変化量について、リラグルチドに対するIDegLiraの優越性が示された。群差（IDegLira群－リラグルチド群）の推定値は-0.48%（95%信頼区間：[-0.60; -0.37]、p<0.0001）であった。

体重

- 体重の変化量は、IDegLira群で2.9 kg、IDeg群で4.1 kg、リラグルチド群で-1.0 kgであった。
- 検証的セカンダリーエンドポイントである体重のベースラインから投与後52週までの変化量について、IDegに対するIDegLiraの優越性が示された。群差（IDegLira群－IDeg群）の推定値は -1.19 kg（95%信頼区間：[-1.80; -0.59]、p=0.0001）であった。
- 群差（IDegLira群－リラグルチド群）の推定値は3.89 kg（95%信頼区間：[3.29; 4.49]、p<0.0001）であり、投与群間に有意差が認められた（リラグルチド群で好ましい結果）。

低血糖

- 検証的セカンダリーエンドポイントである投与後52週における重大な又は血糖値確定低血糖の発現件数について、IDegに対するIDegLiraの優越性が示された。投与群間（IDegLira群／IDeg群）の比の推定値は0.48（95%信頼区間：[0.35; 0.68]、p<0.0001）であった。
- IDegLira群とリラグルチド群との比較では、重大な又は血糖値確定低血糖の単位時間あたり発現件数は、リラグルチド群と比較してIDegLira群で統計的に有意に多かった〔投与群間（IDegLira群／リラグルチド群）の比の推定値：37.58（95%信頼区間：[19.80; 71.31]、p<0.0001）〕。

安全性の結果：

投与後 52 週において、本試験の IDegLira、IDeg 及びリラグルチドの安全性に関して以下のとおり結論づけられた。

IDegLira、IDeg 及びリラグルチドの忍容性は概して良好であり、IDegLira の投与において新規の安全性及び忍容性に関する問題は認められなかった。

各領域における安全性の検討結果を以下に要約する：

全般的な有害事象プロファイル（低血糖以外）

- 有害事象を発現した被験者の割合は、IDegLira群（83.3%）、IDeg群（79.7%）及びリラグルチド群（83.9%）で同様であった。
- 有害事象の単位時間あたりの発現件数は、IDegLira群で325.7件／100人・年、IDeg群で316.6件／100人・年、リラグルチド群で325.6件／100人・年であった。
- 有害事象の大部分は軽度であり、また事象の大部分は治験責任医師により治験薬との因果関係が「なし」と判定された。
- 器官別大分類の胃腸障害に含まれる有害事象の単位時間あたりの発現件数は、IDegLira群で69.8件／100人・年であり、IDeg群（42.0件／100人・年）と比較して多く、リラグルチド群（80.2件／100人・年）と比較して少なかった。IDegLira群で最も高頻度に報告された胃腸障害の有害事象は、便秘、下痢及び悪心であった。
- 44例で計48件の重篤な有害事象が報告された。事象の単位時間あたりの発現件数は、IDegLira群で6.7件／100人・年、IDeg群で6.1件／100人・年、リラグルチド群で5.2件／100人・年であった。被験者の1%以上で報告された重篤な有害事象は認められなかった。
- 4件の重篤な有害事象（IDegLira群で2件、IDeg群及びリラグルチド群で各1件）は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。
- 20例で計21件の試験の中止に至った有害事象が報告された（IDegLira群で8例、IDeg群及びリラグルチ

ド群で各6例）。このうち7件は重篤な有害事象であった。
- IDegLira群で1件の死亡が報告された。

特に注目すべき安全性領域の有害事象
- 5件の心血管系事象がイベント判定委員会により確定された。これらは主要な心血管イベント（MACE）であった（IDegLira群で3件、IDeg群で2件）。
- IDegLira群の1件の膵炎がイベント判定委員会により確定された。
- 14件の新生物がイベント判定委員会により確定された（IDegLira群で4件、IDeg群で3件、リラグルチド群で7件）。
- イベント判定委員会により確定された甲状腺障害の事象はなかった。
- リパーゼ又はアミラーゼの増加の事象の単位時間あたりの発現件数は、IDegLira群で4.1件／100人・年、リラグルチド群で7.4件／100人・年であった。IDeg群ではリパーゼ又はアミラーゼの増加の事象は報告されなかった。
- 3件のカルシトニンの増加が報告された（IDegLira群で1件、リラグルチド群で2件）。
- その他の特に注目すべき安全性領域（胃腸障害の有害事象を除く）においては、各領域の事象の発現件数が少ない、又は投与群間で違いが認められなかった。

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、IDegLira群で174.3件／100人・年、IDeg群で331.9件／100人・年、リラグルチド群で4.8件／100人・年であった。
- IDegLira群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、IDeg群と比較して統計的に有意に少なく、リラグルチド群と比較して有意に多かった。
- 重大な又は血糖値確定症候性低血糖の単位時間あたりの発現件数は、IDegLira群で50.4件／100人・年、IDeg群で138.3件／100人・年、リラグルチド群で1.5件／100人・年であった。
- 重大な又は血糖値確定夜間低血糖の単位時間あたりの発現件数は、IDegLira群で24.6件／100人・年、IDeg群で50.4件／100人・年であり、リラグルチド群ではこれらの低血糖は報告されなかった。
- 重大な又は血糖値確定症候性夜間低血糖の単位時間あたりの発現件数は、IDegLira群で6.0件／100人・年、IDeg群で16.0件／100人・年であり、リラグルチド群ではこれらの低血糖は報告されなかった。
- ADA分類に基づく低血糖の単位時間あたりの発現件数は、IDegLira群で1802.2件／100人・年、IDeg群で2421.6件／100人・年、リラグルチド群で59.6件／100人・年であった。ADA分類に基づく低血糖の大部分は確定症候性低血糖（documented symptomatic hypoglycaemia）又は無症候性低血糖（asymptomatic hypoglycaemia）であった。
- 7件の重大な低血糖（IDegLira群で1件、IDeg群で6件）が報告された。

臨床検査評価
- 血液学的検査又は血液生化学的検査のパラメータについては、いずれの投与群においてもベースラインから投与終了時までに臨床的に問題のある変化は認められなかった。
- リパーゼのベースラインから投与終了時までの変化量は、IDegLira群で+9.84 U/L、IDeg群で-3.66 U/L、リラグルチド群で+21.23 U/Lであった。
- アミラーゼのベースラインから投与終了時までの増加量は、IDegLira群で9.29 U/L、IDeg群で4.87 U/L、リラグルチド群で8.74 U/Lであった。
- カルシトニンについて、試験期間中に臨床的に問題となるような変化は認められなかった。

抗体検査
- IDeg特異抗体の産生について、IDegLira群とIDeg群との間に違いは認められなかった。
- ヒトインスリンとの交叉抗体が認められた被験者の割合は、IDeg群と比較してIDegLira群で高かったが、HbA1c及び投与量への影響は認められなかった。
- 事後調査来院において、IDegLira群の17.2%及びリラグルチド群の24.9%の被験者で抗リラグルチド抗体が陽性であった。これらの被験者のうち、内因性GLP-1との交叉抗体及び中和抗体が認められたのは少なかった。

バイタルサイン、身体所見及びその他の観察項目 • 脈拍数は、IDegLira群（3.9拍／分）及びリラグルチド群（4.2拍／分）で増加した。IDeg群（0.8拍／分）での増加はわずかであった。 • 投与後52週の身体所見、眼底検査／眼底写真又は心電図の結果について、3つの投与群の間に臨床的に問題となる違いは認められなかった。
全体の結論： 経口糖尿病薬単剤（メトホルミン、α-GI、TZD、SU、SGLT-2 阻害薬又はグリニドのいずれか）による治療で十分な血糖コントロールが得られていない（HbA1c が 7.0%以上 11.0%以下）日本人 2 型糖尿病患者を対象とした、IDegLira とその成分である IDeg 及びリラグルチドを比較する 52 週間の試験における結論は以下のとおりであった： • HbA1cのベースラインからの変化量について、IDeg又はリラグルチドに対するIDegLiraの優越性が示された。 • 体重の変化量について、IDegに対するIDegLiraの優越性が示された。 • 重大な又は血糖値確定低血糖の発現件数について、IDegに対するIDegLiraの優越性が示された。 • IDegLiraの投与において予測できない安全性又は忍容性の問題は認められなかった。
本試験は、ヘルシンキ宣言（64th WMA assembly）の精神及び ICH-GCP（1996 年 6 月）を遵守して実施された（必須文書の保管に関する要件を含む）。

2.7.6.4.2. 有害事象

表2.7.6.4.2-1. 有害事象（器官別大分類及び基本語別）－安全性解析対象（4183 試験）

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	275			271			273			819		
PYE (years)	268.00			261.81			271.84			801.65		
Events	229 (83.3)	873	325.75	216 (79.7)	829	316.65	229 (83.9)	885	325.56	674 (82.3)	2587	322.71
感染症および寄生虫症	155 (56.4)	291	108.58	139 (51.3)	274	104.66	147 (53.8)	271	99.69	441 (53.8)	836	104.29
ウイルス性上気道感染	106 (38.5)	166	61.94	91 (33.6)	161	61.50	94 (34.4)	155	57.02	291 (35.5)	482	60.13
インフルエンザ	15 (5.5)	15	5.60	9 (3.3)	9	3.44	9 (3.3)	9	3.31	33 (4.0)	33	4.12
胃腸炎	12 (4.4)	12	4.48	7 (2.6)	8	3.06	11 (4.0)	12	4.41	30 (3.7)	32	3.99
咽頭炎	11 (4.0)	13	4.85	15 (5.5)	18	6.88	9 (3.3)	9	3.31	35 (4.3)	40	4.99
気管支炎	7 (2.5)	9	3.36	6 (2.2)	7	2.67	8 (2.9)	8	2.94	21 (2.6)	24	2.99
歯周炎	6 (2.2)	6	2.24	6 (2.2)	10	3.82	5 (1.8)	5	1.84	17 (2.1)	21	2.62
副鼻腔炎	5 (1.8)	6	2.24	0			2 (0.7)	4	1.47	7 (0.9)	10	1.25
外耳炎	4 (1.5)	4	1.49	0			3 (1.1)	4	1.47	7 (0.9)	8	1.00
帯状疱疹	4 (1.5)	4	1.49	5 (1.8)	5	1.91	1 (0.4)	1	0.37	10 (1.2)	10	1.25
膀胱炎	4 (1.5)	6	2.24	8 (3.0)	10	3.82	3 (1.1)	3	1.10	15 (1.8)	19	2.37
結膜炎	3 (1.1)	3	1.12	4 (1.5)	4	1.53	6 (2.2)	6	2.21	13 (1.6)	13	1.62
鼻咽頭炎	3 (1.1)	7	2.61	3 (1.1)	5	1.91	3 (1.1)	3	1.10	9 (1.1)	15	1.87
化膿	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
感染性皮膚炎	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
口腔ヘルペス	2 (0.7)	2	0.75	0			2 (0.7)	2	0.74	4 (0.5)	4	0.50
歯肉炎	2 (0.7)	2	0.75	2 (0.7)	2	0.76	2 (0.7)	3	1.10	6 (0.7)	7	0.87
歯肉膿瘍	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
皮膚感染	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
扁桃炎	2 (0.7)	2	0.75	4 (1.5)	4	1.53	2 (0.7)	2	0.74	8 (1.0)	8	1.00
ウイルス性胃腸炎	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
ノロウイルス性胃腸炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
ヘモフィルス性肺炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
ヘリコバクター感染	1 (0.4)	1	0.37	4 (1.5)	4	1.53	4 (1.5)	4	1.47	9 (1.1)	9	1.12
ヘルペスウイルス感染	1 (0.4)	1	0.37	0			2 (0.7)	2	0.74	3 (0.4)	3	0.37
マイコプラズマ感染	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
β 溶血性レンサ球菌感染	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
感染性大腸炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
感染性腸炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
気道感染	1 (0.4)	2	0.75	0			0			1 (0.1)	2	0.25
歯髄炎	1 (0.4)	1	0.37	0			2 (0.7)	2	0.74	3 (0.4)	3	0.37
上気道感染	1 (0.4)	1	0.37	2 (0.7)	3	1.15	4 (1.5)	5	1.84	7 (0.9)	9	1.12
真菌性膀胱炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
足部白癬	1 (0.4)	1	0.37	1 (0.4)	1	0.38	5 (1.8)	5	1.84	7 (0.9)	7	0.87
体部白癬	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
蓄膿	1 (0.4)	2	0.75	0			0			1 (0.1)	2	0.25
爪囲炎	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
頭部白癬	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
尿管炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
尿道炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
肺炎	1 (0.4)	1	0.37	1 (0.4)	1	0.38	3 (1.1)	3	1.10	5 (0.6)	5	0.62
麦粒腫	1 (0.4)	1	0.37	0			3 (1.1)	3	1.10	4 (0.5)	4	0.50
鼻炎	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
毛包炎	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
せつ	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
ウイルス性結膜炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
ヘリコバクター性胃炎	0			1 (0.4)	1	0.38	2 (0.7)	2	0.74	3 (0.4)	3	0.37
マイコプラズマ性肺炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
咽頭扁桃炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
陰部ヘルペス	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
感染性湿疹	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
感染性皮膚嚢腫	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
急性副鼻腔炎	0			1 (0.4)	2	0.76	1 (0.4)	1	0.37	2 (0.2)	3	0.37
限局性感染	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
細菌性胃腸炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
細菌性気管支炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
細菌性腸炎	0			0			1 (0.4)	2	0.74	1 (0.1)	2	0.25
食道カンジダ症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
腎盂腎炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
須毛瘡	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
帯状疱疹性髄膜炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
中耳炎	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
爪の皮膚糸状菌症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
尿路感染	0			3 (1.1)	3	1.15	0			3 (0.4)	3	0.37
膿痂疹性湿疹	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
白癬感染	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
腹部膿瘍	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
蜂巣炎	0			1 (0.4)	1	0.38	3 (1.1)	3	1.10	4 (0.5)	4	0.50
扁桃周囲炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
腟感染	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
胃腸障害	96 (34.9)	187	69.78	62 (22.9)	110	42.02	114 (41.8)	218	80.19	272 (33.2)	515	64.24
便秘	27 (9.8)	28	10.45	12 (4.4)	12	4.58	38 (13.9)	42	15.45	77 (9.4)	82	10.23
下痢	15 (5.5)	20	7.46	12 (4.4)	14	5.35	24 (8.8)	31	11.40	51 (6.2)	65	8.11
胃食道逆流性疾患	13 (4.7)	13	4.85	7 (2.6)	7	2.67	8 (2.9)	8	2.94	28 (3.4)	28	3.49

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
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Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
口内炎	10 (3.6)	11	4.10	3 (1.1)	4	1.53	1 (0.4)	1	0.37	14 (1.7)	16	2.00
悪心	9 (3.3)	13	4.85	5 (1.8)	7	2.67	23 (8.4)	30	11.04	37 (4.5)	50	6.24
齲歯	9 (3.3)	9	3.36	7 (2.6)	7	2.67	7 (2.6)	8	2.94	23 (2.8)	24	2.99
腹部膨満	8 (2.9)	8	2.99	3 (1.1)	3	1.15	3 (1.1)	3	1.10	14 (1.7)	14	1.75
慢性胃炎	8 (2.9)	8	2.99	8 (3.0)	8	3.06	7 (2.6)	8	2.94	23 (2.8)	24	2.99
上腹部痛	7 (2.5)	8	2.99	5 (1.8)	5	1.91	3 (1.1)	3	1.10	15 (1.8)	16	2.00
消化不良	6 (2.2)	7	2.61	1 (0.4)	1	0.38	10 (3.7)	12	4.41	17 (2.1)	20	2.49
大腸ポリープ	6 (2.2)	6	2.24	3 (1.1)	3	1.15	4 (1.5)	4	1.47	13 (1.6)	13	1.62
胃炎	5 (1.8)	5	1.87	2 (0.7)	2	0.76	4 (1.5)	4	1.47	11 (1.3)	11	1.37
歯周病	4 (1.5)	5	1.87	3 (1.1)	3	1.15	5 (1.8)	5	1.84	12 (1.5)	13	1.62
大腸炎	3 (1.1)	3	1.12	2 (0.7)	2	0.76	2 (0.7)	2	0.74	7 (0.9)	7	0.87
腹痛	3 (1.1)	3	1.12	3 (1.1)	5	1.91	3 (1.1)	4	1.47	9 (1.1)	12	1.50
腹部不快感	3 (1.1)	4	1.49	6 (2.2)	7	2.67	9 (3.3)	9	3.31	18 (2.2)	20	2.49
バレット食道	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
胃ポリープ	2 (0.7)	2	0.75	3 (1.1)	3	1.15	5 (1.8)	5	1.84	10 (1.2)	10	1.25
胃潰瘍	2 (0.7)	2	0.75	1 (0.4)	1	0.38	0			3 (0.4)	3	0.37
耳下腺腫大	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
食中毒	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
腸炎	2 (0.7)	3	1.12	0			0			2 (0.2)	3	0.37
直腸炎	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
裂孔ヘルニア	2 (0.7)	2	0.75	2 (0.7)	2	0.76	0			4 (0.5)	4	0.50
嘔吐	2 (0.7)	4	1.49	3 (1.1)	3	1.15	10 (3.7)	12	4.41	15 (1.8)	19	2.37
おくび	1 (0.4)	1	0.37	0			2 (0.7)	2	0.74	3 (0.4)	3	0.37
びらん性胃炎	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
胃酸過多	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
胃十二指腸炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
急性膵炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
血便排泄	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
口腔内不快感	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
歯痛	1 (0.4)	1	0.37	1 (0.4)	1	0.38	3 (1.1)	3	1.10	5 (0.6)	5	0.62
痔核	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
十二指腸炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
小腸炎	1 (0.4)	2	0.75	1 (0.4)	1	0.38	0			2 (0.2)	3	0.37
食道ポリープ	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
軟便	1 (0.4)	1	0.37	1 (0.4)	1	0.38	3 (1.1)	4	1.47	5 (0.6)	6	0.75
鼡径ヘルニア	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
ブルンネル腺過形成	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
メレナ	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
胃腸障害	0			0			2 (0.7)	3	1.10	2 (0.2)	3	0.37
下腹部痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
機能性胃腸障害	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
鼓腸	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
口の感覚鈍麻	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
口腔内潰瘍形成	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
口内乾燥	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
歯周の炎症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
歯肉腫脹	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
痔出血	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
自己免疫性膵炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
十二指腸ポリープ	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
腸憩室	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
糞塊	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
裂肛	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
膵萎縮	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
膵嚢胞	0				1	(0.4)	1	0.38	1	(0.4)	1	0.37	2	(0.2)	2	0.25
筋骨格系および結合組織障害	53	(19.3)	63	23.51	51	(18.8)	71	27.12	41	(15.0)	60	22.07	145	(17.7)	194	24.20
背部痛	12	(4.4)	12	4.48	12	(4.4)	12	4.58	13	(4.8)	16	5.89	37	(4.5)	40	4.99
関節痛	7	(2.5)	7	2.61	6	(2.2)	7	2.67	5	(1.8)	6	2.21	18	(2.2)	20	2.49
筋肉痛	6	(2.2)	6	2.24	3	(1.1)	3	1.15	2	(0.7)	2	0.74	11	(1.3)	11	1.37
筋痙縮	4	(1.5)	6	2.24	2	(0.7)	2	0.76	4	(1.5)	6	2.21	10	(1.2)	14	1.75
変形性脊椎症	4	(1.5)	4	1.49	4	(1.5)	4	1.53	2	(0.7)	2	0.74	10	(1.2)	10	1.25
関節周囲炎	3	(1.1)	3	1.12	5	(1.8)	5	1.91	2	(0.7)	2	0.74	10	(1.2)	10	1.25
筋骨格硬直	3	(1.1)	3	1.12	1	(0.4)	1	0.38	4	(1.5)	5	1.84	8	(1.0)	9	1.12
椎間板突出	3	(1.1)	3	1.12	2	(0.7)	2	0.76	2	(0.7)	2	0.74	7	(0.9)	7	0.87
変形性関節症	3	(1.1)	3	1.12	6	(2.2)	6	2.29	2	(0.7)	2	0.74	11	(1.3)	11	1.37
関節炎	2	(0.7)	2	0.75	1	(0.4)	1	0.38	1	(0.4)	1	0.37	4	(0.5)	4	0.50
筋骨格痛	2	(0.7)	2	0.75	2	(0.7)	3	1.15	1	(0.4)	1	0.37	5	(0.6)	6	0.75
四肢痛	2	(0.7)	2	0.75	2	(0.7)	2	0.76	1	(0.4)	1	0.37	5	(0.6)	5	0.62
腱鞘炎	2	(0.7)	2	0.75	2	(0.7)	2	0.76	3	(1.1)	3	1.10	7	(0.9)	7	0.87
関節拘縮	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
関節腫脹	1	(0.4)	1	0.37	1	(0.4)	1	0.38	1	(0.4)	1	0.37	3	(0.4)	3	0.37
筋骨格系胸痛	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
頚部痛	1	(0.4)	1	0.37	1	(0.4)	1	0.38	1	(0.4)	1	0.37	3	(0.4)	3	0.37
骨炎	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
骨粗鬆症	1	(0.4)	1	0.37	2	(0.7)	2	0.76	0				3	(0.4)	3	0.37
側腹部痛	1	(0.4)	1	0.37	2	(0.7)	2	0.76	0				3	(0.4)	3	0.37
腱痛	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
横紋筋融解症	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
滑液嚢腫	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
関節リウマチ	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
筋膜炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
頚部脊柱管狭窄症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
結節性変形性関節症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
腰部脊柱管狭窄症	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
骨痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
脊柱管狭窄症	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
脊椎すべり症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
足底筋膜炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
弾発指	0			4 (1.5)	5	1.91	1 (0.4)	1	0.37	5 (0.6)	6	0.75
椎間板障害	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
肋間筋肉痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
腱炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
鼡径部痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
眼障害	45 (16.4)	52	19.40	28 (10.3)	37	14.13	39 (14.3)	48	17.66	112 (13.7)	137	17.09
糖尿病網膜症	17 (6.2)	17	6.34	12 (4.4)	14	5.35	11 (4.0)	11	4.05	40 (4.9)	42	5.24
アレルギー性結膜炎	4 (1.5)	5	1.87	2 (0.7)	2	0.76	2 (0.7)	2	0.74	8 (1.0)	9	1.12
白内障	4 (1.5)	4	1.49	4 (1.5)	4	1.53	5 (1.8)	5	1.84	13 (1.6)	13	1.62
眼乾燥	3 (1.1)	3	1.12	2 (0.7)	2	0.76	1 (0.4)	1	0.37	6 (0.7)	6	0.75
黄斑線維症	2 (0.7)	2	0.75	0			1 (0.4)	1	0.37	3 (0.4)	3	0.37
硝子体浮遊物	2 (0.7)	2	0.75	1 (0.4)	1	0.38	2 (0.7)	2	0.74	5 (0.6)	5	0.62
糖尿病性網膜浮腫	2 (0.7)	2	0.75	0			1 (0.4)	1	0.37	3 (0.4)	3	0.37
網膜出血	2 (0.7)	2	0.75	1 (0.4)	1	0.38	1 (0.4)	1	0.37	4 (0.5)	4	0.50
緑内障	2 (0.7)	2	0.75	0			3 (1.1)	3	1.10	5 (0.6)	5	0.62
黄斑円孔	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
眼の炎症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
眼出血	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
眼精疲労	1 (0.4)	1	0.37	3 (1.1)	3	1.15	4 (1.5)	4	1.47	8 (1.0)	8	1.00
結膜出血	1 (0.4)	1	0.37	1 (0.4)	2	0.76	0			2 (0.2)	3	0.37
後嚢部混濁	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
視力障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
増殖性網膜症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
兎眼性角膜炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
嚢胞様黄斑浮腫	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
霧視	1 (0.4)	1	0.37	2 (0.7)	2	0.76	1 (0.4)	1	0.37	4 (0.5)	4	0.50
網膜剥離	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
網膜裂孔	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
アレルギー性眼瞼炎	0			1 (0.4)	2	0.76	0			1 (0.1)	2	0.25
黄斑浮腫	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
黄斑変性	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
加齢黄斑変性	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
角膜炎	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
眼部不快感	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
眼瞼炎	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
眼瞼紅斑	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
眼瞼痙攣	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
結膜弛緩症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
硝子体出血	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
網膜症	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
網膜変性	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
網膜滲出物	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
網脈絡膜症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
乱視	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
皮膚および皮下組織障害	32	(11.6)	35	13.06	32	(11.8)	40	15.28	28	(10.3)	33	12.14	92	(11.2)	108	13.47
湿疹	16	(5.8)	18	6.72	6	(2.2)	6	2.29	9	(3.3)	10	3.68	31	(3.8)	34	4.24
そう痒症	3	(1.1)	3	1.12	3	(1.1)	4	1.53	3	(1.1)	3	1.10	9	(1.1)	10	1.25
接触皮膚炎	2	(0.7)	2	0.75	1	(0.4)	1	0.38	6	(2.2)	7	2.58	9	(1.1)	10	1.25
発疹	2	(0.7)	2	0.75	3	(1.1)	3	1.15	0				5	(0.6)	5	0.62
アトピー性皮膚炎	1	(0.4)	1	0.37	2	(0.7)	2	0.76	0				3	(0.4)	3	0.37
アレルギー性皮膚炎	1	(0.4)	1	0.37	2	(0.7)	2	0.76	0				3	(0.4)	3	0.37
乾癬	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
汗疹	1	(0.4)	1	0.37	2	(0.7)	2	0.76	0				3	(0.4)	3	0.37
脂漏性皮膚炎	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
日光皮膚炎	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
皮下出血	1	(0.4)	1	0.37	1	(0.4)	3	1.15	0				2	(0.2)	4	0.50
皮膚嚢腫	1	(0.4)	1	0.37	0				1	(0.4)	1	0.37	2	(0.2)	2	0.25
薬疹	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
蕁麻疹	1	(0.4)	1	0.37	3	(1.1)	4	1.53	0				4	(0.5)	5	0.62
ざ瘡	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
異汗性湿疹	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
過角化	0				3	(1.1)	3	1.15	0				3	(0.4)	3	0.37
環状肉芽腫	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
顔面腫脹	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
手皮膚炎	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
色素沈着障害	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
水疱	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
爪甲剥離症	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
爪破損	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
爪肥厚	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
皮脂欠乏症	0				0				3	(1.1)	3	1.10	3	(0.4)	3	0.37

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Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
皮膚炎	0				2	(0.7)	2	0.76	0				2	(0.2)	2	0.25
皮膚乾燥	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
皮膚腫瘤	0				0				2	(0.7)	2	0.74	2	(0.2)	2	0.25
慢性色素性紫斑	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
嵌入爪	0				1	(0.4)	1	0.38	1	(0.4)	1	0.37	2	(0.2)	2	0.25
痂皮	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
臨床検査	30	(10.9)	43	16.04	27	(10.0)	43	16.42	34	(12.5)	39	14.35	91	(11.1)	125	15.59
リパーゼ増加	6	(2.2)	8	2.99	0				15	(5.5)	15	5.52	21	(2.6)	23	2.87
血中プロインスリン減少	5	(1.8)	5	1.87	3	(1.1)	3	1.15	1	(0.4)	1	0.37	9	(1.1)	9	1.12
体重増加	4	(1.5)	4	1.49	19	(7.0)	19	7.26	1	(0.4)	1	0.37	24	(2.9)	24	2.99
遊離脂肪酸減少	4	(1.5)	5	1.87	4	(1.5)	5	1.91	1	(0.4)	1	0.37	9	(1.1)	11	1.37
インスリンＣペプチド減少	3	(1.1)	3	1.12	4	(1.5)	4	1.53	0				7	(0.9)	7	0.87
ヘリコバクター検査陽性	3	(1.1)	3	1.12	1	(0.4)	1	0.38	2	(0.7)	2	0.74	6	(0.7)	6	0.75
アミラーゼ増加	2	(0.7)	2	0.75	0				3	(1.1)	3	1.10	5	(0.6)	5	0.62
心電図Ｔ波振幅減少	2	(0.7)	2	0.75	0				0				2	(0.2)	2	0.25
アスパラギン酸アミノトランスフェラーゼ増加	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
アラニンアミノトランスフェラーゼ増加	1	(0.4)	1	0.37	1	(0.4)	1	0.38	2	(0.7)	2	0.74	4	(0.5)	4	0.50
γ－グルタミルトランスフェラーゼ増加	1	(0.4)	1	0.37	0				1	(0.4)	1	0.37	2	(0.2)	2	0.25
血圧上昇	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
血中カルシトニン増加	1	(0.4)	1	0.37	0				2	(0.7)	2	0.74	3	(0.4)	3	0.37
血中クレアチンホスホキナーゼMM増加	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
血中トリグリセリド増加	1	(0.4)	1	0.37	0				2	(0.7)	2	0.74	3	(0.4)	3	0.37

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
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PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
糸球体濾過率減少	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
心電図ＱＴ延長	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
尿中ケトン体陽性	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
白血球数増加	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
Ｃ－反応性蛋白増加	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
ウエスト周囲径増加	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
リウマチ因子増加	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
肝酵素上昇	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
眼圧上昇	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
頚動脈内膜中膜肥厚度増加	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
血中カリウム増加	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
血中クレアチンホスホキナーゼ増加	0				3	(1.1)	4	1.53	1	(0.4)	1	0.37	4	(0.5)	5	0.62
好酸球数増加	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
心雑音	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
体重減少	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
糖鎖抗原１２５増加	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
便潜血陽性	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
膵酵素増加	0				0				2	(0.7)	2	0.74	2	(0.2)	2	0.25
呼吸器、胸郭および縦隔障害	28	(10.2)	36	13.43	24	(8.9)	30	11.46	16	(5.9)	20	7.36	68	(8.3)	86	10.73
アレルギー性鼻炎	7	(2.5)	7	2.61	2	(0.7)	2	0.76	2	(0.7)	2	0.74	11	(1.3)	11	1.37
上気道の炎症	6	(2.2)	8	2.99	6	(2.2)	7	2.67	6	(2.2)	7	2.58	18	(2.2)	22	2.74
喘息	4	(1.5)	4	1.49	5	(1.8)	5	1.91	3	(1.1)	3	1.10	12	(1.5)	12	1.50
咳嗽	3	(1.1)	3	1.12	4	(1.5)	6	2.29	1	(0.4)	1	0.37	8	(1.0)	10	1.25
口腔咽頭痛	2	(0.7)	2	0.75	3	(1.1)	3	1.15	4	(1.5)	4	1.47	9	(1.1)	9	1.12
睡眠時無呼吸症候群	2	(0.7)	2	0.75	4	(1.5)	4	1.53	1	(0.4)	1	0.37	7	(0.9)	7	0.87

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PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
鼻漏	2 (0.7)	2	0.75	1 (0.4)	1	0.38	0			3 (0.4)	3	0.37
くしゃみ	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
呼吸障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
湿性咳嗽	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
肺気腫	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
肺線維症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
発声障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
慢性気管支炎	1 (0.4)	2	0.75	0			0			1 (0.1)	2	0.25
咽頭浮腫	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
胸膜痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
慢性閉塞性肺疾患	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
傷害、中毒および処置合併症	22 (8.0)	24	8.96	29 (10.7)	37	14.13	28 (10.3)	36	13.24	79 (9.6)	97	12.10
挫傷	5 (1.8)	5	1.87	6 (2.2)	7	2.67	9 (3.3)	10	3.68	20 (2.4)	22	2.74
脊椎圧迫骨折	2 (0.7)	2	0.75	0			1 (0.4)	1	0.37	3 (0.4)	3	0.37
節足動物咬傷	2 (0.7)	2	0.75	2 (0.7)	2	0.76	1 (0.4)	1	0.37	5 (0.6)	5	0.62
過量投与	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
眼内異物	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
胸椎骨折	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
偶発的過量投与	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
口唇損傷	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
歯牙損傷	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
節足動物刺傷	1 (0.4)	1	0.37	1 (0.4)	2	0.76	3 (1.1)	3	1.10	5 (0.6)	6	0.75
頭部損傷	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
熱中症	1 (0.4)	1	0.37	0			2 (0.7)	2	0.74	3 (0.4)	3	0.37
半月板損傷	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
皮下血腫	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
裂傷	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
肋骨骨折	1 (0.4)	1	0.37	2 (0.7)	2	0.76	1 (0.4)	1	0.37	4 (0.5)	4	0.50
靱帯捻挫	1 (0.4)	2	0.75	4 (1.5)	5	1.91	4 (1.5)	4	1.47	9 (1.1)	11	1.37
引っかき傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
下肢骨折	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
胸部損傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
筋損傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
誤薬投与	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
誤用量投与	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
腰椎骨折	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
骨挫傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
鎖骨骨折	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
擦過傷	0			0			1 (0.4)	2	0.74	1 (0.1)	2	0.25
刺創	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
四肢損傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
歯牙破折	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
手骨折	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
上顆炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
正中神経損傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
創傷	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
大腿骨頚部骨折	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
恥骨骨折	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
肉離れ	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
熱射病	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
熱傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
剥離骨折	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
皮膚擦過傷	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25

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Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
縫合関連合併症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
神経系障害	21 (7.6)	29	10.82	36 (13.3)	49	18.72	31 (11.4)	35	12.88	88 (10.7)	113	14.10
頭痛	7 (2.5)	11	4.10	7 (2.6)	12	4.58	15 (5.5)	17	6.25	29 (3.5)	40	4.99
浮動性めまい	3 (1.1)	6	2.24	8 (3.0)	9	3.44	3 (1.1)	3	1.10	14 (1.7)	18	2.25
感覚鈍麻	2 (0.7)	3	1.12	6 (2.2)	6	2.29	3 (1.1)	3	1.10	11 (1.3)	12	1.50
糖尿病性ニューロパチー	2 (0.7)	2	0.75	4 (1.5)	4	1.53	2 (0.7)	2	0.74	8 (1.0)	8	1.00
顔面麻痺	1 (0.4)	1	0.37	2 (0.7)	2	0.76	1 (0.4)	1	0.37	4 (0.5)	4	0.50
傾眠	1 (0.4)	1	0.37	1 (0.4)	2	0.76	0			2 (0.2)	3	0.37
頚動脈狭窄	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
腰髄神経根障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
視床梗塞	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
脳梗塞	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
咬舌	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
意識消失	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
頚動脈硬化症	0			3 (1.1)	3	1.15	0			3 (0.4)	3	0.37
頚腕症候群	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
血栓性脳梗塞	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
坐骨神経痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
失神寸前の状態	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
手根管症候群	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
神経痛	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
低血糖性意識消失	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
頭部不快感	0			1 (0.4)	1	0.38	1 (0.4)	2	0.74	2 (0.2)	3	0.37
平衡障害	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
片頭痛	0			2 (0.7)	2	0.76	1 (0.4)	1	0.37	3 (0.4)	3	0.37
末梢性ニューロパチー	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

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Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
味覚異常	0			0			3 (1.1)	3	1.10	3 (0.4)	3	0.37
肋間神経痛	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
一般・全身障害および投与部位の状態	18 (6.5)	19	7.09	25 (9.2)	27	10.31	29 (10.6)	34	12.51	72 (8.8)	80	9.98
末梢性浮腫	4 (1.5)	4	1.49	7 (2.6)	8	3.06	1 (0.4)	1	0.37	12 (1.5)	13	1.62
倦怠感	2 (0.7)	2	0.75	3 (1.1)	3	1.15	6 (2.2)	7	2.58	11 (1.3)	12	1.50
注射部位そう痒感	2 (0.7)	2	0.75	0			1 (0.4)	1	0.37	3 (0.4)	3	0.37
注射部位反応	2 (0.7)	2	0.75	0			2 (0.7)	2	0.74	4 (0.5)	4	0.50
異常感	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
脂肪組織増加	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
注射部位紅斑	1 (0.4)	1	0.37	0			3 (1.1)	3	1.10	4 (0.5)	4	0.50
注射部位腫脹	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
注射部位出血	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
注射部位変色	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
注射部位疼痛	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
投与部位腫瘤	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
末梢腫脹	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
悪寒	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
炎症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
胸部不快感	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
苦悶感	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
空腹	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
口渇	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
注射部位硬結	0			1 (0.4)	1	0.38	3 (1.1)	4	1.47	4 (0.5)	5	0.62
注射部位腫瘤	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
注射部位内出血	0			2 (0.7)	2	0.76	2 (0.7)	2	0.74	4 (0.5)	4	0.50

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
注入部位内出血	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
熱感	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
発熱	0			2 (0.7)	2	0.76	1 (0.4)	1	0.37	3 (0.4)	3	0.37
疲労	0			1 (0.4)	1	0.38	3 (1.1)	3	1.10	4 (0.5)	4	0.50
浮腫	0			3 (1.1)	3	1.15	2 (0.7)	2	0.74	5 (0.6)	5	0.62
無力症	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
疼痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
血管障害	15 (5.5)	15	5.60	16 (5.9)	16	6.11	7 (2.6)	8	2.94	38 (4.6)	39	4.86
高血圧	10 (3.6)	10	3.73	12 (4.4)	12	4.58	4 (1.5)	4	1.47	26 (3.2)	26	3.24
動脈硬化症	2 (0.7)	2	0.75	1 (0.4)	1	0.38	1 (0.4)	1	0.37	4 (0.5)	4	0.50
ほてり	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
起立性低血圧	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
内出血	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
静脈瘤	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
低血圧	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
末梢動脈閉塞性疾患	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
肝胆道系障害	10 (3.6)	13	4.85	12 (4.4)	17	6.49	12 (4.4)	15	5.52	34 (4.2)	45	5.61
脂肪肝	6 (2.2)	6	2.24	3 (1.1)	3	1.15	3 (1.1)	3	1.10	12 (1.5)	12	1.50
胆石症	3 (1.1)	3	1.12	3 (1.1)	3	1.15	3 (1.1)	3	1.10	9 (1.1)	9	1.12
肝嚢胞	1 (0.4)	1	0.37	1 (0.4)	1	0.38	2 (0.7)	2	0.74	4 (0.5)	4	0.50
胆嚢ポリープ	1 (0.4)	1	0.37	5 (1.8)	5	1.91	2 (0.7)	2	0.74	8 (1.0)	8	1.00
胆嚢炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
非アルコール性脂肪肝	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
肝機能異常	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
肝腫瘤	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12

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MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
肝障害	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
肝石灰化	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
急性胆嚢炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
慢性肝炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
薬物性肝障害	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
腎および尿路障害	10 (3.6)	10	3.73	7 (2.6)	9	3.44	6 (2.2)	7	2.58	23 (2.8)	26	3.24
腎嚢胞	5 (1.8)	5	1.87	2 (0.7)	2	0.76	2 (0.7)	2	0.74	9 (1.1)	9	1.12
尿管結石症	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
腎結石症	1 (0.4)	1	0.37	4 (1.5)	4	1.53	1 (0.4)	1	0.37	6 (0.7)	6	0.75
糖尿病性腎症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
尿閉	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
ネフローゼ症候群	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
腎機能障害	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
腎石灰沈着症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
水腎症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
尿路結石	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
慢性腎臓病	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
代謝および栄養障害	10 (3.6)	10	3.73	13 (4.8)	14	5.35	15 (5.5)	17	6.25	38 (4.6)	41	5.11
過体重	2 (0.7)	2	0.75	1 (0.4)	1	0.38	0			3 (0.4)	3	0.37
脂質異常症	2 (0.7)	2	0.75	2 (0.7)	2	0.76	2 (0.7)	2	0.74	6 (0.7)	6	0.75
高リパーゼ血症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
高脂血症	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
高尿酸血症	1 (0.4)	1	0.37	3 (1.1)	3	1.15	1 (0.4)	1	0.37	5 (0.6)	5	0.62
食欲減退	1 (0.4)	1	0.37	3 (1.1)	3	1.15	11 (4.0)	11	4.05	15 (1.8)	15	1.87
低カリウム血症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12

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Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
低血糖	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
高トリグリセリド血症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
脱水	0			1 (0.4)	1	0.38	1 (0.4)	2	0.74	2 (0.2)	3	0.37
痛風	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
肥満	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
耳および迷路障害	9 (3.3)	11	4.10	5 (1.8)	6	2.29	5 (1.8)	5	1.84	19 (2.3)	22	2.74
回転性めまい	5 (1.8)	7	2.61	2 (0.7)	3	1.15	3 (1.1)	3	1.10	10 (1.2)	13	1.62
頭位性回転性めまい	2 (0.7)	2	0.75	0			1 (0.4)	1	0.37	3 (0.4)	3	0.37
耳鳴	1 (0.4)	1	0.37	2 (0.7)	2	0.76	1 (0.4)	1	0.37	4 (0.5)	4	0.50
突発性難聴	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
耳漏	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
心臓障害	7 (2.5)	7	2.61	9 (3.3)	9	3.44	11 (4.0)	11	4.05	27 (3.3)	27	3.37
狭心症	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
心室性期外収縮	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
心障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
動悸	1 (0.4)	1	0.37	1 (0.4)	1	0.38	3 (1.1)	3	1.10	5 (0.6)	5	0.62
頻脈	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
冠動脈狭窄	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
完全房室ブロック	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
急性心筋梗塞	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
上室性期外収縮	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
上室性頻脈	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
心拡大	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
心筋虚血	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
心房細動	0			2 (0.7)	2	0.76	2 (0.7)	2	0.74	4 (0.5)	4	0.50

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Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
第一度房室ブロック	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
洞結節機能不全	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
洞性不整脈	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
精神障害	6 (2.2)	6	2.24	9 (3.3)	9	3.44	6 (2.2)	6	2.21	21 (2.6)	21	2.62
不眠症	6 (2.2)	6	2.24	6 (2.2)	6	2.29	2 (0.7)	2	0.74	14 (1.7)	14	1.75
うつ病	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
自殺企図	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
神経症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
睡眠障害	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
不安	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	6 (2.2)	6	2.24	6 (2.2)	8	3.06	5 (1.8)	5	1.84	17 (2.1)	19	2.37
皮膚乳頭腫	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
胃癌第１期	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
甲状腺新生物	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
子宮平滑筋腫	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
膀胱の良性新生物	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
アクロコルドン	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
リンパ節転移	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
基底細胞癌	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
甲状腺の良性新生物	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
大腸腺腫	0			0			3 (1.1)	3	1.10	3 (0.4)	3	0.37
乳癌	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
肺の悪性新生物	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
肺腺癌	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
副腎新生物	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
乏突起神経膠腫	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
生殖系および乳房障害	5 (1.8)	5	1.87	7 (2.6)	9	3.44	3 (1.1)	7	2.58	15 (1.8)	21	2.62
陰部そう痒症	1 (0.4)	1	0.37	3 (1.1)	3	1.15	0			4 (0.5)	4	0.50
亀頭包皮炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
前立腺石灰化	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
卵巣嚢胞	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
良性前立腺肥大症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
月経過多	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
子宮頚管ポリープ	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
子宮頚部嚢胞	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
子宮出血	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
子宮障害	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
子宮脱	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
子宮内膜増殖症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
女性化乳房	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
不規則月経	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
閉経期症状	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
内分泌障害	4 (1.5)	4	1.49	6 (2.2)	7	2.67	2 (0.7)	2	0.74	12 (1.5)	13	1.62
甲状腺嚢腫	2 (0.7)	2	0.75	5 (1.8)	5	1.91	1 (0.4)	1	0.37	8 (1.0)	8	1.00
甲状腺腫瘤	1 (0.4)	1	0.37	2 (0.7)	2	0.76	0			3 (0.4)	3	0.37
無痛性甲状腺炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
甲状腺機能亢進症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12

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	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
免疫系障害	3 (1.1)	4	1.49	2 (0.7)	2	0.76	2 (0.7)	2	0.74	7 (0.9)	8	1.00
季節性アレルギー	2 (0.7)	2	0.75	1 (0.4)	1	0.38	2 (0.7)	2	0.74	5 (0.6)	5	0.62
節足動物刺傷アレルギー	1 (0.4)	2	0.75	0			0			1 (0.1)	2	0.25
過敏症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
血液およびリンパ系障害	2 (0.7)	2	0.75	1 (0.4)	1	0.38	4 (1.5)	4	1.47	7 (0.9)	7	0.87
鉄欠乏性貧血	1 (0.4)	1	0.37	1 (0.4)	1	0.38	2 (0.7)	2	0.74	4 (0.5)	4	0.50
貧血	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
赤血球増加症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
脾腫	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
外科および内科処置	1 (0.4)	1	0.37	2 (0.7)	3	1.15	2 (0.7)	2	0.74	5 (0.6)	6	0.75
抜歯	1 (0.4)	1	0.37	1 (0.4)	2	0.76	0			2 (0.2)	3	0.37
心臓アブレーション	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
大腸ポリープ切除	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
白内障手術	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
先天性、家族性および遺伝性障害	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
表皮融解	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
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MedDRA version 20.0

表2.7.6.4.2-2. 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（器官別大分類及び基本語別）－安全性解析対象（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	275				271				273				819			
PYE (years)	268.00				261.81				271.84				801.65			
Events	88	(32.0)	152	56.72	55	(20.3)	84	32.08	108	(39.6)	210	77.25	251	(30.6)	446	55.64
胃腸障害	42	(15.3)	68	25.37	11	(4.1)	13	4.97	76	(27.8)	128	47.09	129	(15.8)	209	26.07
便秘	22	(8.0)	22	8.21	3	(1.1)	3	1.15	31	(11.4)	35	12.88	56	(6.8)	60	7.48
悪心	9	(3.3)	12	4.48	1	(0.4)	1	0.38	19	(7.0)	26	9.56	29	(3.5)	39	4.86
下痢	7	(2.5)	7	2.61	4	(1.5)	4	1.53	12	(4.4)	16	5.89	23	(2.8)	27	3.37
腹部膨満	5	(1.8)	5	1.87	0				3	(1.1)	3	1.10	8	(1.0)	8	1.00
胃食道逆流性疾患	4	(1.5)	4	1.49	0				1	(0.4)	1	0.37	5	(0.6)	5	0.62
胃炎	3	(1.1)	3	1.12	0				0				3	(0.4)	3	0.37
嘔吐	2	(0.7)	4	1.49	0				5	(1.8)	6	2.21	7	(0.9)	10	1.25
おくび	1	(0.4)	1	0.37	0				2	(0.7)	2	0.74	3	(0.4)	3	0.37
バレット食道	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
胃酸過多	1	(0.4)	1	0.37	0				1	(0.4)	1	0.37	2	(0.2)	2	0.25
胃潰瘍	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
十二指腸炎	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
消化不良	1	(0.4)	1	0.37	1	(0.4)	1	0.38	9	(3.3)	11	4.05	11	(1.3)	13	1.62
上腹部痛	1	(0.4)	1	0.37	1	(0.4)	1	0.38	2	(0.7)	2	0.74	4	(0.5)	4	0.50
軟便	1	(0.4)	1	0.37	0				3	(1.1)	4	1.47	4	(0.5)	5	0.62
腹部不快感	1	(0.4)	1	0.37	1	(0.4)	2	0.76	8	(2.9)	8	2.94	10	(1.2)	11	1.37
慢性胃炎	1	(0.4)	1	0.37	0				1	(0.4)	1	0.37	2	(0.2)	2	0.25
裂孔ヘルニア	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
びらん性胃炎	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12

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MedDRA version 20.0

Adverse events possibly or probably related to investigational medicinal product by system organ class and preferred term
treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
メレナ	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
胃腸障害	0			0			2 (0.7)	3	1.10	2 (0.2)	3	0.37
下腹部痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
鼓腸	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
口の感覚鈍麻	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
自己免疫性膵炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
腹痛	0			0			2 (0.7)	3	1.10	2 (0.2)	3	0.37
糞塊	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
臨床検査	18 (6.5)	29	10.82	23 (8.5)	36	13.75	19 (7.0)	22	8.09	60 (7.3)	87	10.85
リパーゼ増加	6 (2.2)	8	2.99	0			10 (3.7)	10	3.68	16 (2.0)	18	2.25
血中プロインスリン減少	5 (1.8)	5	1.87	3 (1.1)	3	1.15	1 (0.4)	1	0.37	9 (1.1)	9	1.12
体重増加	4 (1.5)	4	1.49	19 (7.0)	19	7.26	0			23 (2.8)	23	2.87
遊離脂肪酸減少	4 (1.5)	5	1.87	4 (1.5)	5	1.91	1 (0.4)	1	0.37	9 (1.1)	11	1.37
インスリンＣペプチド減少	3 (1.1)	3	1.12	4 (1.5)	4	1.53	0			7 (0.9)	7	0.87
アミラーゼ増加	2 (0.7)	2	0.75	0			3 (1.1)	3	1.10	5 (0.6)	5	0.62
血中カルシトニン増加	1 (0.4)	1	0.37	0			2 (0.7)	2	0.74	3 (0.4)	3	0.37
心電図ＱＴ延長	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
アラニンアミノトランスフェラーゼ増加	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
ウエスト周囲径増加	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
肝酵素上昇	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
頚動脈内膜中膜肥厚度増加	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
血中カリウム増加	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
血中クレアチンホスホキナーゼ増加	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

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Adverse events possibly or probably related to investigational medicinal product by system organ class and preferred term
treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
体重減少	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
糖鎖抗原１２５増加	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
膵酵素増加	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
一般・全身障害および投与部位の状態	12 (4.4)	13	4.85	10 (3.7)	10	3.82	15 (5.5)	18	6.62	37 (4.5)	41	5.11
倦怠感	2 (0.7)	2	0.75	1 (0.4)	1	0.38	3 (1.1)	3	1.10	6 (0.7)	6	0.75
注射部位そう痒感	2 (0.7)	2	0.75	0			1 (0.4)	1	0.37	3 (0.4)	3	0.37
注射部位反応	2 (0.7)	2	0.75	0			1 (0.4)	1	0.37	3 (0.4)	3	0.37
脂肪組織増加	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
注射部位紅斑	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
注射部位腫脹	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
注射部位変色	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
注射部位疼痛	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
投与部位腫瘤	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
末梢性浮腫	1 (0.4)	1	0.37	3 (1.1)	3	1.15	0			4 (0.5)	4	0.50
胸部不快感	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
空腹	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
口渇	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
注射部位硬結	0			1 (0.4)	1	0.38	3 (1.1)	4	1.47	4 (0.5)	5	0.62
注射部位腫瘤	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
注射部位内出血	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
疲労	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
浮腫	0			2 (0.7)	2	0.76	1 (0.4)	1	0.37	3 (0.4)	3	0.37
無力症	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25

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Adverse events possibly or probably related to investigational medicinal product by system organ class and preferred term
treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
眼障害	7 (2.5)	7	2.61	5 (1.8)	5	1.91	6 (2.2)	6	2.21	18 (2.2)	18	2.25
糖尿病網膜症	4 (1.5)	4	1.49	4 (1.5)	4	1.53	3 (1.1)	3	1.10	11 (1.3)	11	1.37
硝子体浮遊物	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
糖尿病性網膜浮腫	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
霧視	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
眼瞼紅斑	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
後嚢部混濁	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
網膜出血	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
網膜症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
代謝および栄養障害	6 (2.2)	6	2.24	2 (0.7)	2	0.76	10 (3.7)	10	3.68	18 (2.2)	18	2.25
過体重	2 (0.7)	2	0.75	1 (0.4)	1	0.38	0			3 (0.4)	3	0.37
高リパーゼ血症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
食欲減退	1 (0.4)	1	0.37	0			10 (3.7)	10	3.68	11 (1.3)	11	1.37
低カリウム血症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
低血糖	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
肥満	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
感染症および寄生虫症	5 (1.8)	5	1.87	0			2 (0.7)	2	0.74	7 (0.9)	7	0.87
胃腸炎	2 (0.7)	2	0.75	0			1 (0.4)	1	0.37	3 (0.4)	3	0.37
歯髄炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
副鼻腔炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
膀胱炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
ウイルス性上気道感染	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
皮膚および皮下組織障害	5 (1.8)	5	1.87	2 (0.7)	2	0.76	1 (0.4)	1	0.37	8 (1.0)	8	1.00

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Adverse events possibly or probably related to investigational medicinal product by system organ class and preferred term
treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
そう痒症	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
アトピー性皮膚炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
湿疹	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
蕁麻疹	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
皮下出血	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
皮膚腫瘤	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
神経系障害	4 (1.5)	7	2.61	7 (2.6)	8	3.06	10 (3.7)	11	4.05	21 (2.6)	26	3.24
感覚鈍麻	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
糖尿病性ニューロパチー	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
頭痛	1 (0.4)	1	0.37	1 (0.4)	1	0.38	4 (1.5)	4	1.47	6 (0.7)	6	0.75
浮動性めまい	1 (0.4)	4	1.49	3 (1.1)	3	1.15	2 (0.7)	2	0.74	6 (0.7)	9	1.12
傾眠	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
低血糖性意識消失	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
頭部不快感	0			0			1 (0.4)	2	0.74	1 (0.1)	2	0.25
片頭痛	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
味覚異常	0			0			3 (1.1)	3	1.10	3 (0.4)	3	0.37
耳および迷路障害	2 (0.7)	2	0.75	1 (0.4)	2	0.76	0			3 (0.4)	4	0.50
回転性めまい	2 (0.7)	2	0.75	1 (0.4)	2	0.76	0			3 (0.4)	4	0.50
傷害、中毒および処置合併症	2 (0.7)	2	0.75	2 (0.7)	2	0.76	0			4 (0.5)	4	0.50
皮下血腫	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
裂傷	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
偶発的過量投与	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
誤用量投与	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

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treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
肝胆道系障害	1 (0.4)	2	0.75	2 (0.7)	2	0.76	2 (0.7)	3	1.10	5 (0.6)	7	0.87
胆石症	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
胆嚢炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
肝機能異常	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
肝障害	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
胆嚢ポリープ	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
薬物性肝障害	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
筋骨格系および結合組織障害	1 (0.4)	1	0.37	1 (0.4)	1	0.38	2 (0.7)	4	1.47	4 (0.5)	6	0.75
腱鞘炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
関節痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
筋膜炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
四肢痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
背部痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
末径部痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
血管障害	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
内出血	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
高血圧	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
呼吸器、胸郭および縦隔障害	1 (0.4)	3	1.12	0			1 (0.4)	1	0.37	2 (0.2)	4	0.50
咳嗽	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
湿性咳嗽	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
鼻漏	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
胸膜痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
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treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
心臓障害	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
頻脈	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
上室性期外収縮	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
動悸	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
血液およびリンパ系障害	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
赤血球増加症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
大腸腺腫	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

表2.7.6.4.2-3. 重篤な有害事象（器官別大分類及び基本語別）－安全性解析対象（4183 試験）

	IDegLira N (%)	E	R	IDeg N (%)	E	R	Lira N (%)	E	R	Total N (%)	E	R
Number of subjects	275			271			273			819		
PYE (years)	268.00			261.81			271.84			801.65		
Events	17 (6.2)	18	6.72	13 (4.8)	16	6.11	14 (5.1)	14	5.15	44 (5.4)	48	5.99
胃腸障害	3 (1.1)	3	1.12	0			1 (0.4)	1	0.37	4 (0.5)	4	0.50
胃食道逆流性疾患	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
急性膵炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
大腸ポリープ	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
自己免疫性膵炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
傷害、中毒および処置合併症	3 (1.1)	3	1.12	0			1 (0.4)	1	0.37	4 (0.5)	4	0.50
胸椎骨折	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
脊椎圧迫骨折	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
半月板損傷	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
大腿骨頚部骨折	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
心臓障害	3 (1.1)	3	1.12	3 (1.1)	3	1.15	1 (0.4)	1	0.37	7 (0.9)	7	0.87
狭心症	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
心障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
完全房室ブロック	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
急性心筋梗塞	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
心筋虚血	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
洞結節機能不全	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
神経系障害	2 (0.7)	2	0.75	3 (1.1)	3	1.15	1 (0.4)	1	0.37	6 (0.7)	6	0.75

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
視床梗塞	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
脳梗塞	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
顔面麻痺	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
血栓性脳梗塞	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
手根管症候群	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
低血糖性意識消失	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	2 (0.7)	2	0.75	2 (0.7)	4	1.53	1 (0.4)	1	0.37	5 (0.6)	7	0.87
胃癌第１期	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
膀胱の良性新生物	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
リンパ節転移	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
乳癌	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
肺の悪性新生物	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
肺腺癌	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
副腎新生物	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
感染症および寄生虫症	1 (0.4)	1	0.37	2 (0.7)	2	0.76	2 (0.7)	2	0.74	5 (0.6)	5	0.62
ヘモフィルス性肺炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
帯状疱疹性髄膜炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
肺炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
蜂巣炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
扁桃炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
肝胆道系障害	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
胆嚢炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
急性胆嚢炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
眼障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
網膜剥離	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
呼吸器、胸郭および縦隔障害	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
睡眠時無呼吸症候群	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
代謝および栄養障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
低血糖	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
一般・全身障害および投与部位の状態	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
悪寒	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
外科および内科処置	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
心臓アブレーション	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
大腸ポリープ切除	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
血管障害	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
静脈瘤	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
末梢動脈閉塞性疾患	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
生殖系および乳房障害	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
子宮脱	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
子宮内膜増殖症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Serious adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
精神障害	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
自殺企図	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

表2.7.6.4.2-4. 重度の有害事象（器官別大分類及び基本語別）－安全性解析対象（4183 試験）

	IDegLira N (%)	E	R	IDeg N (%)	E	R	Lira N (%)	E	R	Total N (%)	E	R
Number of subjects	275			271			273			819		
PYE (years)	268.00			261.81			271.84			801.65		
Events	6 (2.2)	6	2.24	6 (2.2)	8	3.06	4 (1.5)	4	1.47	16 (2.0)	18	2.25
胃腸障害	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
急性膵炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
大腸炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
心臓障害	2 (0.7)	2	0.75	1 (0.4)	1	0.38	0			3 (0.4)	3	0.37
狭心症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
心障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
完全房室ブロック	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
肝胆道系障害	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
胆嚢炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
急性胆嚢炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
眼障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
網膜剥離	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
一般・全身障害および投与部位の状態	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
末梢性浮腫	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
感染症および寄生虫症	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Severe adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
帯状疱疹性髄膜炎	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
肺炎	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
呼吸器、胸郭および縦隔障害	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
胸膜痛	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
神経系障害	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
低血糖性意識消失	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	0				2	(0.7)	4	1.53	1	(0.4)	1	0.37	3	(0.4)	5	0.62
リンパ節転移	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
乳癌	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
肺の悪性新生物	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
肺腺癌	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
副腎新生物	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

表2.7.6.4.2-5. 中等度の有害事象（器官別大分類及び基本語別）－安全性解析対象（4183 試験）

	IDegLira N (%)	E	R	IDeg N (%)	E	R	Lira N (%)	E	R	Total N (%)	E	R
Number of subjects	275			271			273			819		
PYE (years)	268.00			261.81			271.84			801.65		
Events	31 (11.3)	40	14.93	29 (10.7)	40	15.28	23 (8.4)	29	10.67	83 (10.1)	109	13.60
感染症および寄生虫症	8 (2.9)	10	3.73	9 (3.3)	10	3.82	2 (0.7)	2	0.74	19 (2.3)	22	2.74
インフルエンザ	3 (1.1)	3	1.12	1 (0.4)	1	0.38	1 (0.4)	1	0.37	5 (0.6)	5	0.62
ウイルス性上気道感染	2 (0.7)	2	0.75	3 (1.1)	3	1.15	0			5 (0.6)	5	0.62
胃腸炎	2 (0.7)	2	0.75	1 (0.4)	1	0.38	0			3 (0.4)	3	0.37
マイコプラズマ感染	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
感染性腸炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
帯状疱疹	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
咽頭炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
咽頭扁桃炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
扁桃炎	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
膀胱炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
筋骨格系および結合組織障害	6 (2.2)	6	2.24	4 (1.5)	4	1.53	2 (0.7)	3	1.10	12 (1.5)	13	1.62
変形性関節症	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
骨粗鬆症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
背部痛	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
変形性脊椎症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
腱鞘炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
関節リウマチ	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
関節炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
関節周囲炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Moderate adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
関節痛	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
弾発指	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
椎間板突出	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
胃腸障害	5 (1.8)	5	1.87	3 (1.1)	3	1.15	6 (2.2)	8	2.94	14 (1.7)	16	2.00
下痢	1 (0.4)	1	0.37	1 (0.4)	1	0.38	2 (0.7)	3	1.10	4 (0.5)	5	0.62
耳下腺腫大	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
上腹部痛	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
食中毒	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
便秘	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
胃食道逆流性疾患	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
胃腸障害	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
自己免疫性膵炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
裂肛	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
嘔吐	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
齲歯	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
傷害、中毒および処置合併症	4 (1.5)	4	1.49	4 (1.5)	4	1.53	4 (1.5)	4	1.47	12 (1.5)	12	1.50
胸椎骨折	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
脊椎圧迫骨折	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
半月板損傷	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
裂傷	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
下肢骨折	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
偶発的過量投与	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
腰椎骨折	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
創傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
大腿骨頚部骨折	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Moderate adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
熱傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
肋骨骨折	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
靭帯捻挫	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
代謝および栄養障害	3 (1.1)	3	1.12	4 (1.5)	4	1.53	0			7 (0.9)	7	0.87
過体重	2 (0.7)	2	0.75	1 (0.4)	1	0.38	0			3 (0.4)	3	0.37
低血糖	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
脱水	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
痛風	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
肥満	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
呼吸器、胸郭および縦隔障害	2 (0.7)	3	1.12	3 (1.1)	3	1.15	2 (0.7)	2	0.74	7 (0.9)	8	1.00
上気道の炎症	1 (0.4)	2	0.75	0			1 (0.4)	1	0.37	2 (0.2)	3	0.37
睡眠時無呼吸症候群	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
咳嗽	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
慢性閉塞性肺疾患	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
神経系障害	2 (0.7)	2	0.75	3 (1.1)	3	1.15	3 (1.1)	3	1.10	8 (1.0)	8	1.00
視床梗塞	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
脳梗塞	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
顔面麻痺	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
頚腕症候群	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
血栓性脳梗塞	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
坐骨神経痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
手根管症候群	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
眼障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12

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Moderate adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
視力障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
耳および迷路障害	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
回転性めまい	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
心臓障害	1 (0.4)	1	0.37	2 (0.7)	2	0.76	0			3 (0.4)	3	0.37
狭心症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
急性心筋梗塞	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
心筋虚血	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
内分泌障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
無痛性甲状腺炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
皮膚および皮下組織障害	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
アトピー性皮膚炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
嵌入爪	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
胃癌第１期	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
基底細胞癌	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
臨床検査	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
体重増加	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12

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MedDRA version 20.0

Moderate adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
一般・全身障害および投与部位の状態	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
末梢性浮腫	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
肝胆道系障害	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
胆嚢ポリープ	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
血管障害	0				2	(0.7)	2	0.76	2	(0.7)	2	0.74	4	(0.5)	4	0.50
起立性低血圧	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
高血圧	0				1	(0.4)	1	0.38	1	(0.4)	1	0.37	2	(0.2)	2	0.25
末梢動脈閉塞性疾患	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
腎および尿路障害	0				1	(0.4)	1	0.38	1	(0.4)	1	0.37	2	(0.2)	2	0.25
ネフローゼ症候群	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
尿路結石	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
生殖系および乳房障害	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
子宮内膜増殖症	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
精神障害	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
自殺企図	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
免疫系障害	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
過敏症	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12

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MedDRA version 20.0

表2.7.6.4.2-6. 軽度の有害事象（器官別大分類及び基本語別）－安全性解析対象（4183 試験）

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	275				271				273				819			
PYE (years)	268.00				261.81				271.84				801.65			
Events	223	(81.1)	827	308.58	209	(77.1)	781	298.31	225	(82.4)	852	313.42	657	(80.2)	2460	306.87
感染症および寄生虫症	150	(54.5)	281	104.85	133	(49.1)	263	100.46	146	(53.5)	268	98.59	429	(52.4)	812	101.29
ウイルス性上気道感染	105	(38.2)	164	61.19	91	(33.6)	158	60.35	94	(34.4)	155	57.02	290	(35.4)	477	59.50
インフルエンザ	12	(4.4)	12	4.48	8	(3.0)	8	3.06	8	(2.9)	8	2.94	28	(3.4)	28	3.49
咽頭炎	11	(4.0)	13	4.85	14	(5.2)	17	6.49	9	(3.3)	9	3.31	34	(4.2)	39	4.86
胃腸炎	10	(3.6)	10	3.73	6	(2.2)	7	2.67	11	(4.0)	12	4.41	27	(3.3)	29	3.62
気管支炎	7	(2.5)	9	3.36	6	(2.2)	7	2.67	8	(2.9)	8	2.94	21	(2.6)	24	2.99
歯周炎	6	(2.2)	6	2.24	6	(2.2)	10	3.82	5	(1.8)	5	1.84	17	(2.1)	21	2.62
副鼻腔炎	5	(1.8)	6	2.24	0				2	(0.7)	4	1.47	7	(0.9)	10	1.25
外耳炎	4	(1.5)	4	1.49	0				3	(1.1)	4	1.47	7	(0.9)	8	1.00
膀胱炎	4	(1.5)	6	2.24	7	(2.6)	9	3.44	3	(1.1)	3	1.10	14	(1.7)	18	2.25
結膜炎	3	(1.1)	3	1.12	4	(1.5)	4	1.53	6	(2.2)	6	2.21	13	(1.6)	13	1.62
帯状疱疹	3	(1.1)	3	1.12	4	(1.5)	4	1.53	1	(0.4)	1	0.37	8	(1.0)	8	1.00
鼻咽頭炎	3	(1.1)	7	2.61	3	(1.1)	5	1.91	3	(1.1)	3	1.10	9	(1.1)	15	1.87
化膿	2	(0.7)	2	0.75	0				0				2	(0.2)	2	0.25
感染性皮膚炎	2	(0.7)	2	0.75	0				0				2	(0.2)	2	0.25
口腔ヘルペス	2	(0.7)	2	0.75	0				2	(0.7)	2	0.74	4	(0.5)	4	0.50
歯肉炎	2	(0.7)	2	0.75	2	(0.7)	2	0.76	2	(0.7)	3	1.10	6	(0.7)	7	0.87
歯肉膿瘍	2	(0.7)	2	0.75	0				0				2	(0.2)	2	0.25
皮膚感染	2	(0.7)	2	0.75	0				0				2	(0.2)	2	0.25
扁桃炎	2	(0.7)	2	0.75	2	(0.7)	2	0.76	2	(0.7)	2	0.74	6	(0.7)	6	0.75
ウイルス性胃腸炎	1	(0.4)	1	0.37	1	(0.4)	1	0.38	1	(0.4)	1	0.37	3	(0.4)	3	0.37

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Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
ノロウイルス性胃腸炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
ヘモフィルス性肺炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
ヘリコバクター感染	1 (0.4)	1	0.37	4 (1.5)	4	1.53	4 (1.5)	4	1.47	9 (1.1)	9	1.12
ヘルペスウイルス感染	1 (0.4)	1	0.37	0			2 (0.7)	2	0.74	3 (0.4)	3	0.37
β 溶血性レンサ球菌感染	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
感染性大腸炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
気道感染	1 (0.4)	2	0.75	0			0			1 (0.1)	2	0.25
歯髄炎	1 (0.4)	1	0.37	0			2 (0.7)	2	0.74	3 (0.4)	3	0.37
上気道感染	1 (0.4)	1	0.37	2 (0.7)	3	1.15	4 (1.5)	5	1.84	7 (0.9)	9	1.12
真菌性膀胱炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
足部白癬	1 (0.4)	1	0.37	1 (0.4)	1	0.38	5 (1.8)	5	1.84	7 (0.9)	7	0.87
体部白癬	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
蓄膿	1 (0.4)	2	0.75	0			0			1 (0.1)	2	0.25
爪囲炎	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
頭部白癬	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
尿管炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
尿道炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
肺炎	1 (0.4)	1	0.37	1 (0.4)	1	0.38	2 (0.7)	2	0.74	4 (0.5)	4	0.50
麦粒腫	1 (0.4)	1	0.37	0			3 (1.1)	3	1.10	4 (0.5)	4	0.50
鼻炎	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
毛包炎	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
せつ	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
ウイルス性結膜炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
ヘリコバクター性胃炎	0			1 (0.4)	1	0.38	2 (0.7)	2	0.74	3 (0.4)	3	0.37
マイコプラズマ性肺炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
陰部ヘルペス	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
感染性湿疹	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

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Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
感染性皮膚嚢腫	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
急性副鼻腔炎	0				1	(0.4)	2	0.76	1	(0.4)	1	0.37	2	(0.2)	3	0.37
限局性感染	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
細菌性胃腸炎	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
細菌性気管支炎	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
細菌性腸炎	0				0				1	(0.4)	2	0.74	1	(0.1)	2	0.25
食道カンジダ症	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
腎盂腎炎	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
須毛瘡	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
中耳炎	0				1	(0.4)	1	0.38	1	(0.4)	1	0.37	2	(0.2)	2	0.25
爪の皮膚糸状菌症	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
尿路感染	0				3	(1.1)	3	1.15	0				3	(0.4)	3	0.37
膿痂疹性湿疹	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
白癬感染	0				2	(0.7)	2	0.76	0				2	(0.2)	2	0.25
腹部膿瘍	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
蜂巣炎	0				1	(0.4)	1	0.38	3	(1.1)	3	1.10	4	(0.5)	4	0.50
扁桃周囲炎	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
膣感染	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
胃腸障害	95	(34.5)	180	67.16	61	(22.5)	107	40.87	112	(41.0)	210	77.25	268	(32.7)	497	62.00
便秘	26	(9.5)	27	10.07	12	(4.4)	12	4.58	37	(13.6)	41	15.08	75	(9.2)	80	9.98
下痢	14	(5.1)	19	7.09	11	(4.1)	13	4.97	23	(8.4)	28	10.30	48	(5.9)	60	7.48
胃食道逆流性疾患	13	(4.7)	13	4.85	7	(2.6)	7	2.67	7	(2.6)	7	2.58	27	(3.3)	27	3.37
口内炎	10	(3.6)	11	4.10	3	(1.1)	4	1.53	1	(0.4)	1	0.37	14	(1.7)	16	2.00
悪心	9	(3.3)	13	4.85	5	(1.8)	7	2.67	23	(8.4)	30	11.04	37	(4.5)	50	6.24
齲歯	9	(3.3)	9	3.36	6	(2.2)	6	2.29	7	(2.6)	8	2.94	22	(2.7)	23	2.87
腹部膨満	8	(2.9)	8	2.99	3	(1.1)	3	1.15	3	(1.1)	3	1.10	14	(1.7)	14	1.75

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MedDRA version 20.0

Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
慢性胃炎	8 (2.9)	8	2.99	8 (3.0)	8	3.06	7 (2.6)	8	2.94	23 (2.8)	24	2.99
上腹部痛	7 (2.5)	7	2.61	5 (1.8)	5	1.91	3 (1.1)	3	1.10	15 (1.8)	15	1.87
消化不良	6 (2.2)	7	2.61	1 (0.4)	1	0.38	10 (3.7)	12	4.41	17 (2.1)	20	2.49
大腸ポリープ	6 (2.2)	6	2.24	3 (1.1)	3	1.15	4 (1.5)	4	1.47	13 (1.6)	13	1.62
胃炎	5 (1.8)	5	1.87	2 (0.7)	2	0.76	4 (1.5)	4	1.47	11 (1.3)	11	1.37
歯周病	4 (1.5)	5	1.87	3 (1.1)	3	1.15	5 (1.8)	5	1.84	12 (1.5)	13	1.62
腹痛	3 (1.1)	3	1.12	3 (1.1)	5	1.91	3 (1.1)	4	1.47	9 (1.1)	12	1.50
腹部不快感	3 (1.1)	4	1.49	6 (2.2)	7	2.67	9 (3.3)	9	3.31	18 (2.2)	20	2.49
バレット食道	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
胃ポリープ	2 (0.7)	2	0.75	3 (1.1)	3	1.15	5 (1.8)	5	1.84	10 (1.2)	10	1.25
胃潰瘍	2 (0.7)	2	0.75	1 (0.4)	1	0.38	0			3 (0.4)	3	0.37
大腸炎	2 (0.7)	2	0.75	2 (0.7)	2	0.76	2 (0.7)	2	0.74	6 (0.7)	6	0.75
腸炎	2 (0.7)	3	1.12	0			0			2 (0.2)	3	0.37
直腸炎	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
裂孔ヘルニア	2 (0.7)	2	0.75	2 (0.7)	2	0.76	0			4 (0.5)	4	0.50
嘔吐	2 (0.7)	4	1.49	3 (1.1)	3	1.15	9 (3.3)	11	4.05	14 (1.7)	18	2.25
おくび	1 (0.4)	1	0.37	0			2 (0.7)	2	0.74	3 (0.4)	3	0.37
びらん性胃炎	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
胃酸過多	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
胃十二指腸炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
血便排泄	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
口腔内不快感	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
歯痛	1 (0.4)	1	0.37	1 (0.4)	1	0.38	3 (1.1)	3	1.10	5 (0.6)	5	0.62
痔核	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
耳下腺腫大	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
十二指腸炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
小腸炎	1 (0.4)	2	0.75	1 (0.4)	1	0.38	0			2 (0.2)	3	0.37

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MedDRA version 20.0

Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
食中毒	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
食道ポリープ	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
軟便	1 (0.4)	1	0.37	1 (0.4)	1	0.38	3 (1.1)	4	1.47	5 (0.6)	6	0.75
鼡径ヘルニア	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
ブルンネル腺過形成	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
メレナ	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
胃腸障害	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
下腹部痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
機能性胃腸障害	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
鼓腸	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
口の感覚鈍麻	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
口腔内潰瘍形成	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
口内乾燥	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
歯周の炎症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
歯肉腫脹	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
痔出血	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
十二指腸ポリープ	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
腸憩室	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
糞塊	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
裂肛	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
膵萎縮	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
膵嚢胞	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
筋骨格系および結合組織障害	48 (17.5)	57	21.27	48 (17.7)	67	25.59	39 (14.3)	57	20.97	135 (16.5)	181	22.58
背部痛	11 (4.0)	11	4.10	12 (4.4)	12	4.58	12 (4.4)	15	5.52	35 (4.3)	38	4.74
関節痛	7 (2.5)	7	2.61	5 (1.8)	6	2.29	5 (1.8)	6	2.21	17 (2.1)	19	2.37
筋肉痛	6 (2.2)	6	2.24	3 (1.1)	3	1.15	2 (0.7)	2	0.74	11 (1.3)	11	1.37

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Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
筋痙縮	4 (1.5)	6	2.24	2 (0.7)	2	0.76	4 (1.5)	6	2.21	10 (1.2)	14	1.75
関節周囲炎	3 (1.1)	3	1.12	4 (1.5)	4	1.53	2 (0.7)	2	0.74	9 (1.1)	9	1.12
筋骨格硬直	3 (1.1)	3	1.12	1 (0.4)	1	0.38	4 (1.5)	5	1.84	8 (1.0)	9	1.12
椎間板突出	3 (1.1)	3	1.12	2 (0.7)	2	0.76	1 (0.4)	1	0.37	6 (0.7)	6	0.75
変形性脊椎症	3 (1.1)	3	1.12	4 (1.5)	4	1.53	2 (0.7)	2	0.74	9 (1.1)	9	1.12
関節炎	2 (0.7)	2	0.75	0			1 (0.4)	1	0.37	3 (0.4)	3	0.37
筋骨格痛	2 (0.7)	2	0.75	2 (0.7)	3	1.15	1 (0.4)	1	0.37	5 (0.6)	6	0.75
四肢痛	2 (0.7)	2	0.75	2 (0.7)	2	0.76	1 (0.4)	1	0.37	5 (0.6)	5	0.62
関節拘縮	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
関節腫脹	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
筋骨格系胸痛	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
頚部痛	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
骨炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
側腹部痛	1 (0.4)	1	0.37	2 (0.7)	2	0.76	0			3 (0.4)	3	0.37
変形性関節症	1 (0.4)	1	0.37	6 (2.2)	6	2.29	2 (0.7)	2	0.74	9 (1.1)	9	1.12
腱鞘炎	1 (0.4)	1	0.37	2 (0.7)	2	0.76	3 (1.1)	3	1.10	6 (0.7)	6	0.75
腱痛	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
横紋筋融解症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
滑液嚢腫	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
筋膜炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
頚部脊柱管狭窄症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
結節性変形性関節症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
腰部脊柱管狭窄症	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
骨粗鬆症	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
骨痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
脊柱管狭窄症	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
脊椎すべり症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

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MedDRA version 20.0

Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira				IDeg				Lira				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
足底筋膜炎	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
弾発指	0				4	(1.5)	4	1.53	1	(0.4)	1	0.37	5	(0.6)	5	0.62
椎間板障害	0				1	(0.4)	1	0.38	1	(0.4)	1	0.37	2	(0.2)	2	0.25
肋間筋肉痛	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
腱炎	0				1	(0.4)	1	0.38	0				1	(0.1)	1	0.12
肖径部痛	0				0				1	(0.4)	1	0.37	1	(0.1)	1	0.12
眼障害	43	(15.6)	50	18.66	28	(10.3)	37	14.13	39	(14.3)	48	17.66	110	(13.4)	135	16.84
糖尿病網膜症	17	(6.2)	17	6.34	12	(4.4)	14	5.35	11	(4.0)	11	4.05	40	(4.9)	42	5.24
アレルギー性結膜炎	4	(1.5)	5	1.87	2	(0.7)	2	0.76	2	(0.7)	2	0.74	8	(1.0)	9	1.12
白内障	4	(1.5)	4	1.49	4	(1.5)	4	1.53	5	(1.8)	5	1.84	13	(1.6)	13	1.62
眼乾燥	3	(1.1)	3	1.12	2	(0.7)	2	0.76	1	(0.4)	1	0.37	6	(0.7)	6	0.75
黄斑線維症	2	(0.7)	2	0.75	0				1	(0.4)	1	0.37	3	(0.4)	3	0.37
硝子体浮遊物	2	(0.7)	2	0.75	1	(0.4)	1	0.38	2	(0.7)	2	0.74	5	(0.6)	5	0.62
糖尿病性網膜浮腫	2	(0.7)	2	0.75	0				1	(0.4)	1	0.37	3	(0.4)	3	0.37
網膜出血	2	(0.7)	2	0.75	1	(0.4)	1	0.38	1	(0.4)	1	0.37	4	(0.5)	4	0.50
緑内障	2	(0.7)	2	0.75	0				3	(1.1)	3	1.10	5	(0.6)	5	0.62
黄斑円孔	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
眼の炎症	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
眼出血	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
眼精疲労	1	(0.4)	1	0.37	3	(1.1)	3	1.15	4	(1.5)	4	1.47	8	(1.0)	8	1.00
結膜出血	1	(0.4)	1	0.37	1	(0.4)	2	0.76	0				2	(0.2)	3	0.37
後嚢部混濁	1	(0.4)	1	0.37	0				1	(0.4)	1	0.37	2	(0.2)	2	0.25
増殖性網膜症	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
兎眼性角膜炎	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
嚢胞様黄斑浮腫	1	(0.4)	1	0.37	0				0				1	(0.1)	1	0.12
霧視	1	(0.4)	1	0.37	2	(0.7)	2	0.76	1	(0.4)	1	0.37	4	(0.5)	4	0.50

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Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
網膜裂孔	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
アレルギー性眼瞼炎	0			1 (0.4)	2	0.76	0			1 (0.1)	2	0.25
黄斑浮腫	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
黄斑変性	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
加齢黄斑変性	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
角膜炎	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
眼部不快感	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
眼瞼炎	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
眼瞼紅斑	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
眼瞼痙攣	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
結膜弛緩症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
硝子体出血	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
網膜症	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
網膜剥離	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
網膜変性	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
網膜滲出物	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
網脈絡膜症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
乱視	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
皮膚および皮下組織障害	31 (11.3)	34	12.69	32 (11.8)	39	14.90	28 (10.3)	33	12.14	91 (11.1)	106	13.22
湿疹	16 (5.8)	18	6.72	6 (2.2)	6	2.29	9 (3.3)	10	3.68	31 (3.8)	34	4.24
そう痒症	3 (1.1)	3	1.12	3 (1.1)	4	1.53	3 (1.1)	3	1.10	9 (1.1)	10	1.25
接触皮膚炎	2 (0.7)	2	0.75	1 (0.4)	1	0.38	6 (2.2)	7	2.58	9 (1.1)	10	1.25
発疹	2 (0.7)	2	0.75	3 (1.1)	3	1.15	0			5 (0.6)	5	0.62
アレルギー性皮膚炎	1 (0.4)	1	0.37	2 (0.7)	2	0.76	0			3 (0.4)	3	0.37
乾癬	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
汗疹	1 (0.4)	1	0.37	2 (0.7)	2	0.76	0			3 (0.4)	3	0.37

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	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
脂漏性皮膚炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
日光皮膚炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
皮下出血	1 (0.4)	1	0.37	1 (0.4)	3	1.15	0			2 (0.2)	4	0.50
皮膚嚢腫	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
薬疹	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
蕁麻疹	1 (0.4)	1	0.37	3 (1.1)	4	1.53	0			4 (0.5)	5	0.62
ざ瘡	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
アトピー性皮膚炎	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
異汗性湿疹	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
過角化	0			3 (1.1)	3	1.15	0			3 (0.4)	3	0.37
環状肉芽腫	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
顔面腫脹	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
手皮膚炎	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
色素沈着障害	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
水疱	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
爪甲剥離症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
爪破損	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
爪肥厚	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
皮脂欠乏症	0			0			3 (1.1)	3	1.10	3 (0.4)	3	0.37
皮膚炎	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
皮膚乾燥	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
皮膚腫瘤	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
慢性色素性紫斑	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
嵌入爪	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
痂皮	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
臨床検査	29 (10.5)	42	15.67	27 (10.0)	43	16.42	34 (12.5)	39	14.35	90 (11.0)	124	15.47

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
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PYE: Patient years of exposure (1 PYE = 365.25 days)
Treatment emergent: 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.
MedDRA version 20.0

Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
リパーゼ増加	6 (2.2)	8	2.99	0			15 (5.5)	15	5.52	21 (2.6)	23	2.87
血中プロインスリン減少	5 (1.8)	5	1.87	3 (1.1)	3	1.15	1 (0.4)	1	0.37	9 (1.1)	9	1.12
遊離脂肪酸減少	4 (1.5)	5	1.87	4 (1.5)	5	1.91	1 (0.4)	1	0.37	9 (1.1)	11	1.37
インスリンＣペプチド減少	3 (1.1)	3	1.12	4 (1.5)	4	1.53	0			7 (0.9)	7	0.87
ヘリコバクター検査陽性	3 (1.1)	3	1.12	1 (0.4)	1	0.38	2 (0.7)	2	0.74	6 (0.7)	6	0.75
体重増加	3 (1.1)	3	1.12	19 (7.0)	19	7.26	1 (0.4)	1	0.37	23 (2.8)	23	2.87
アミラーゼ増加	2 (0.7)	2	0.75	0			3 (1.1)	3	1.10	5 (0.6)	5	0.62
心電図Ｔ波振幅減少	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
アスパラギン酸アミノトランスフェラーゼ増加	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
アラニンアミノトランスフェラーゼ増加	1 (0.4)	1	0.37	1 (0.4)	1	0.38	2 (0.7)	2	0.74	4 (0.5)	4	0.50
γ－グルタミルトランスフェラーゼ増加	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
血圧上昇	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
血中カルシトニン増加	1 (0.4)	1	0.37	0			2 (0.7)	2	0.74	3 (0.4)	3	0.37
血中クレアチンホスホキナーゼMM増加	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
血中トリグリセリド増加	1 (0.4)	1	0.37	0			2 (0.7)	2	0.74	3 (0.4)	3	0.37
糸球体濾過率減少	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
心電図ＱＴ延長	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
尿中ケトン体陽性	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
白血球数増加	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
Ｃ－反応性蛋白増加	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
ウエスト周囲径増加	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
リウマチ因子増加	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
肝酵素上昇	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

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MedDRA version 20.0

Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
眼圧上昇	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
頚動脈内膜中膜肥厚度増加	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
血中カリウム増加	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
血中クレアチンホスホキナーゼ増加	0			3 (1.1)	4	1.53	1 (0.4)	1	0.37	4 (0.5)	5	0.62
好酸球数増加	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
心雑音	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
体重減少	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
糖鎖抗原１２５増加	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
便潜血陽性	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
膵酵素増加	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
呼吸器、胸郭および縦隔障害	26 (9.5)	33	12.31	21 (7.7)	27	10.31	14 (5.1)	17	6.25	61 (7.4)	77	9.61
アレルギー性鼻炎	7 (2.5)	7	2.61	2 (0.7)	2	0.76	2 (0.7)	2	0.74	11 (1.3)	11	1.37
上気道の炎症	5 (1.8)	6	2.24	6 (2.2)	7	2.67	5 (1.8)	6	2.21	16 (2.0)	19	2.37
喘息	4 (1.5)	4	1.49	5 (1.8)	5	1.91	3 (1.1)	3	1.10	12 (1.5)	12	1.50
咳嗽	3 (1.1)	3	1.12	3 (1.1)	5	1.91	1 (0.4)	1	0.37	7 (0.9)	9	1.12
口腔咽頭痛	2 (0.7)	2	0.75	3 (1.1)	3	1.15	4 (1.5)	4	1.47	9 (1.1)	9	1.12
鼻漏	2 (0.7)	2	0.75	1 (0.4)	1	0.38	0			3 (0.4)	3	0.37
くしゃみ	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
呼吸障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
湿性咳嗽	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
睡眠時無呼吸症候群	1 (0.4)	1	0.37	3 (1.1)	3	1.15	0			4 (0.5)	4	0.50
肺気腫	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
肺線維症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
発声障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
慢性気管支炎	1 (0.4)	2	0.75	0			0			1 (0.1)	2	0.25

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MedDRA version 20.0

Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
咽頭浮腫	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
神経系障害	19 (6.9)	27	10.07	32 (11.8)	45	17.19	28 (10.3)	32	11.77	79 (9.6)	104	12.97
頭痛	7 (2.5)	11	4.10	7 (2.6)	12	4.58	15 (5.5)	17	6.25	29 (3.5)	40	4.99
浮動性めまい	3 (1.1)	6	2.24	8 (3.0)	9	3.44	3 (1.1)	3	1.10	14 (1.7)	18	2.25
感覚鈍麻	2 (0.7)	3	1.12	6 (2.2)	6	2.29	3 (1.1)	3	1.10	11 (1.3)	12	1.50
糖尿病性ニューロパチー	2 (0.7)	2	0.75	4 (1.5)	4	1.53	2 (0.7)	2	0.74	8 (1.0)	8	1.00
顔面麻痺	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
傾眠	1 (0.4)	1	0.37	1 (0.4)	2	0.76	0			2 (0.2)	3	0.37
頚動脈狭窄	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
腰髄神経根障害	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
咬舌	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
意識消失	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
頚動脈硬化症	0			3 (1.1)	3	1.15	0			3 (0.4)	3	0.37
失神寸前の状態	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
神経痛	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
頭部不快感	0			1 (0.4)	1	0.38	1 (0.4)	2	0.74	2 (0.2)	3	0.37
平衡障害	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
片頭痛	0			2 (0.7)	2	0.76	1 (0.4)	1	0.37	3 (0.4)	3	0.37
末梢性ニューロパチー	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
味覚異常	0			0			3 (1.1)	3	1.10	3 (0.4)	3	0.37
肋間神経痛	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
一般・全身障害および投与部位の状態	18 (6.5)	19	7.09	24 (8.9)	25	9.55	29 (10.6)	34	12.51	71 (8.7)	78	9.73
末梢性浮腫	4 (1.5)	4	1.49	6 (2.2)	6	2.29	1 (0.4)	1	0.37	11 (1.3)	11	1.37
倦怠感	2 (0.7)	2	0.75	3 (1.1)	3	1.15	6 (2.2)	7	2.58	11 (1.3)	12	1.50

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Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
注射部位そう痒感	2 (0.7)	2	0.75	0			1 (0.4)	1	0.37	3 (0.4)	3	0.37
注射部位反応	2 (0.7)	2	0.75	0			2 (0.7)	2	0.74	4 (0.5)	4	0.50
異常感	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
脂肪組織増加	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
注射部位紅斑	1 (0.4)	1	0.37	0			3 (1.1)	3	1.10	4 (0.5)	4	0.50
注射部位腫脹	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
注射部位出血	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
注射部位変色	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
注射部位疼痛	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
投与部位腫瘤	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
末梢腫脹	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
悪寒	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
炎症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
胸部不快感	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
苦悶感	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
空腹	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
口渇	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
注射部位硬結	0			1 (0.4)	1	0.38	3 (1.1)	4	1.47	4 (0.5)	5	0.62
注射部位腫瘤	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
注射部位内出血	0			2 (0.7)	2	0.76	2 (0.7)	2	0.74	4 (0.5)	4	0.50
注入部位内出血	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
熱感	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
発熱	0			2 (0.7)	2	0.76	1 (0.4)	1	0.37	3 (0.4)	3	0.37
疲労	0			1 (0.4)	1	0.38	3 (1.1)	3	1.10	4 (0.5)	4	0.50
浮腫	0			3 (1.1)	3	1.15	2 (0.7)	2	0.74	5 (0.6)	5	0.62
無力症	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
疼痛	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12

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MedDRA version 20.0

Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
傷害、中毒および処置合併症	18 (6.5)	20	7.46	25 (9.2)	33	12.60	24 (8.8)	32	11.77	67 (8.2)	85	10.60
挫傷	5 (1.8)	5	1.87	6 (2.2)	7	2.67	9 (3.3)	10	3.68	20 (2.4)	22	2.74
節足動物咬傷	2 (0.7)	2	0.75	2 (0.7)	2	0.76	1 (0.4)	1	0.37	5 (0.6)	5	0.62
過量投与	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
眼内異物	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
偶発的過量投与	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
口唇損傷	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
歯牙損傷	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
脊椎圧迫骨折	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
節足動物刺傷	1 (0.4)	1	0.37	1 (0.4)	2	0.76	3 (1.1)	3	1.10	5 (0.6)	6	0.75
頭部損傷	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
熱中症	1 (0.4)	1	0.37	0			2 (0.7)	2	0.74	3 (0.4)	3	0.37
皮下血腫	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
肋骨骨折	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
靭帯捻挫	1 (0.4)	2	0.75	4 (1.5)	5	1.91	3 (1.1)	3	1.10	8 (1.0)	10	1.25
引っかき傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
胸部損傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
筋損傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
誤薬投与	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
誤用量投与	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
骨挫傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
鎖骨骨折	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
擦過傷	0			0			1 (0.4)	2	0.74	1 (0.1)	2	0.25
刺創	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
四肢損傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
歯牙破折	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
手骨折	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12

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MedDRA version 20.0

Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
上顎炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
正中神経損傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
創傷	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
恥骨骨折	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
肉離れ	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
熱射病	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
剥離骨折	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
皮膚擦過傷	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
縫合関連合併症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
裂傷	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
血管障害	15 (5.5)	15	5.60	14 (5.2)	14	5.35	5 (1.8)	6	2.21	34 (4.2)	35	4.37
高血圧	10 (3.6)	10	3.73	11 (4.1)	11	4.20	3 (1.1)	3	1.10	24 (2.9)	24	2.99
動脈硬化症	2 (0.7)	2	0.75	1 (0.4)	1	0.38	1 (0.4)	1	0.37	4 (0.5)	4	0.50
ほてり	1 (0.4)	1	0.37	0			1 (0.4)	1	0.37	2 (0.2)	2	0.25
起立性低血圧	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
内出血	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
静脈瘤	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
低血圧	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
末梢動脈閉塞性疾患	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
肝胆道系障害	10 (3.6)	12	4.48	12 (4.4)	17	6.49	11 (4.0)	13	4.78	33 (4.0)	42	5.24
脂肪肝	6 (2.2)	6	2.24	3 (1.1)	3	1.15	3 (1.1)	3	1.10	12 (1.5)	12	1.50
胆石症	3 (1.1)	3	1.12	3 (1.1)	3	1.15	3 (1.1)	3	1.10	9 (1.1)	9	1.12
肝嚢胞	1 (0.4)	1	0.37	1 (0.4)	1	0.38	2 (0.7)	2	0.74	4 (0.5)	4	0.50
胆嚢ポリープ	1 (0.4)	1	0.37	5 (1.8)	5	1.91	1 (0.4)	1	0.37	7 (0.9)	7	0.87
非アルコール性脂肪肝	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37

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Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
肝機能異常	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
肝腫瘤	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
肝障害	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
肝石灰化	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
慢性肝炎	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
薬物性肝障害	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
腎および尿路障害	10 (3.6)	10	3.73	7 (2.6)	8	3.06	5 (1.8)	6	2.21	22 (2.7)	24	2.99
腎嚢胞	5 (1.8)	5	1.87	2 (0.7)	2	0.76	2 (0.7)	2	0.74	9 (1.1)	9	1.12
尿管結石症	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
腎結石症	1 (0.4)	1	0.37	4 (1.5)	4	1.53	1 (0.4)	1	0.37	6 (0.7)	6	0.75
糖尿病性腎症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
尿閉	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
腎機能障害	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
腎石灰沈着症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
水腎症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
尿路結石	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
慢性腎臓病	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
耳および迷路障害	8 (2.9)	10	3.73	5 (1.8)	6	2.29	4 (1.5)	4	1.47	17 (2.1)	20	2.49
回転性めまい	4 (1.5)	6	2.24	2 (0.7)	3	1.15	2 (0.7)	2	0.74	8 (1.0)	11	1.37
頭位性回転性めまい	2 (0.7)	2	0.75	0			1 (0.4)	1	0.37	3 (0.4)	3	0.37
耳鳴	1 (0.4)	1	0.37	2 (0.7)	2	0.76	1 (0.4)	1	0.37	4 (0.5)	4	0.50
突発性難聴	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
耳漏	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
代謝および栄養障害	7 (2.5)	7	2.61	9 (3.3)	10	3.82	15 (5.5)	17	6.25	31 (3.8)	34	4.24

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Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
脂質異常症	2 (0.7)	2	0.75	2 (0.7)	2	0.76	2 (0.7)	2	0.74	6 (0.7)	6	0.75
高リパーゼ血症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
高脂血症	1 (0.4)	1	0.37	1 (0.4)	1	0.38	0			2 (0.2)	2	0.25
高尿酸血症	1 (0.4)	1	0.37	3 (1.1)	3	1.15	1 (0.4)	1	0.37	5 (0.6)	5	0.62
食欲減退	1 (0.4)	1	0.37	3 (1.1)	3	1.15	11 (4.0)	11	4.05	15 (1.8)	15	1.87
低カリウム血症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
高トリグリセリド血症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
脱水	0			0			1 (0.4)	2	0.74	1 (0.1)	2	0.25
痛風	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
精神障害	6 (2.2)	6	2.24	9 (3.3)	9	3.44	5 (1.8)	5	1.84	20 (2.4)	20	2.49
不眠症	6 (2.2)	6	2.24	6 (2.2)	6	2.29	2 (0.7)	2	0.74	14 (1.7)	14	1.75
うつ病	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
神経症	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
睡眠障害	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
不安	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
生殖系および乳房障害	5 (1.8)	5	1.87	6 (2.2)	8	3.06	3 (1.1)	7	2.58	14 (1.7)	20	2.49
陰部そう痒症	1 (0.4)	1	0.37	3 (1.1)	3	1.15	0			4 (0.5)	4	0.50
亀頭包皮炎	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
前立腺石灰化	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
卵巣嚢胞	1 (0.4)	1	0.37	1 (0.4)	1	0.38	1 (0.4)	1	0.37	3 (0.4)	3	0.37
良性前立腺肥大症	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
月経過多	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
子宮頚管ポリープ	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
子宮頚部嚢胞	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
子宮出血	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12

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Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
子宮障害	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
子宮脱	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
女性化乳房	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
不規則月経	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
閉経期症状	0			1 (0.4)	1	0.38	1 (0.4)	1	0.37	2 (0.2)	2	0.25
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	5 (1.8)	5	1.87	4 (1.5)	4	1.53	3 (1.1)	3	1.10	12 (1.5)	12	1.50
皮膚乳頭腫	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
甲状腺新生物	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
子宮平滑筋腫	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
膀胱の良性新生物	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
アクロコルドン	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
甲状腺の良性新生物	0			2 (0.7)	2	0.76	0			2 (0.2)	2	0.25
大腸腺腫	0			0			3 (1.1)	3	1.10	3 (0.4)	3	0.37
乏突起神経膠腫	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
心臓障害	4 (1.5)	4	1.49	6 (2.2)	6	2.29	11 (4.0)	11	4.05	21 (2.6)	21	2.62
心室性期外収縮	2 (0.7)	2	0.75	0			0			2 (0.2)	2	0.25
動悸	1 (0.4)	1	0.37	1 (0.4)	1	0.38	3 (1.1)	3	1.10	5 (0.6)	5	0.62
頻脈	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
冠動脈狭窄	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
上室性期外収縮	0			0			2 (0.7)	2	0.74	2 (0.2)	2	0.25
上室性頻脈	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
心拡大	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
心筋虚血	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

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	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
心房細動	0			2 (0.7)	2	0.76	2 (0.7)	2	0.74	4 (0.5)	4	0.50
第一度房室ブロック	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
洞結節機能不全	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
洞性不整脈	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
内分泌障害	3 (1.1)	3	1.12	6 (2.2)	7	2.67	2 (0.7)	2	0.74	11 (1.3)	12	1.50
甲状腺嚢腫	2 (0.7)	2	0.75	5 (1.8)	5	1.91	1 (0.4)	1	0.37	8 (1.0)	8	1.00
甲状腺腫瘤	1 (0.4)	1	0.37	2 (0.7)	2	0.76	0			3 (0.4)	3	0.37
甲状腺機能亢進症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
免疫系障害	3 (1.1)	4	1.49	1 (0.4)	1	0.38	2 (0.7)	2	0.74	6 (0.7)	7	0.87
季節性アレルギー	2 (0.7)	2	0.75	1 (0.4)	1	0.38	2 (0.7)	2	0.74	5 (0.6)	5	0.62
節足動物刺傷アレルギー	1 (0.4)	2	0.75	0			0			1 (0.1)	2	0.25
血液およびリンパ系障害	2 (0.7)	2	0.75	1 (0.4)	1	0.38	4 (1.5)	4	1.47	7 (0.9)	7	0.87
鉄欠乏性貧血	1 (0.4)	1	0.37	1 (0.4)	1	0.38	2 (0.7)	2	0.74	4 (0.5)	4	0.50
貧血	1 (0.4)	1	0.37	0			0			1 (0.1)	1	0.12
赤血球増加症	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
脾腫	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
外科および内科処置	1 (0.4)	1	0.37	2 (0.7)	3	1.15	2 (0.7)	2	0.74	5 (0.6)	6	0.75
抜歯	1 (0.4)	1	0.37	1 (0.4)	2	0.76	0			2 (0.2)	3	0.37
心臓アブレーション	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
大腸ポリープ切除	0			0			1 (0.4)	1	0.37	1 (0.1)	1	0.12
白内障手術	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

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	IDegLira			IDeg			Lira			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
先天性、家族性および遺伝性障害	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12
表皮融解	0			1 (0.4)	1	0.38	0			1 (0.1)	1	0.12

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
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表2.7.6.4.2-7. 試験の中止に至った有害事象の一覧－FAS（4183 試験）

Subject ID/ Treatment/ Age/Sex/BMI	AE No./ Adj. No.	System Organ Class/ Preferred Term/ Reported Term	Onset date/ Outcome/ Adj. date	Study day/ Duration (days)	Serious/ Severity	Related to technical complaint	Related to trial product/ Action
503001/ Lira/ 72/Male/22.9	2/ NA	胃腸障害/ 胃腸障害/ GASTROINTESTINAL DISORDERS	08FEB2016/ Recovered/Resolved	61/ 9	Non-serious/ Moderate	No	Probable/ Drug Withdrawn
509025/ IDegLira/ 72/Male/23.8	1/ 1	良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）/ 胃癌第１期/ GASTRIC CANCER(CSTAGE IA)	08MAR2017/ Recovered/Resolved/ 13MAR2017	181/ 90	Serious/ Moderate	No	Unlikely/ Drug Withdrawn
511017/ IDegLira/ 47/Female/35.6	3/ NA	代謝および栄養障害/ 過体重/ OVER BODY WEIGHT	07JAN2017/ Not recovered/Not resolved	185/ UNK	Non-serious/ Moderate	No	Possible/ Drug Withdrawn
511018/ IDegLira/ 49/Female/36.8	2/ NA	代謝および栄養障害/ 過体重/ OVER BODY WEIGHT	16JAN2017/ Not recovered/Not resolved	182/ UNK	Non-serious/ Moderate	No	Possible/ Drug Withdrawn
511019/ IDeg/ 35/Female/33.8	1/ NA	代謝および栄養障害/ 過体重/ OVER BODY WEIGHT	12APR2017/ Not recovered/Not resolved	267/ UNK	Non-serious/ Moderate	No	Probable/ Drug Withdrawn
512015/ Lira/ 51/Female/30.1	3/ NA	肝胆道系障害/ 薬物性肝障害/ DRUG HEPATOPATHY	24MAR2017/ Not recovered/Not resolved	183/ UNK	Non-serious/ Mild	No	Possible/ Drug Withdrawn
517037/ IDegLira/ 56/Male/27.4	2/ NA	胃腸障害/ 便秘/ CONSTIPATION WORENING	01JAN2017/ Not recovered/Not resolved	93/ UNK	Non-serious/ Mild	No	Possible/ Drug Withdrawn

BMI: Body mass index (kg/m^2) at baseline, Age: Age in years at baseline, AE: Adverse event
Adj: adjudication, No: Number, NA: Not Applicable, UNK: Unknown
Treatment emergent: 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.
Treatment emergent is evaluated based on investigators onset date.
Relationship is based on investigator(s) assessment. MedDRA version 20.0.

Adverse events leading to withdrawal - full analysis set

Subject ID/ Treatment/ Age/Sex/BMI	AE No./ Adj. No.	System Organ Class/ Preferred Term/ Reported Term	Onset date/ Outcome/ Adj. date	Study day/ Duration (days)	Serious/ Severity	Related to technical complaint	Related to trial product/ Action
519003/ IDeg/ 68/Male/23.9	1/ NA	胃腸障害/ 口の感覚鈍麻/ NUMBNESS OF TONGUE	20FEB2016/ Not recovered/Not resolved	45/ UNK	Non-serious/ Mild	No	Possible/ Drug Withdrawn
519007/ IDegLira/ 70/Male/20.6	1/ NA	耳および迷路障害/ 回転性めまい/ VERTIGO	29JUN2016/ Not recovered/Not resolved	96/ UNK	Non-serious/ Moderate	No	Possible/ Drug Withdrawn
525016/ IDegLira/ 70/Male/24.1	1/ 1	胃腸障害/ 急性膵炎/ PANCREATITIS ACUTE	25SEP2016/ Recovered/Resolved/ 28SEP2016	62/ 20	Serious/ Severe	No	Unlikely/ Drug Withdrawn
529025/ Lira/ 67/Female/22.8	6/ 2	胃腸障害/ 自己免疫性膵炎/ TYPE2 AUTOIMMUNE PANCREATITIS	24JAN2017/ Recovering/Resolving	194/ 310	Serious/ Moderate	No	Possible/ Drug Withdrawn
548012/ IDeg/ 67/Female/43.3	2/ NA	臨床検査/ 体重増加/ WEIGHT INCREASED	10NOV2016/ Not recovered/Not resolved	141/ UNK	Non-serious/ Mild	No	Probable/ Drug Withdrawn
553009/ IDeg/ 70/Male/24.6	1/ NA	感染症および寄生虫症/ 帯状疱疹性髄膜炎/ VARICELLA-ZOSTER VIRUS MENINGITIS	08OCT2016/ Recovering/Resolving	54/ 39	Serious/ Severe	No	Unlikely/ Drug Withdrawn
556010/ IDegLira/ 75/Female/20.9	1/ 1	心臓障害/ 心障害/ HEART DISEASE, UNSPECIFIED (SUSPECTED)	11APR2017/ Fatal/ 11APR2017	291/ 1	Serious/ Severe	No	Unlikely/ Dose Not Changed

BMI: Body mass index (kg/m^2) at baseline, Age: Age in years at baseline, AE: Adverse event
Adj: adjudication, No: Number, NA: Not Applicable, UNK: Unknown
Treatment emergent: 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.
Treatment emergent is evaluated based on investigators onset date.
Relationship is based on investigator(s) assessment. MedDRA version 20.0.

Adverse events leading to withdrawal - full analysis set

Subject ID/ Treatment/ Age/Sex/BMI	AE No./ Adj. No.	System Organ Class/ Preferred Term/ Reported Term	Onset date/ Outcome/ Adj. date	Study day/ Duration (days)	Serious/ Severity	Related to technical complaint	Related to trial product/ Action
561011/ Lira/ 51/Female/28.5	6/ 1	良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）/ 乳癌/ BREAST CARCINOMA(RIGHT)	26APR2017/ Recovering/Resolving / 01MAY2017	265/ 64	Serious/ Severe	No	Unlikely/ Drug Withdrawn
563003/ IDegLira/ 53/Male/23.2	1/ NA	臨床検査/ リパーゼ増加/ LIPASE INCREASED	12APR2016/ Recovered/Resolved	30/ 28	Non-serious/ Mild	No	Possible/ Drug Withdrawn
	2/ NA	臨床検査/ アミラーゼ増加/ BLOOD PANCREATIC AMYLASE INCREASED	26APR2016/ Recovered/Resolved	44/ 14	Non-serious/ Mild	No	Possible/ Drug Withdrawn
567004/ IDeg/ 44/Male/31.1	1/ 1	良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）/ 乏突起神経膠腫/ SUSPICION OF OLIGODENDROGLIOMA	05OCT2016/ Not recovered/Not resolved	63/ UNK	Non-serious/ Mild	No	Unlikely/ Drug Withdrawn
567009/ Lira/ 41/Female/34.2	2/ NA	精神障害/ 自殺企図/ UNSUCCESSFUL SUICIDE	18DEC2016/ Recovered/Resolved	101/ 10	Serious/ Moderate	No	Unlikely/ Drug Withdrawn
572019/ IDeg/ 53/Female/23.9	1/ NA	感染症および寄生虫症/ 帯状疱疹/ HERPES ZOSTER	23SEP2016/ Not recovered/Not resolved	22/ UNK	Non-serious/ Moderate	No	Unlikely/ Drug Withdrawn
578003/ Lira/ 49/Male/25.2	4/ NA	胃腸障害/ 嘔吐/ VOMITING	02OCT2016/ Recovered/Resolved	16/ 1	Non-serious/ Mild	No	Probable/ Drug Withdrawn

BMI: Body mass index (kg/m^2) at baseline, Age: Age in years at baseline, AE: Adverse event
Adj: adjudication, No: Number, NA: Not Applicable, UNK: Unknown
Treatment emergent: 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.
Treatment emergent is evaluated based on investigators onset date.
Relationship is based on investigator(s) assessment. MedDRA version 20.0.

2.7.6.5. NN9068-4184

2.7.6.5.1 臨床試験概要

治験依頼者名： Novo Nordisk A/S, Novo Allé, 2880 Bagsværd, Denmark	
有効成分名： インスリン デグルデク／リラグルチド（IDegLira）	
治験 ID： NN9068-4184	
Trial Registration ID-number： NCT02911948	UTN：U1111-1178-3453 Japanese registration number：JapicCTI-163385
治験の標題： DUAL™ II Japan：経口糖尿病薬と Basal インスリン又は混合／配合インスリンとの併用療法で十分な血糖コントロールが得られていない日本人 2 型糖尿病患者を対象とした、メトホルミン併用下におけるインスリン デグルデク／リラグルチド及びインスリン デグルデクの有効性及び安全性を比較する二重盲検試験	
治験責任医師名： 計 38 名の治験責任医師（治験実施施設ごとに 1 名）が任命された。以下の治験責任医師が「治験総括報告書への署名責任を有する医師（signatory investigator）」に任命された： Dr. [redacted]	
治験実施施設： 日本国内 38 施設で本試験を実施し、38 施設でスクリーニング、37 施設で無作為割り付けを行った。	
公表文献（引用文献）： 本治験総括報告書作成時点での公表文献はなし	
治験期間： 開始日：2016 年 9 月 21 日 終了日：2017 年 11 月 22 日	**開発のフェーズ**： 第 3a 相
Cut-off date： ここに提示する結果は、2017 年 12 月 11 日時点での臨床データベースに基づいている。	
報告書作成日： 2018 年 4 月 23 日	
目的： 主要目的： • 日本人2型糖尿病患者を対象として、投与後26週における血糖コントロールについて、IDegLiraのIDegに対する優越性を検証する。 副次的目的： • 日本人2型糖尿病患者を対象として、投与後26週におけるIDegLira及びIDegの全般的な有効性及び安全性を比較検討する。	
治験方法： 本試験は、日本人 2 型糖尿病患者を対象とした、26 週間、無作為割り付け、2 群並行、二重盲検、多施設、treat-to-target 試験であった。メトホルミン単剤又はメトホルミンと経口糖尿病薬〔スルホニルウレア薬（SU）、グリニド、α-グルコシダーゼ阻害薬（α-GI）、ナトリウム-グルコース共輸送体 2（SGLT-2）阻害薬又はチアゾリジン薬（TZD）のいずれか〕を併用した Basal インスリン又は混合／配合インスリンによる	

治療で十分な血糖コントロールが得られていない被験者を適格例とした。「十分な血糖コントロールが得られていない 2 型糖尿病患者」とは、HbA1c が 7.5%（58 mmol/mol）以上 11.0%（97 mmol/mol）以下の患者と定義した。本試験では日本人 2 型糖尿病患者における IDegLira の有効性及び安全性を IDeg と比較した。IDeg の最高用量は 50 単位とした。

計画及び解析された被験者数：

計画された被験者数（各群に 1：1 の割合で無作為割り付け）は 210 例であった。203 例が試験を完了した。

	IDegLira N (%)	IDeg N (%)	Total N (%)
Screened			267
Screening failures			57
Randomised	105 (100.0)	105 (100.0)	210 (100.0)
Exposed	105 (100.0)	105 (100.0)	210 (100.0)
Withdrawn at/after randomisation	0	7 (6.7)	7 (3.3)
Included in the trial in violation of the inclusion and/or exclusion criteria	0	1 (1.0)	1 (0.5)
Lack of efficacy	0	1 (1.0)	1 (0.5)
Withdrawal of consent	0	2 (1.9)	2 (1.0)
Other	0	3 (2.9)	3 (1.4)
Completed	105 (100.0)	98 (93.3)	203 (96.7)
Full analysis set (FAS)	105 (100.0)	105 (100.0)	210 (100.0)
Safety analysis set (SAS)	105 (100.0)	105 (100.0)	210 (100.0)

N: Number of subjects, %: Percentage of randomised subjects

診断及び主要な組入れ基準：

被験者の募集率が非常に低かったため、試験開始日から 3 ヵ月後の 2016 年 12 月に、選択基準及び除外基準を変更した。この時点での被験者の登録率は約 40%であった。

前治療のインスリン及び経口糖尿病薬の安定した治療の期間を「90 日」以上から「60 日」以上とし、この 60 日間のインスリン投与量の変動幅を「10%」以内から「20%」以内に変更した。

ジペプチジルペプチダーゼ 4（DPP-4）阻害薬の使用が許容されない期間も同様に「90 日」以上から「60 日」以上とし、さらに、過去に GLP-1 受容体作動薬で治療されていた被験者であっても、少なくとも 60 日間治療されていない被験者であれば組み入れ可能とした。

<u>主な選択基準：</u>

- 性別不問、同意取得時点で年齢20歳以上の日本人被験者。
- 2型糖尿病患者と診断され（臨床診断に基づく）、スクリーニング前の罹病期間が6ヶ月以上の被験者。
- HbA1c 7.5%（58 mmol/mol）以上、11.0%（97 mmol/mol）以下（中央検査機関で測定）の被験者。
- スクリーニングの60日以上前から安定した投与量での、Basalインスリン（IDeg、インスリン グラルギン、インスリン デテミル又はNPHインスリン等）又は混合／配合インスリン（二相性インスリン アスパルト、インスリン デグルデク／インスリン アスパルト等）の1日1回又は2回の投与を受けている被験者。スクリーニング前の60日間は、1日総インスリン投与量は20単位以上50単位以下で（スクリーニング実施日も同様）、かつ投与量の変動は±20%以内とした。また、以下と併用したインスリン治療であることとした。

- スクリーニングの60日以上前から安定した投与量での、国内で承認されている用法・用量に従ったメトホルミンによる治療
- メトホルミンに加えて、スクリーニングの60日以上前から安定した投与量での、国内で承認されている用法・用量に従った経口糖尿病薬単剤（SU、グリニド、α-GI、SGLT-2阻害薬又はTZDのいずれか）による治療

- BMI（kg/m^2）が23以上の被験者。

主な除外基準：

- スクリーニング前30日以内に何らかの治験薬の投与を受けた被験者。
- スクリーニング前60日以内に糖尿病治療薬（混合／配合インスリン、Basalインスリン、メトホルミン、SU、グリニド、α-GI、SGLT-2阻害薬又はTZDを除く）の投与を受けた、又は糖代謝に影響を及ぼすと考えられる併用薬剤の変更が予測される被験者（副腎皮質ステロイド剤の全身投与、Bolusインスリンの投与等）（治験責任医師の判断による）。
- スクリーニング前60 日以内にGLP-1 受容体作動薬の投与を受けた被験者、又はいずれかの時点で安全性に対する懸念、忍容性上の問題、又は薬効欠如（治験責任医師の判断による）の理由によりGLP-1 受容体作動薬の投与を中止した被験者。
- スクリーニング前60日以内にDPP-4阻害薬の投与を受けた被験者。
- 肝機能障害（アラニンアミノトランスフェラーゼ又はアスパラギン酸アミノトランスフェラーゼが基準範囲上限の2.5倍以上）を有する被験者。
- 腎機能障害（CKD-EPI式によるeGFRが60 ml/min/1.73m^2未満）を有する被験者。
- スクリーニング時のカルシトニン濃度が50 ng/L以上である被験者。
- 急性又は慢性膵炎の既往歴を有する被験者。
- 本人又は家族が、甲状腺髄様癌又は多発性内分泌腫瘍症候群2型の既往歴を有する被験者。
- 心不全（NYHA分類クラスIV）を有する被験者。

被験薬及び使用機器、用量及び投与方法、ロット番号：

IDegLira（Xultophy®）

1 mL あたり IDeg 100 単位とリラグルチド 3.6 mg の固定比率の配合剤、ペン型注入器（PDS290、3 mL）と一体化したプレフィルド製剤として提供された。大腿部、上腕部（三角筋部）又は腹〕に皮下注射した。IDegLira の推奨開始用量は 10 用量ステップ（IDeg 10 単位／リラグルチド 0.36 mg）とし、治験責任医師の判断により 16 用量ステップ（IDeg 16 単位／リラグルチド 0.6 mg）まで選択可能とした。最高用量の 50 用量ステップ（IDeg 50 単位／リラグルチド 1.8 mg）まで、朝食前血糖値 4.0～5.0 mmol/L（72～90 mg/dL）を目標として、事前に規定した投与量調節アルゴリズムに従い、1 週間に 2 回投与量調節を行った。ロット番号：FP51596（有効期限：2018 年 2 月 4 日）

投与期間：

試験期間は約 29 週間（2 週間のスクリーニング期間、26 週間の投与期間、及び投与終了来院 7 日後の電話コンタクトによる事後調査）であった。

対照薬及び使用機器、用量及び投与方法、ロット番号：

IDeg（トレシーバ®）

1 mL あたり 100 単位、ペン型注入器（PDS290、3 mL）と一体化したプレフィルド製剤として提供された。大腿部、上腕部（三角筋部）又は腹〕に皮下注射した。IDeg の推奨開始用量は 10 単位とし、治験責任医師の判断により 16 単位まで選択可能とした。最高用量の 50 単位まで、朝食前血糖値 4.0～5.0 mmol/L（72～90 mg/dL）を目標とした規定の投与量調節アルゴリズムに従い、1 週間に 2 回投与量調節を行った。ロット番号：FP51569（有効期限：2018 年 5 月 13 日）

評価基準：有効性

プライマリーエンドポイント：

HbA1c のベースラインから投与後 26 週までの変化量

有効性に関する補足的セカンダリーエンドポイント：

- 投与後26週における1日インスリン投与量
- 体重のベースラインから投与後26週までの変化量
- 投与後26週におけるレスポンダー（はい／いいえ）：
  - HbA1cが7.0%未満
  - HbA1cが7.0%未満、体重の増加がみられない
  - HbA1cが7.0%未満、投与期間の最後の12週間に重大な又は血糖値確定症候性低血糖の発現がない
  - HbA1cが7.0%未満、体重の増加がなく、かつ投与期間の最後の12週間に重大な又は血糖値確定症候性低血糖の発現がない
  - HbA1cが6.5%以下
  - HbA1cが6.5%以下、体重の増加がみられない
  - HbA1cが6.5%以下、投与期間の最後の12週間に重大な又は血糖値確定症候性低血糖の発現がない
  - HbA1cが6.5%以下で、体重の増加がなく、かつ投与期間の最後の12週間に重大な又は血糖値確定症候性低血糖の発現がない
- 以下の項目ベースラインから投与後26週までの変化量：
  - 空腹時血糖値
  - ウエスト周囲径
  - 血圧（収縮期及び拡張期）
  - 9点血糖値プロファイル（血糖自己測定）
    - 9点血糖値プロファイル（各測定点）
    - 9点血糖値プロファイルの平均
    - 食後血糖増加量（朝食、昼食及び夕食前から各食後90分までの増加量に基づく）の平均。すべての食事による増加量の平均は、すべての利用可能な増加量の平均として計算される。
- 投与後26週における脂質プロファイル〔総コレステロール、低比重リポタンパク質（LDL）コレステロール、高比重リポタンパク質（HDL）コレステロール、超低比重リポタンパク質（VLDL）コレステロール、トリグリセリド及び遊離脂肪酸〕
- 以下の患者報告アウトカム（PRO）におけるベースラインから投与後26週までの変化：
  - Diabetes Therapy-Related Quality of life（DTR-QOL）質問票
  - EuroQol-5D-5L（EQ-5D-5L）質問票

評価基準：安全性

- 26週間の治験薬投与下の有害事象の発現件数
- 26週間の治験薬投与下の重大な又は血糖値確定低血糖の発現件数
- 26週間の治験薬投与下の重大な又は血糖値確定症候性低血糖の発現件数
- 26週間の治験薬投与下の重大な又は血糖値確定症候性夜間低血糖の発現件数
- 26週間の治験薬投与下のADAの低血糖分類による低血糖の発現件数
- 以下の臨床評価におけるベースラインから投与後26週までの変化：
  - 身体検査
  - 眼底検査又は眼底写真
  - 心電図
  - 脈拍数
- 以下の臨床検査におけるベースラインから投与後26週までの変化：
  - 血液生化学的検査（アミラーゼ及びリパーゼ含む）
  - 血液学的検査
  - カルシトニン

統計手法：

検出力の算出：

- 被験者数は、有意水準5%の両側検定、完了例の治療間差の平均を0.45%、中止例（15%と仮定）における有効性の維持を0.2%、及び標準偏差を1.0%と仮定し、t-統計量を用いて決定した。優越性の検定はFASを対象に行うこととした。これらの仮定は、IDegLira及びIDegの第3a相開発プロフラムでの経験に基づいた。これらの仮定及び1：1の無作為割り付けの比率に基づき、被験者数を各投与群105例（計210例を無作為割り付け）とした。これにより少なくとも84.5%の検出力が確保された。

解析対象集団：

- 最大の解析対象集団（FAS）：FASには無作為割り付けされたすべての被験者が含まれた。FASにおける統計的な評価はintention-to-treatの原則に従い、被験者はas randomisedの評価に寄与した。
- 安全性解析対象集団（SAS）：SASには被験薬又は対照薬の投与を少なくとも1回受けたすべての被験者が含まれた。SASの被験者はas treatedの評価に寄与した。

統計解析：

プライマリーエンドポイントであるベースラインから投与後 26 週までの HbA1c の変化量は、共分散分析（ANCOVA）を用いて解析した。FAS を対象として HbA1c のベースラインからの変化量に関する治療間差の平均値の 95%信頼区間が完全に 0.0%未満の場合に、IDeg に対する IDegLira の優越性が結論付けられることとした。欠測データは LOCF 法を用いて補完した。

被験者背景：

人口統計学的特性及びベースライン特性

	IDegLira N (%)	IDeg N (%)	Total N (%)
Number of subjects	105	105	210
Age group			
N	105 (100.0)	105 (100.0)	210 (100.0)
18<= to <40 years	5 (4.8)	4 (3.8)	9 (4.3)
40<= to <65 years	70 (66.7)	81 (77.1)	151 (71.9)
65<= to <75 years	28 (26.7)	19 (18.1)	47 (22.4)
Elderly (75<= years)	2 (1.9)	1 (1.0)	3 (1.4)
Age group (EudraCT)			
N	105 (100.0)	105 (100.0)	210 (100.0)
18<= to <65 years	75 (71.4)	85 (81.0)	160 (76.2)
65<= to <85 years	30 (28.6)	20 (19.0)	50 (23.8)
85<= years	0	0	0
Sex			
N	105 (100.0)	105 (100.0)	210 (100.0)
Female	35 (33.3)	42 (40.0)	77 (36.7)
Male	70 (66.7)	63 (60.0)	133 (63.3)
Race			
N	105 (100.0)	105 (100.0)	210 (100.0)
Asian	105 (100.0)	105 (100.0)	210 (100.0)
Smoker status			
N	105 (100.0)	105 (100.0)	210 (100.0)
Current smoker	28 (26.7)	30 (28.6)	58 (27.6)
Never smoked	46 (43.8)	49 (46.7)	95 (45.2)
Previous smoker	31 (29.5)	26 (24.8)	57 (27.1)

N: Number of subjects, %: Percentage of subjects
EudraCT: European union drug regulating authorities clinical trials.

ベースライン特性及び糖尿病特性

	IDegLira	IDeg	Total
Number of subjects	105	105	210
Age (years)			
N	105	105	210
Mean (SD)	56.6 (10.4)	55.5 (10.0)	56.0 (10.2)
Median	56.0	56.0	56.0
Min ; Max	35 ; 79	27 ; 81	27 ; 81
Body weight (kg)			
N	105	105	210
Mean (SD)	73.9 (11.9)	75.5 (14.0)	74.7 (13.0)
Median	74.4	72.9	73.8
Min ; Max	51.9 ; 114.0	51.6 ; 133.5	51.6 ; 133.5
BMI (kg/m^2)			
N	105	105	210
Mean (SD)	27.3 (3.1)	28.1 (4.4)	27.7 (3.8)
Median	26.6	27.5	27.0
Min ; Max	22.6 ; 37.0	22.7 ; 46.4	22.6 ; 46.4
HbA1c (%)			
N	105	105	210
Mean (SD)	8.61 (0.88)	8.56 (0.80)	8.58 (0.84)
Median	8.50	8.40	8.50
Min ; Max	7.20 ; 10.70	7.30 ; 10.40	7.20 ; 10.70
Fasting plasma glucose (mg/dL)			
N	105	105	210
Mean (SD)	161.31 (46.95)	155.62 (45.37)	158.47 (46.15)
Median	161.00	149.00	154.00
Min ; Max	66.00 ; 287.00	56.00 ; 300.00	56.00 ; 300.00
Duration of diabetes (years)			
N	105	105	210
Mean (SD)	14.33 (7.79)	13.77 (7.46)	14.05 (7.61)
Median	12.84	13.15	12.91
Min ; Max	1.02 ; 38.92	0.74 ; 37.20	0.74 ; 38.92
eGFR (mL/min/1.73m^2)			
N	105	105	210
Mean (SD)	77.94 (9.19)	78.04 (8.95)	77.99 (9.05)
Median	77.00	78.00	77.00
Min ; Max	60.00 ; 103.00	60.00 ; 97.00	60.00 ; 103.00

N: Number of subjects, SD: Standard deviation,
BMI: Body mass index, HbA1c: Haemoglobin A1c,
FPG: Fasting plasma glucose, eGFR: estimated glomerular filtration rate,
Baseline refers to week 0 except for height and eGFR, these were taken at screening.
The duration of diabetes is calculated as the time from date of diagnosis to the randomisation date.
eGFR was calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.

有効性の結果：

IDegLira 及び IDeg（いずれもメトホルミンとの併用）による 26 週間の治療について、以下の結論を得た。

HbA1c

- HbA1cは、IDegLira群で8.61%から6.66%へ、IDeg群で8.56%から7.91%へと低下した。
- プライマリーエンドポイントであるHbA1cのベースラインから投与後26週の変化量について、IDegLiraのIDegに対する優越性が示された。群差（IDegLira群－IDeg群）の推定値は-1.28 %（95%信頼区間：

[-1.50; -1.06]、p < 0.0001）であった。

インスリン投与量

- 投与後26週における1日総インスリン投与量は、IDegLira群で37.6単位、IDeg群で41.2単位であった。
- 投与後26週における1日総インスリン投与量は、IDeg群と比較してIDegLira群で統計的有意に低かった。群差（IDegLira群－IDeg群）の推定値は-3.08単位（95%信頼区間：[-6.08; -0.08]、p=0.0444）であった。

HbA1c レスポンダー及び HbA1c 複合エンドポイント

- HbA1c目標値を達成した被験者の割合はIDeg群と比較してIDegLira群で高かった。HbA1c 7%未満を達成した被験者の割合は、IDeg群（21.9%）と比較してIDegLira群（71.4%）で高かった。目標の達成に関するオッズ比の推定値は17.40（95%信頼区間：[7.79; 38.86]、p <0.0001）であった。同様に、HbA1c 6.5%以下を達成した被験者の割合はIDeg群（8.6%）と比較してIDegLira群（54.3%）で高かった。目標の達成に関するオッズ比の推定値は19.17（95%信頼区間：[7.95; 46.20]、p <0.0001）であった。
- 2～3の項目からなるHbA1cレスポンダーの複合エンドポイントについて、いずれのエンドポイントでも、目標の達成に関するオッズ比の推定値に統計的な有意差が認められた（IDegLira群で好ましい結果、いずれもp<0.0001）。これらの複合エンドポイントは、HbA1c目標値の達成と、投与期間の最後の12週間に重大な又は血糖値確定症候性低血糖の発現なし及び／又はベースラインから投与後26週まで体重増加なし、を組み合わせたものであった。これらのエンドポイントのレスポンダーの割合は以下のとおりであった。
    - HbA1c 7.0%未満、低血糖の発現なし：IDegLira群で66.7%、IDeg群で19.8%
    - HbA1c 7.0%未満、体重の増加なし：IDegLira群で47.6%、IDeg群で8.6%
    - HbA1c 7.0%未満、低血糖の発現なし、体重の増加なし：IDegLira群で46.7%、IDeg群で6.9%
    - HbA1c 6.5%以下、低血糖の発現なし：IDegLira群で50.5%、IDeg群で7.9%
    - HbA1c 6.5%以下、体重の増加なし：IDegLira群で36.2%、IDeg群で3.8%
    - HbA1c 6.5%以下、低血糖の発現なし、体重の増加なし：IDegLira群で35.2%、IDeg群で3.0%

体重

- 体重のベースラインから投与後26週までの変化量は、IDegLira群で-0.7 kg（ベースライン：73.9 kg）、IDeg群で0.7 kg（ベースライン：75.5 kg）であった。
- 体重のベースラインから投与後26週までの変化量について、IDeg群とIDegLira群の差は統計的に有意であり、IDegLira群に好ましい結果となった。群差（IDegLira群－IDeg群）の推定値は-1.41 kg（95%信頼区間：[-2.26; -0.56]、p = 0.0012）であった。

ウエスト周囲径

- ウエスト周囲径のベースラインから投与後26週までの変化量は、IDegLira群で-0.6 cm、IDeg群で0.1 cmであった。
- ウエスト周囲径のベースラインから投与後26週までの変化量について、IDeg群とIDegLira群との間に統計的な有意差は認められなかった。群差（IDegLira群－IDeg群）の推定値は-0.76 cm（95%信頼区間：[-1.77; 0.25]、p = 0.1413）であった。

空腹時血糖値

- 空腹時血糖値のベースラインから投与後26週までの変化量は、IDegLira群で-50.6 mg/dL、IDeg群で-41.3 mg/dLであった。
- 空腹時血糖値のベースラインから投与後26週までの変化量について、IDeg群とIDegLira群との間に統計的な有意差は認められなかった。群差（IDegLira群－IDeg群）の推定値は-4.59 mg/dL（95%信頼区間：[-14.62; 5.44]、p = 0.3678）であった。

血糖自己測定値

- 投与後26週の9点血糖値プロファイル（血糖自己測定による）について、朝食前を除くすべての時点おいて、IDegLira群とIDeg群の差は統計的に有意であり、IDegLira群に好ましい結果となった（p値：p< 0.0001からp=0.0240）。
- 投与後26週の9点血糖値プロファイルの平均は、IDegLira群でベースラインの207.0 mg/dLから155.0 mg/dLに、IDeg群でベースラインの202.0 mg/dLから182.0 mg/dLに低下した。

- 9点血糖値プロファイルの平均のベースラインから投与後26週までの変化量について、IDegLira群とIDeg群の差は統計的に有意であり、IDegLira群に好ましい結果となった。群差（IDegLira群－IDeg群）の推定値は-29.04 mg/dL（95%信頼区間：[-39.23; -18.85]、p < 0.0001）であった。
- 食後血糖増加量のベースラインから投与後26週の変化量は、朝食、昼食及びすべての食事の平均において投与群間に有意差が認められ、いずれもIDegLira群に好ましい結果となった。すべての食事の平均における群差（IDegLira群－IDeg群）の推定値は-19.39 mg/dL（95%信頼区間：[-29.77; -9.02]、p=0.0003）であった。

<u>血圧</u>

- 収縮期血圧及び拡張期血圧のベースラインから投与後26週までの変化量について、投与群間に統計的な有意差は認められなかった。群差（IDegLira群－IDeg群）の推定値は、収縮期血圧及び拡張期血圧でそれぞれ、-0.57 mmHg（95%信頼区間：[-4.17; 3.04]、p = 0.7575）及び0.89 mmHg（95%信頼区間：[-1.37; 3.14]、p = 0.4381）であった。

<u>空腹時脂質プロファイル</u>

- 投与後26週における総コレステロール、LDLコレステロール及びHDLコレステロールについて、投与群間に統計的な有意差が認められた。IDegLira群とIDeg群の比の推定値は以下のとおりであった。
  - 総コレステロール：0.94（95%信頼区間：[0.91; 0.97]、p = 0.0008）
  - LDLコレステロール：0.89（95%信頼区間：[0.83; 0.94]、p = 0.0002）
  - HDLコレステロール：0.95（95%信頼区間：[0.91; 0.99]、p = 0.0143）

<u>患者報告アウトカム</u>

- DTR-QOL総スコア、及び4ドメインのうち3ドメイン（低血糖以外のすべて）のスコアのベースラインから投与後26週までの変化量について、投与群間に統計的な有意差が認められ、IDegLira群に好ましい結果となった。DTR-QOL総スコアの群差（IDegLira群－IDeg群）の推定値は7.39（95%信頼区間：[3.82; 10.97]、p < 0.0001）であった。
- EQ-5D-DL VASスコア及びEQ-5D-5L indexスコアのベースラインから投与後26週までの変化量について、投与群間に統計的な有意差が認められ、IDegLira群に好ましい結果となった。群差（IDegLira群－IDeg群）の推定値は以下のとおりであった。
  - EQ-5D-5L VASスコア：4.67（95%信頼区間：[0.91; 8.43]、p = 0.0151）
  - EQ-5D-5L indexスコア：0.03（95%信頼区間：[0.01; 0.05]、p = 0.0136）

安全性の結果：

投与後 26 週において、本試験の IDegLira 及び IDeg の安全性に関して以下のとおり結論づけられた。
IDegLira 及び IDeg の忍容性は概して良好であり、IDegLira の投与において新規の安全性及び忍容性に関する問題は認められなかった。
各領域における安全性の検討結果を以下に要約する：

<u>全体的な有害事象プロファイル（低血糖以外）</u>

- 死亡は報告されなかった。
- 有害事象を発現した被験者の割合は、IDegLira群で78.1%、IDeg群で76.2%であった。
- 有害事象の単位時間あたりの発現件数は、IDegLira群で515.9件／100人・年、IDeg群で401.8件／100人・年であった。
- 有害事象の大部分（490件中459件）は軽度であり、また事象の大部分（490件中372件）が治験責任医師により治験薬との因果関係が「なし」と判定された。
- 器官別大分類の胃腸障害に含まれる有害事象の単位時間あたりの発現件数は、IDeg群（76.5件／100人・年）と比較してIDegLira群（162.1件／100人・年）で多かった。胃腸障害の有害事象は、いずれも非重篤であり、1件を除きすべて軽度であった。IDegLira群で最も高頻度で報告された胃腸障害の有害事象は下痢、悪心、便秘及び嘔吐であった。
- 7例10件の重篤な有害事象が報告され、その単位時間あたりの発現件数はIDegLira群で7.4件／100人・年、IDeg群で11.5件／100人・年であった。被験者の1%以上で報告された重篤な有害事象は認められず、この10件のうち7件は治験責任医師より治験薬との因果関係は「なし」と判定された。3件の重篤な

有害事象（IDegLira群の意識消失2件及び急性胆嚢炎1件）は治験薬との因果関係は「可能性あり」と判定された。
- 試験の中止に至った有害事象は報告されなかった。

特に注目すべき安全性領域の有害事象
- 1件の心血管系事象（IDegLira群）がイベント判定委員会により確定された。本事象は主要な心血管イベント（MACE）であった。
- 3件の新生物がイベント判定委員会により確定された（IDegLira群で2件、IDeg群で1件）。
- イベント判定委員会により確定された膵炎又は甲状腺障害の事象はなかった。
- IDegLira群で2例2件のリパーゼ増加の事象が特定された。
- アミラーゼ増加又はカルシトニン増加（20 ng/L以上）の事象は特定されなかった。
- 胃腸障害の有害事象以外では、注目すべき安全性領域に該当する有害事象の発現件数は少なかった：腎機能の悪化2件、アレルギー反応8件、注射部位反応4件、稀な事象6件、及び投薬過誤1件。これらの事象で、過去の所見と比較して新たに特定されるような重要な懸念を示すものはなかった。低血糖、及び治験薬による病原体感染の疑いに関する事象は報告されなかった。
- IDeg群で1例が膵癌と診断され、その10日後に試験を中止した。

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、IDegLira群で228.5件／100人・年、IDeg群で208.6件／100人・年であった。統計的な有意差は認められなかった。
- 重大な又は血糖値確定症候性低血糖の単位時間あたりの発現件数は、IDegLira群で95.8件／100人・年、IDeg群で82.3件／100人・年であった。統計的な有意差は認められなかった。
- 重大な又は血糖値確定夜間低血糖の単位時間あたりの発現件数は、IDegLira群で47.9件／100人・年、IDeg群で36.4件／100人・年であった。統計的な有意差は認められなかった。
- 重大な又は血糖値確定症候性夜間低血糖の単位時間あたりの発現件数は、IDegLira群で7.4件／100人・年、IDeg群で15.3件／100人・年であった。統計的な有意差は認められなかった。。
- ADA分類に基づく低血糖の単位時間あたりの発現件数は、IDegLira群及びIDeg群でそれぞれ1437.1件／100人・年及び1371.8件／100人・年であった。ADA分類に基づく低血糖の大部分は、確定症候性低血糖（documented symptomatic hypoglycaemia）及び無症候性低血糖（asymptomatic hypoglycaemia）であった。
- IDegLira群で1件の非重篤な、重大な低血糖が報告された。

臨床検査項目評価
- いずれの投与群でも、ベースラインから投与終了までに血液学的検査及び血液生化学的検査のパラメータで臨床的に問題となる変化は認められなかった。
- ベースラインから投与終了までに、IDegLira群ではリパーゼ及びアミラーゼがそれぞれ18.47 U/L及び8.40 U/L増加した。IDeg群では、リパーゼの変化量は-1.95 U/L、アミラーゼの変化量は3.87 U/Lであった。
- カルシトニンについて、試験期間中に臨床的に問題となるような変化は認められなかった。

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
- IDegLira群で脈拍数の増加（6.1拍／分）がみられたが、IDeg群では脈拍数の変化はみられなかった。脈拍数の増加は、IDeg群と比較してIDegLira群で統計的に大きかった。
- 投与後26週における身体所見、眼底検査／眼底写真及び心電図の結果について、投与群の間で臨床的に問題となるような違いは認められなかった。

全体の結論：

Basalインスリン又は混合／配合インスリン＋メトホルミン±経口糖尿病薬単剤（SU、グリニド、α-GI、SGLT-2阻害薬又はTZDのいずれか）の併用による治療を実施中の日本人2型糖尿病患者を対象とした、IDegLiraとIDeg（最高用量はそれぞれ50用量ステップ及び50単位）を比較する26週の試験の結論は以下のとおりであった。

- HbA1cのベースラインからの変化量について、IDegLiraのIDegに対する優越性が示された。
- 上記のIDegLiraの優越性は、IDegと比較して少ないインスリン投与量で達成されており、血糖コントロール全般にリラグルチドが大きく寄与していることが支持された。
- HbA1cの目標値を達成した被験者（2～3の項目からなるHbA1cレスポンダーの複合エンドポイントを含む）の割合は、IDeg群と比較してIDegLira群で高かった。
- IDegLiraの投与において、予測できない安全性又は忍容性の問題は認められなかった。

本試験は、ヘルシンキ宣言（64th WMA Assembly）及びICH-GCP（1996年6月）を遵守して実施された。

2.7.6.5.2. 有害事象

表2.7.6.5.2-1. 有害事象（器官別大分類及び基本語別）－安全性解析対象（4184 試験）

	IDegLira				IDeg				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	105				105				210			
PYE (Years)	54.28				52.27				106.54			
Events	82	(78.1)	280	515.86	80	(76.2)	210	401.79	162	(77.1)	490	459.91
胃腸障害	45	(42.9)	88	162.13	24	(22.9)	40	76.53	69	(32.9)	128	120.14
下痢	15	(14.3)	20	36.85	5	(4.8)	6	11.48	20	(9.5)	26	24.40
悪心	10	(9.5)	12	22.11	4	(3.8)	5	9.57	14	(6.7)	17	15.96
便秘	9	(8.6)	10	18.42	4	(3.8)	4	7.65	13	(6.2)	14	13.14
嘔吐	9	(8.6)	11	20.27	2	(1.9)	2	3.83	11	(5.2)	13	12.20
腹部不快感	8	(7.6)	8	14.74	5	(4.8)	5	9.57	13	(6.2)	13	12.20
胃食道逆流性疾患	3	(2.9)	3	5.53	2	(1.9)	2	3.83	5	(2.4)	5	4.69
消化不良	3	(2.9)	4	7.37	1	(1.0)	1	1.91	4	(1.9)	5	4.69
慢性胃炎	3	(2.9)	4	7.37	1	(1.0)	1	1.91	4	(1.9)	5	4.69
裂孔ヘルニア	3	(2.9)	3	5.53	0				3	(1.4)	3	2.82
胃炎	2	(1.9)	2	3.68	1	(1.0)	1	1.91	3	(1.4)	3	2.82
びらん性胃炎	1	(1.0)	1	1.84	1	(1.0)	1	1.91	2	(1.0)	2	1.88
胃酸過多	1	(1.0)	2	3.68	0				1	(0.5)	2	1.88
小腸炎	1	(1.0)	2	3.68	1	(1.0)	1	1.91	2	(1.0)	3	2.82
食道障害	1	(1.0)	1	1.84	0				1	(0.5)	1	0.94
食道静脈瘤	1	(1.0)	1	1.84	0				1	(0.5)	1	0.94
大腸ポリープ	1	(1.0)	1	1.84	0				1	(0.5)	1	0.94
軟便	1	(1.0)	1	1.84	1	(1.0)	1	1.91	2	(1.0)	2	1.88
腹痛	1	(1.0)	1	1.84	1	(1.0)	1	1.91	2	(1.0)	2	1.88
齲歯	1	(1.0)	1	1.84	1	(1.0)	1	1.91	2	(1.0)	2	1.88
口内炎	0				1	(1.0)	1	1.91	1	(0.5)	1	0.94
歯周病	0				1	(1.0)	1	1.91	1	(0.5)	1	0.94
十二指腸潰瘍	0				1	(1.0)	1	1.91	1	(0.5)	1	0.94

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Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
消化管運動障害	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
食中毒	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
心窩部不快感	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
舌炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
腹部膨満	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
感染症および寄生虫症	35 (33.3)	57	105.02	38 (36.2)	52	99.49	73 (34.8)	109	102.31
ウイルス性上気道感染	21 (20.0)	27	49.74	24 (22.9)	30	57.40	45 (21.4)	57	53.50
咽頭炎	5 (4.8)	6	11.05	1 (1.0)	2	3.83	6 (2.9)	8	7.51
胃腸炎	4 (3.8)	6	11.05	2 (1.9)	2	3.83	6 (2.9)	8	7.51
副鼻腔炎	3 (2.9)	3	5.53	0			3 (1.4)	3	2.82
歯周炎	2 (1.9)	2	3.68	0			2 (1.0)	2	1.88
帯状疱疹	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82
インフルエンザ	1 (1.0)	1	1.84	2 (1.9)	2	3.83	3 (1.4)	3	2.82
感染性皮膚嚢腫	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
気管支炎	1 (1.0)	1	1.84	5 (4.8)	5	9.57	6 (2.9)	6	5.63
歯肉炎	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
上気道感染	1 (1.0)	1	1.84	2 (1.9)	3	5.74	3 (1.4)	4	3.75
足部白癬	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
単純ヘルペス	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
尿路感染	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
扁桃炎	1 (1.0)	2	3.68	0			1 (0.5)	2	1.88
膀胱炎	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
アデノウイルス結膜炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
外耳炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
細菌性上気道感染	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
膿瘍	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
麦粒腫	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
蜂巣炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94

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	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
眼障害	22 (21.0)	24	44.22	20 (19.0)	23	44.01	42 (20.0)	47	44.11
糖尿病網膜症	17 (16.2)	18	33.16	17 (16.2)	18	34.44	34 (16.2)	36	33.79
眼瞼痙攣	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
結膜出血	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
白内障	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
網膜出血	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
網膜症	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
瞼裂斑炎	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
核性白内障	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
眼乾燥	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
後嚢部混濁	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
網膜剥離	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
代謝および栄養障害	15 (14.3)	15	27.64	3 (2.9)	3	5.74	18 (8.6)	18	16.89
食欲減退	8 (7.6)	8	14.74	0			8 (3.8)	8	7.51
高尿酸血症	3 (2.9)	3	5.53	0			3 (1.4)	3	2.82
脂質異常症	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82
痛風	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82
脱水	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
筋骨格系および結合組織障害	14 (13.3)	18	33.16	14 (13.3)	15	28.70	28 (13.3)	33	30.97
背部痛	5 (4.8)	6	11.05	5 (4.8)	5	9.57	10 (4.8)	11	10.32
関節痛	3 (2.9)	3	5.53	1 (1.0)	1	1.91	4 (1.9)	4	3.75
筋骨格痛	2 (1.9)	2	3.68	0			2 (1.0)	2	1.88
筋痙縮	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
頚部痛	1 (1.0)	2	3.68	0			1 (0.5)	2	1.88
弾発指	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
椎間板突出	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
変形性関節症	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94

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	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
腱鞘炎	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
関節炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
関節周囲炎	0			2 (1.9)	2	3.83	2 (1.0)	2	1.88
筋骨格硬直	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
筋肉痛	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
側腹部痛	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
傷害、中毒および処置合併症	10 (9.5)	14	25.79	10 (9.5)	11	21.05	20 (9.5)	25	23.46
転倒	3 (2.9)	3	5.53	0			3 (1.4)	3	2.82
挫傷	2 (1.9)	2	3.68	3 (2.9)	3	5.74	5 (2.4)	5	4.69
裂傷	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82
股関節部骨折	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
擦過傷	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
歯牙損傷	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
術後発熱	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
節足動物咬傷	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
熱射病	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
靭帯捻挫	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
誤薬投与	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
歯牙破折	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
足骨折	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
熱傷	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
熱中症	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
尾骨骨折	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
脛骨骨折	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
一般・全身障害および投与部位の状態	9 (8.6)	10	18.42	10 (9.5)	10	19.13	19 (9.0)	20	18.77
倦怠感	2 (1.9)	3	5.53	1 (1.0)	1	1.91	3 (1.4)	4	3.75
発熱	2 (1.9)	2	3.68	2 (1.9)	2	3.83	4 (1.9)	4	3.75

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	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
末梢性浮腫	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82
炎症	1 (1.0)	1	1.84	2 (1.9)	2	3.83	3 (1.4)	3	2.82
全身性浮腫	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
注射部位硬結	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
硬結	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
注射部位不快感	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
投与部位硬結	0			2 (1.9)	2	3.83	2 (1.0)	2	1.88
神経系障害	9 (8.6)	11	20.27	11 (10.5)	14	26.79	20 (9.5)	25	23.46
頭痛	3 (2.9)	3	5.53	1 (1.0)	1	1.91	4 (1.9)	4	3.75
感覚鈍麻	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82
浮動性めまい	2 (1.9)	2	3.68	4 (3.8)	5	9.57	6 (2.9)	7	6.57
ラクナ梗塞	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
手根管症候群	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
糖尿病性ニューロパチー	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
片頭痛	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
意識消失	0			1 (1.0)	2	3.83	1 (0.5)	2	1.88
坐骨神経痛	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
末梢性ニューロパチー	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
味覚異常	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
臨床検査	7 (6.7)	7	12.90	5 (4.8)	5	9.57	12 (5.7)	12	11.26
リパーゼ増加	2 (1.9)	2	3.68	0			2 (1.0)	2	1.88
ヘリコバクター検査陽性	1 (1.0)	1	1.84	2 (1.9)	2	3.83	3 (1.4)	3	2.82
γ－グルタミルトランスフェラーゼ増加	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
酸素飽和度低下	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
心電図ＳＴ－Ｔ部分下降	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
体重減少	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
糸球体濾過率減少	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94

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	N	(%)	E R	N	(%)	E R	N	(%)	E R
心電図Ｔ波逆転	0			1	(1.0)	1 1.91	1	(0.5)	1 0.94
遊離脂肪酸減少	0			1	(1.0)	1 1.91	1	(0.5)	1 0.94
呼吸器、胸郭および縦隔障害	6	(5.7)	9 16.58	6	(5.7)	6 11.48	12	(5.7)	15 14.08
口腔咽頭痛	2	(1.9)	2 3.68	0			2	(1.0)	2 1.88
咳嗽	1	(1.0)	1 1.84	1	(1.0)	1 1.91	2	(1.0)	2 1.88
胸水	1	(1.0)	1 1.84	0			1	(0.5)	1 0.94
上気道の炎症	1	(1.0)	2 3.68	3	(2.9)	3 5.74	4	(1.9)	5 4.69
無気肺	1	(1.0)	1 1.84	0			1	(0.5)	1 0.94
喀痰増加	1	(1.0)	1 1.84	0			1	(0.5)	1 0.94
痰貯留	1	(1.0)	1 1.84	0			1	(0.5)	1 0.94
気道の炎症	0			1	(1.0)	1 1.91	1	(0.5)	1 0.94
慢性気管支炎	0			1	(1.0)	1 1.91	1	(0.5)	1 0.94
血管障害	5	(4.8)	5 9.21	2	(1.9)	2 3.83	7	(3.3)	7 6.57
高血圧	3	(2.9)	3 5.53	2	(1.9)	2 3.83	5	(2.4)	5 4.69
起立性低血圧	1	(1.0)	1 1.84	0			1	(0.5)	1 0.94
動脈硬化症	1	(1.0)	1 1.84	0			1	(0.5)	1 0.94
腎および尿路障害	4	(3.8)	7 12.90	3	(2.9)	3 5.74	7	(3.3)	10 9.39
腎結石症	2	(1.9)	2 3.68	2	(1.9)	2 3.83	4	(1.9)	4 3.75
腎嚢胞	2	(1.9)	2 3.68	1	(1.0)	1 1.91	3	(1.4)	3 2.82
急性腎障害	1	(1.0)	1 1.84	0			1	(0.5)	1 0.94
血尿	1	(1.0)	1 1.84	0			1	(0.5)	1 0.94
尿管結石症	1	(1.0)	1 1.84	0			1	(0.5)	1 0.94
皮膚および皮下組織障害	4	(3.8)	5 9.21	10	(9.5)	10 19.13	14	(6.7)	15 14.08
湿疹	2	(1.9)	2 3.68	4	(3.8)	4 7.65	6	(2.9)	6 5.63
過角化	1	(1.0)	1 1.84	0			1	(0.5)	1 0.94

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	N (%)	E	R	N (%)	E	R	N (%)	E	R
汗疹	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
膿疱性乾癬	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
ざ瘡	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
陰茎潰瘍形成	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
発疹	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
皮膚炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
皮膚刺激	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
皮膚腫脹	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
心臓障害	2 (1.9)	3	5.53	0			2 (1.0)	3	2.82
うっ血性心不全	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
急性心筋梗塞	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
上室性期外収縮	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	2 (1.9)	2	3.68	2 (1.9)	2	3.83	4 (1.9)	4	3.75
子宮平滑筋腫	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
腺癌	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
腎細胞癌	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
膵癌	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
肝胆道系障害	1 (1.0)	1	1.84	3 (2.9)	3	5.74	4 (1.9)	4	3.75
肝硬変	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
急性胆嚢炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
脂肪肝	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
胆石症	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
耳および迷路障害	1 (1.0)	1	1.84	2 (1.9)	3	5.74	3 (1.4)	4	3.75
回転性めまい	1 (1.0)	1	1.84	2 (1.9)	3	5.74	3 (1.4)	4	3.75

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

Adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
精神障害	1 (1.0)	1	1.84	2 (1.9)	2	3.83	3 (1.4)	3	2.82
不眠症	1 (1.0)	1	1.84	2 (1.9)	2	3.83	3 (1.4)	3	2.82
内分泌障害	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
甲状腺腫瘤	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
免疫系障害	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
季節性アレルギー	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
血液およびリンパ系障害	0			1 (1.0)	3	5.74	1 (0.5)	3	2.82
リンパ球減少症	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
好中球減少症	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
白血球減少症	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
生殖系および乳房障害	0			1 (1.0)	3	5.74	1 (0.5)	3	2.82
子宮腫瘤	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
子宮嚢胞	0			1 (1.0)	2	3.83	1 (0.5)	2	1.88

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

表2.7.6.5.2-2. 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（器官別大分類及び基本語別）－安全性解析対象（4184 試験）

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	105			105			210		
PYE (Years)	54.28			52.27			106.54		
Events	38 (36.2)	72	132.65	26 (24.8)	41	78.45	64 (30.5)	113	106.06
胃腸障害	30 (28.6)	50	92.12	16 (15.2)	22	42.09	46 (21.9)	72	67.58
下痢	11 (10.5)	12	22.11	4 (3.8)	4	7.65	15 (7.1)	16	15.02
腹部不快感	8 (7.6)	8	14.74	5 (4.8)	5	9.57	13 (6.2)	13	12.20
悪心	7 (6.7)	8	14.74	4 (3.8)	4	7.65	11 (5.2)	12	11.26
便秘	6 (5.7)	7	12.90	3 (2.9)	3	5.74	9 (4.3)	10	9.39
嘔吐	5 (4.8)	6	11.05	0			5 (2.4)	6	5.63
消化不良	2 (1.9)	3	5.53	1 (1.0)	1	1.91	3 (1.4)	4	3.75
慢性胃炎	2 (1.9)	2	3.68	0			2 (1.0)	2	1.88
胃酸過多	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
小腸炎	1 (1.0)	2	3.68	0			1 (0.5)	2	1.88
軟便	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
胃炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
消化管運動障害	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
心窩部不快感	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
腹部膨満	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
眼障害	9 (8.6)	9	16.58	3 (2.9)	4	7.65	12 (5.7)	13	12.20
糖尿病網膜症	7 (6.7)	7	12.90	3 (2.9)	4	7.65	10 (4.8)	11	10.32
網膜出血	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
網膜症	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
代謝および栄養障害	8 (7.6)	8	14.74	1 (1.0)	1	1.91	9 (4.3)	9	8.45

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

Adverse events possibly or probably related to investigational medicinal product by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
食欲減退	7 (6.7)	7	12.90	0			7 (3.3)	7	6.57
高尿酸血症	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
脂質異常症	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
臨床検査	4 (3.8)	4	7.37	1 (1.0)	1	1.91	5 (2.4)	5	4.69
リパーゼ増加	2 (1.9)	2	3.68	0			2 (1.0)	2	1.88
心電図ＳＴ－Ｔ部分下降	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
体重減少	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
遊離脂肪酸減少	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
一般・全身障害および投与部位の状態	1 (1.0)	1	1.84	2 (1.9)	2	3.83	3 (1.4)	3	2.82
注射部位硬結	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
倦怠感	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
注射部位不快感	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
肝胆道系障害	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
急性胆嚢炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
耳および迷路障害	0			2 (1.9)	3	5.74	2 (1.0)	3	2.82
回転性めまい	0			2 (1.9)	3	5.74	2 (1.0)	3	2.82
神経系障害	0			4 (3.8)	5	9.57	4 (1.9)	5	4.69
意識消失	0			1 (1.0)	2	3.83	1 (0.5)	2	1.88
糖尿病性ニューロパチー	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
浮動性めまい	0			2 (1.9)	2	3.83	2 (1.0)	2	1.88
腎および尿路障害	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
腎結石症	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

Adverse events possibly or probably related to investigational medicinal product by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Total		
	N	(%)	E R	N	(%)	E R	N	(%)	E R
皮膚および皮下組織障害	0			1	(1.0)	1 1.91	1	(0.5)	1 0.94
発疹	0			1	(1.0)	1 1.91	1	(0.5)	1 0.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

表2.7.6.5.2-3. 重篤な有害事象（器官別大分類及び基本語別）－安全性解析対象（4184 試験）

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	105			105			210		
PYE (Years)	54.28			52.27			106.54		
Events	3 (2.9)	4	7.37	4 (3.8)	6	11.48	7 (3.3)	10	9.39
感染症および寄生虫症	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
胃腸炎	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
傷害、中毒および処置合併症	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
股関節部骨折	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
心臓障害	1 (1.0)	2	3.68	0			1 (0.5)	2	1.88
うっ血性心不全	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
急性心筋梗塞	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
肝胆道系障害	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
急性胆嚢炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
眼障害	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
網膜剥離	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
神経系障害	0			1 (1.0)	2	3.83	1 (0.5)	2	1.88
意識消失	0			1 (1.0)	2	3.83	1 (0.5)	2	1.88
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	0			2 (1.9)	2	3.83	2 (1.0)	2	1.88
腎細胞癌	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
膵癌	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

表2.7.6.5.2-4. 重度の有害事象（器官別大分類及び基本語別）－安全性解析対象（4184 試験）

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	105			105			210		
PYE (Years)	54.28			52.27			106.54		
Events	3 (2.9)	4	7.37	1 (1.0)	2	3.83	4 (1.9)	6	5.63
感染症および寄生虫症	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
胃腸炎	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
傷害、中毒および処置合併症	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
股関節部骨折	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
心臓障害	1 (1.0)	2	3.68	0			1 (0.5)	2	1.88
うっ血性心不全	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
急性心筋梗塞	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
神経系障害	0			1 (1.0)	2	3.83	1 (0.5)	2	1.88
意識消失	0			1 (1.0)	2	3.83	1 (0.5)	2	1.88

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

表2.7.6.5.2-5. 中等度の有害事象（器官別大分類及び基本語別）－安全性解析対象（4184 試験）

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	105			105			210		
PYE (Years)	54.28			52.27			106.54		
Events	10 (9.5)	14	25.79	9 (8.6)	11	21.05	19 (9.0)	25	23.46
感染症および寄生虫症	2 (1.9)	2	3.68	0			2 (1.0)	2	1.88
歯周炎	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
帯状疱疹	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
眼障害	2 (1.9)	2	3.68	1 (1.0)	2	3.83	3 (1.4)	4	3.75
糖尿病網膜症	2 (1.9)	2	3.68	1 (1.0)	2	3.83	3 (1.4)	4	3.75
神経系障害	2 (1.9)	2	3.68	2 (1.9)	2	3.83	4 (1.9)	4	3.75
手根管症候群	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
浮動性めまい	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
坐骨神経痛	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
糖尿病性ニューロパチー	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
胃腸障害	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
悪心	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
筋骨格系および結合組織障害	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
筋骨格痛	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
血管障害	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
高血圧	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
傷害、中毒および処置合併症	1 (1.0)	1	1.84	3 (2.9)	3	5.74	4 (1.9)	4	3.75

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

Moderate adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
挫傷	1 (1.0)	1	1.84	2 (1.9)	2	3.83	3 (1.4)	3	2.82
尾骨骨折	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
腎および尿路障害	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
急性腎障害	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
代謝および栄養障害	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
食欲減退	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
脂質異常症	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
腺癌	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
腎細胞癌	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
臨床検査	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
リパーゼ増加	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
肝胆道系障害	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
急性胆嚢炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
呼吸器、胸郭および縦隔障害	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
慢性気管支炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

表2.7.6.5.2-6. 軽度の有害事象（器官別大分類及び基本語別）－安全性解析対象（4184 試験）

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	105			105			210		
PYE (Years)	54.28			52.27			106.54		
Events	82 (78.1)	262	482.70	80 (76.2)	197	376.92	162 (77.1)	459	430.81
胃腸障害	45 (42.9)	87	160.29	24 (22.9)	40	76.53	69 (32.9)	127	119.20
下痢	15 (14.3)	20	36.85	5 (4.8)	6	11.48	20 (9.5)	26	24.40
悪心	10 (9.5)	11	20.27	4 (3.8)	5	9.57	14 (6.7)	16	15.02
便秘	9 (8.6)	10	18.42	4 (3.8)	4	7.65	13 (6.2)	14	13.14
嘔吐	9 (8.6)	11	20.27	2 (1.9)	2	3.83	11 (5.2)	13	12.20
腹部不快感	8 (7.6)	8	14.74	5 (4.8)	5	9.57	13 (6.2)	13	12.20
胃食道逆流性疾患	3 (2.9)	3	5.53	2 (1.9)	2	3.83	5 (2.4)	5	4.69
消化不良	3 (2.9)	4	7.37	1 (1.0)	1	1.91	4 (1.9)	5	4.69
慢性胃炎	3 (2.9)	4	7.37	1 (1.0)	1	1.91	4 (1.9)	5	4.69
裂孔ヘルニア	3 (2.9)	3	5.53	0			3 (1.4)	3	2.82
胃炎	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82
びらん性胃炎	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
胃酸過多	1 (1.0)	2	3.68	0			1 (0.5)	2	1.88
小腸炎	1 (1.0)	2	3.68	1 (1.0)	1	1.91	2 (1.0)	3	2.82
食道障害	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
食道静脈瘤	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
大腸ポリープ	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
軟便	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
腹痛	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
齲歯	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
口内炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
歯周病	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
十二指腸潰瘍	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
R: Rate (number of adverse events divided by patient years of exposure multiplied by 100)
PYE: Patient years of exposure (1 PYE = 365.25 days)
MedDRA version 20.0

Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
消化管運動障害	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
食中毒	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
心窩部不快感	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
舌炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
腹部膨満	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
感染症および寄生虫症	32 (30.5)	54	99.49	38 (36.2)	52	99.49	70 (33.3)	106	99.49
ウイルス性上気道感染	21 (20.0)	27	49.74	24 (22.9)	30	57.40	45 (21.4)	57	53.50
咽頭炎	5 (4.8)	6	11.05	1 (1.0)	2	3.83	6 (2.9)	8	7.51
胃腸炎	3 (2.9)	5	9.21	2 (1.9)	2	3.83	5 (2.4)	7	6.57
副鼻腔炎	3 (2.9)	3	5.53	0			3 (1.4)	3	2.82
インフルエンザ	1 (1.0)	1	1.84	2 (1.9)	2	3.83	3 (1.4)	3	2.82
感染性皮膚嚢腫	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
気管支炎	1 (1.0)	1	1.84	5 (4.8)	5	9.57	6 (2.9)	6	5.63
歯周炎	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
歯肉炎	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
上気道感染	1 (1.0)	1	1.84	2 (1.9)	3	5.74	3 (1.4)	4	3.75
足部白癬	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
帯状疱疹	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
単純ヘルペス	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
尿路感染	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
扁桃炎	1 (1.0)	2	3.68	0			1 (0.5)	2	1.88
膀胱炎	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
アデノウイルス結膜炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
外耳炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
細菌性上気道感染	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
膿瘍	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
麦粒腫	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
蜂巣炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94

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Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
眼障害	21 (20.0)	22	40.53	19 (18.1)	21	40.18	40 (19.0)	43	40.36
糖尿病網膜症	15 (14.3)	16	29.48	16 (15.2)	16	30.61	31 (14.8)	32	30.03
眼瞼痙攣	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
結膜出血	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
白内障	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
網膜出血	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
網膜症	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
瞼裂斑炎	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
核性白内障	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
眼乾燥	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
後嚢部混濁	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
網膜剥離	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
代謝および栄養障害	14 (13.3)	14	25.79	2 (1.9)	2	3.83	16 (7.6)	16	15.02
食欲減退	7 (6.7)	7	12.90	0			7 (3.3)	7	6.57
高尿酸血症	3 (2.9)	3	5.53	0			3 (1.4)	3	2.82
脂質異常症	2 (1.9)	2	3.68	0			2 (1.0)	2	1.88
痛風	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82
脱水	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
筋骨格系および結合組織障害	13 (12.4)	17	31.32	14 (13.3)	15	28.70	27 (12.9)	32	30.03
背部痛	5 (4.8)	6	11.05	5 (4.8)	5	9.57	10 (4.8)	11	10.32
関節痛	3 (2.9)	3	5.53	1 (1.0)	1	1.91	4 (1.9)	4	3.75
筋骨格痛	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
筋痙縮	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
頚部痛	1 (1.0)	2	3.68	0			1 (0.5)	2	1.88
弾発指	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
椎間板突出	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
変形性関節症	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94

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MedDRA version 20.0

Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
腱鞘炎	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
関節炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
関節周囲炎	0			2 (1.9)	2	3.83	2 (1.0)	2	1.88
筋骨格硬直	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
筋肉痛	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
側腹部痛	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
一般・全身障害および投与部位の状態	9 (8.6)	10	18.42	10 (9.5)	10	19.13	19 (9.0)	20	18.77
倦怠感	2 (1.9)	3	5.53	1 (1.0)	1	1.91	3 (1.4)	4	3.75
発熱	2 (1.9)	2	3.68	2 (1.9)	2	3.83	4 (1.9)	4	3.75
末梢性浮腫	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82
炎症	1 (1.0)	1	1.84	2 (1.9)	2	3.83	3 (1.4)	3	2.82
全身性浮腫	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
注射部位硬結	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
硬結	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
注射部位不快感	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
投与部位硬結	0			2 (1.9)	2	3.83	2 (1.0)	2	1.88
傷害、中毒および処置合併症	8 (7.6)	12	22.11	7 (6.7)	8	15.31	15 (7.1)	20	18.77
転倒	3 (2.9)	3	5.53	0			3 (1.4)	3	2.82
裂傷	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82
挫傷	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
擦過傷	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
歯牙損傷	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
術後発熱	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
節足動物咬傷	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
熱射病	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
靭帯捻挫	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
誤薬投与	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94

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MedDRA version 20.0

Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
歯牙破折	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
足骨折	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
熱傷	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
熱中症	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
脛骨骨折	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
神経系障害	7 (6.7)	9	16.58	9 (8.6)	10	19.13	16 (7.6)	19	17.83
頭痛	3 (2.9)	3	5.53	1 (1.0)	1	1.91	4 (1.9)	4	3.75
感覚鈍麻	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82
ラクナ梗塞	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
糖尿病性ニューロパチー	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
浮動性めまい	1 (1.0)	1	1.84	4 (3.8)	5	9.57	5 (2.4)	6	5.63
片頭痛	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
手根管症候群	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
末梢性ニューロパチー	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
味覚異常	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
呼吸器、胸郭および縦隔障害	6 (5.7)	9	16.58	5 (4.8)	5	9.57	11 (5.2)	14	13.14
口腔咽頭痛	2 (1.9)	2	3.68	0			2 (1.0)	2	1.88
咳嗽	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
胸水	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
上気道の炎症	1 (1.0)	2	3.68	3 (2.9)	3	5.74	4 (1.9)	5	4.69
無気肺	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
喀痰増加	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
痰貯留	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
気道の炎症	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
臨床検査	6 (5.7)	6	11.05	5 (4.8)	5	9.57	11 (5.2)	11	10.32
ヘリコバクター検査陽性	1 (1.0)	1	1.84	2 (1.9)	2	3.83	3 (1.4)	3	2.82

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Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
リパーゼ増加	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
γ－グルタミルトランスフェラーゼ増加	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
酸素飽和度低下	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
心電図ＳＴ－Ｔ部分下降	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
体重減少	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
糸球体濾過率減少	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
心電図Ｔ波逆転	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
遊離脂肪酸減少	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
血管障害	4 (3.8)	4	7.37	2 (1.9)	2	3.83	6 (2.9)	6	5.63
高血圧	2 (1.9)	2	3.68	2 (1.9)	2	3.83	4 (1.9)	4	3.75
起立性低血圧	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
動脈硬化症	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
皮膚および皮下組織障害	4 (3.8)	5	9.21	10 (9.5)	10	19.13	14 (6.7)	15	14.08
湿疹	2 (1.9)	2	3.68	4 (3.8)	4	7.65	6 (2.9)	6	5.63
過角化	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
汗疹	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
膿疱性乾癬	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
ざ瘡	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
陰茎潰瘍形成	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
発疹	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
皮膚炎	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
皮膚刺激	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
皮膚腫脹	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
腎および尿路障害	3 (2.9)	6	11.05	3 (2.9)	3	5.74	6 (2.9)	9	8.45
腎結石症	2 (1.9)	2	3.68	2 (1.9)	2	3.83	4 (1.9)	4	3.75
腎嚢胞	2 (1.9)	2	3.68	1 (1.0)	1	1.91	3 (1.4)	3	2.82

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Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
血尿	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
尿管結石症	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
肝胆道系障害	1 (1.0)	1	1.84	2 (1.9)	2	3.83	3 (1.4)	3	2.82
肝硬変	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
脂肪肝	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
胆石症	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
耳および迷路障害	1 (1.0)	1	1.84	2 (1.9)	3	5.74	3 (1.4)	4	3.75
回転性めまい	1 (1.0)	1	1.84	2 (1.9)	3	5.74	3 (1.4)	4	3.75
心臓障害	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
上室性期外収縮	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
精神障害	1 (1.0)	1	1.84	2 (1.9)	2	3.83	3 (1.4)	3	2.82
不眠症	1 (1.0)	1	1.84	2 (1.9)	2	3.83	3 (1.4)	3	2.82
内分泌障害	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
甲状腺腫瘤	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
免疫系障害	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
季節性アレルギー	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）	1 (1.0)	1	1.84	1 (1.0)	1	1.91	2 (1.0)	2	1.88
子宮平滑筋腫	1 (1.0)	1	1.84	0			1 (0.5)	1	0.94
膵癌	0			1 (1.0)	1	1.91	1 (0.5)	1	0.94
血液およびリンパ系障害	0			1 (1.0)	3	5.74	1 (0.5)	3	2.82

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Mild adverse events by system organ class and preferred term - treatment emergent - summary - safety analysis set

	IDegLira			IDeg			Total		
	N	(%)	E R	N	(%)	E R	N	(%)	E R
リンパ球減少症	0			1	(1.0)	1 1.91	1	(0.5)	1 0.94
好中球減少症	0			1	(1.0)	1 1.91	1	(0.5)	1 0.94
白血球減少症	0			1	(1.0)	1 1.91	1	(0.5)	1 0.94
生殖系および乳房障害	0			1	(1.0)	3 5.74	1	(0.5)	3 2.82
子宮腫瘤	0			1	(1.0)	1 1.91	1	(0.5)	1 0.94
子宮嚢胞	0			1	(1.0)	2 3.83	1	(0.5)	2 1.88

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events
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MedDRA version 20.0

表2.7.6.5.2-7.　試験の中止に至った有害事象の一覧－FAS（4184 試験）

There is no data for this listing

2.7.6.6 NN9068-3697

2.7.6.6.1 臨床試験概要

Trial Registration ID-number： NCT01336023	UTN：U1111-1119-1174 IND number：109/121 EudraCT number：2010-021560-15

治験の標題：

DUAL I‐2 型糖尿病患者におけるリラグルチド及びインスリン デグルデクの Dual Action：2 型糖尿病患者を対象としたインスリン デグルデク／リラグルチド、インスリン デグルデク及びリラグルチドの有効性及び安全性を比較する試験

1～2 種類の経口糖尿病薬で治療中の 2 型糖尿病患者を対象とした、インスリン デグルデクとリラグルチドの固定比率の配合剤と、インスリン デグルデク及びリラグルチドの単剤とを比較する 26 週間（+26 週間の延長期間）、無作為割り付け、3 群並行、非盲検、多施設、国際共同、treat-to-target 試験

本治験総括報告書には、本試験における 26 週間の主要治療期間について記載する。

治験責任医師名：

19 ヵ国で計 286 名の治験責任医師が任命された。以下の治験責任医師が治験総括報告書の内容を確認し、署名する「治験総括報告書への署名責任を有する医師（Signatory Investigator）」に任命された：

Professor [redacted]

治験実施施設：

以下の 19 ヵ国 271 施設において被験者の無作為割り付けが実施された：オーストラリア（7 施設）、カナダ（14 施設）、フィンランド（5 施設）、ドイツ（12 施設）、ハンガリー（6 施設）、インド（23 施設）、アイルランド（2 施設）、イタリア（6 施設）、マレーシア（5 施設）、メキシコ（2 施設）、ロシア（11 施設）、シンガポール（3 施設）、スロバキア（5 施設）、南アフリカ共和国（13 施設）、スペイン（8 施設）、台湾（3 施設）、タイ（4 施設）、英国（16 施設）及び米国（126 施設）

公表文献（引用文献）：

本治験総括報告書作成時点でなし

治験期間：	**開発のフェーズ**：
開始日：2011 年 5 月 23 日 終了日：2012 年 5 月 24 日	第 3a 相

目的：

治験実施計画書及びその改訂版に記載のとおり、本試験の目的は：

主要目的：

- 2型糖尿病患者を対象として、インスリン デグルデク／リラグルチド（IDegLira）の血糖コントロールにおける有効性を検証する。

副次的目的：

- 投与後26週後の体重管理、低血糖、食事に関連する血糖コントロール及びインスリン デグルデク（IDeg）の1日投与量により間接的に評価される血糖コントロールについて、IDegLiraのIDegに対する優越性を検証する。
- 2型糖尿病患者を対象として、投与後52週における血糖コントロールについてIDegLiraの有効性を検証する。

- 投与後26週及び52週におけるIDegLira、IDeg及びリラグルチドの全般的な有効性及び安全性を比較検討する。
  - 当初の副次的目的は投与後26週のみの有効性及び安全性を検討することであった。本試験に26週間の延長期間を追加し（amendment 2）、投与後52週における検討を副次的目的に含めた。

母集団薬物動態の目的：

- 母集団薬物動態解析を用いて、26週間のIDegLiraと各有効成分単剤（個別投与）の臨床用量での薬物動態を比較する。また、事前に規定した共変量の血漿中IDegLira濃度への影響を検討する。

治験方法：

- 本試験は、1～2種類の経口糖尿病薬（メトホルミン単剤又はメトホルミンとピオグリタゾンとの併用）による治療で十分な血糖コントロールが得られていない2型糖尿病患者を対象とした、26週間（+26週間の延長期間）、無作為割り付け、実薬対照、3群並行、非盲検、多施設、国際共同、treat-to-target試験であり、IDegLiraと各有効成分単剤（IDeg及びリラグルチド）の1日1回投与の有効性及び安全性を比較検討した。HbA1cが7.0%以上、10.0%以下を「十分な血糖コントロールが得られていない」とした。
- 適格と判断された被験者をIDegLira、IDeg又はリラグルチドの1日1回投与からなる3つの治療群のいずれかに2：1：1の割合で無作為に割り付けた。メトホルミン単剤又はメトホルミンとピオグリタゾンとの併用による治療は試験開始前の用法・用量で継続した。前治療（メトホルミン単剤、及びメトホルミンとピオグリタゾンとの併用）及びベースラインのHbA1c（8.3%以下、8.3%超）ごとに被験者を層別した。すべての治療は非盲検下で行われた。
- リラグルチド群では、規定の用量漸増法に従い、目標用量の1.8 mgに到達するまで1週間に1回0.6 mgずつ増量した。IDegLira群及びIDeg群では、それぞれ10用量ステップ及び10単位で投与を開始し、朝食前血糖値に基づき、事前に規定したアルゴリズムに従い1週間に2回用量調節を行った。
- 選択された治験実施医療機関では、持続血糖測定（CGM）及び食事負荷試験のサブ試験を行った。
- 無作為割り付け後26週時点ですべての被験者に追加の26週間の投与期間への参加を提案した。被験者は同じ治療〔同じ投与量（リラグルチド群）又は同じ投与方法（IDeg群及びIDegLira群）〕を継続することとした。

計画及び解析された被験者数：

計画された被験者数は、IDegLira群で830例、IDeg群及びリラグルチド群で各415例であり、無作為割り付け予定被験者数は計1,660例であった。サブ試験の予定被験者数は256例であった。

	IDegLira N (%)	IDeg N (%)	Lira N (%)	Total N (%)
Screened				3004
Screening Failures				1341
Withdrawn before Randomisation				0
Randomised	834 (100.0)	414 (100.0)	415 (100.0)	1663 (100.0)
Exposed	826 (99.0)	413 (99.8)	413 (99.5)	1652 (99.3)
Withdrawn at/after Randomisation	98 (11.8)	48 (11.6)	73 (17.6)	219 (13.2)
Adverse Event	10 (1.2)	8 (1.9)	24 (5.8)	42 (2.5)
Ineffective Therapy	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Non-Compliance With Protocol	2 (0.2)	1 (0.2)	0 (0.0)	3 (0.2)
Withdrawal Criteria	69 (8.3)	34 (8.2)	40 (9.6)	143 (8.6)
Other	16 (1.9)	5 (1.2)	9 (2.2)	30 (1.8)
Completed	736 (88.2)	366 (88.4)	342 (82.4)	1444 (86.8)
Full Analysis Set	833 (99.9)	413 (99.8)	414 (99.8)	1660 (99.8)
PP Analysis Set	755 (90.5)	374 (90.3)	362 (87.2)	1491 (89.7)
Safety Analysis Set	825 (98.9)	412 (99.5)	412 (99.3)	1649 (99.2)

診断及び主要な組入れ基準：

主な選択基準

性別不問、年齢 18 歳以上〔シンガポール：21 歳以上、台湾（施設 653）：20 歳以上〕の 2 型糖尿病患者。HbA1c 7.0%以上、10.0%以下の被験者で中央値が 8.3%となることを目標とする。HbA1c 8.3%超の被験者の割合が無作為割り付け予定被験者数の約 50%となった場合には、残りの割り付けられる被験者の HbA1c はすべて 8.3%以下でなければならない。また、HbA1c 8.3%以下の被験者の割合が無作為割り付け予定被験者数の約 50%となった場合には、残りの割り付けられる被験者の HbA1c はすべて 8.3%超でなければならない。スクリーニングの 90 日以上前から、1～2 種類の経口糖尿病薬〔メトホルミン単剤（1500 mg 以上又は最大耐用量）又はメトホルミン（1500 mg 以上又は最大耐用量）とピオグリタゾン（30 mg 以上）との併用〕による安定した（1 日投与量が安定）治療を受けている被験者。BMI（kg/m^2）が 40 以下の被験者。治験実施計画書に従った血糖自己測定、被験者日誌への記録ならびにペン型注入器又はフレックスペン®の使用を受け入れられる被験者。

主な除外基準

インスリン治療歴を有する被験者（ただし、併発疾患のための短期間のインスリン投与については可とする：治験責任医師の判断による）。試験開始前 90 日以内に GLP-1 受容体作動薬、スルホニルウレア薬又はジペプチジルペプチダーゼ 4 阻害薬（DPP-4 阻害薬）の投与を受けた被験者。消化器系、呼吸器系、神経系、泌尿生殖器系又は血液系の臨床的に問題となる活動性（過去 12 ヵ月以内）の疾患を有する被験者。肝機能障害（アラニンアミノトランスフェラーゼが基準範囲上限の 2.5 倍以上）を有する被験者。腎機能障害〔血清クレアチニンが男性で 133 μmol/L 以上（1.5 mg/dL 以上）、女性で 125 μmol/L 以上（1.4 mg/dL 以上）〕を有する被験者。スクリーニング時のカルシトニン濃度が 50 ng/L 以上である被験者。

主な中止・脱落基準

糖代謝又は脂質代謝に影響を及ぼすと考えられる薬剤の全身投与を開始する場合（治験責任医師の判断による）、被験者が妊娠した又は妊娠を希望する場合、高血糖（確定）が発現した場合、急性膵炎と診断された場合、被験者は試験を中止しなければならない。

被験薬、用量及び投与方法、ロット番号：

IDegLira

1 mL あたり IDeg 100 単位とリラグルチド 3.6 mg の固定比率の配合剤、ペン型注入器（フレックスペン®、3 mL）と一体化したプレフィルド製剤として提供された。

IDegLira は 1 日 1 回、毎日同時刻に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。10 用量ステップ（IDeg：10 単位、リラグルチド：0.36 mg に相当）で投与を開始した。各投与量調節日前の連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき、1 週間に 2 回投与量調節を行った。朝食前血糖値 4.0～5.0 mmol/L（72～90 mg/dL）を目標として、2 用量ステップ（IDeg：2 単位、リラグルチド：0.072 mg）ずつ投与量調節を行った。最高用量は 50 用量ステップ（IDeg：50 単位、リラグルチド：1.8 mg）であった。ロット番号：AP50043、YP52274 及び AP50044。

投与期間：

26 週間（主要期間）

対照薬、用量及び投与方法、ロット番号：

IDeg

100 単位/mL、ペン型注入器（フレックスペン®、3 mL）と一体化したプレフィルド製剤として提供された。IDeg は 1 日 1 回、毎日同時刻に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。10 単位で投与を開始し、前述の IDegLira と同様に、連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均に基づき、4.0～5.0 mmol/L（72～90 mg/dL）を目標として、1 週間に 2 回投与量調節を行った。最高用量は設定しなかった。ロット番号：YP52252 及び AP51402。

リラグルチド

6 mg/mL、ペン型注入器（3 mL）と一体化したプレフィルド製剤として提供された。リラグルチドは 1 日 1 回、毎日同時刻に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。0.6 mg／日で投与を開始

し、以降は最高用量 1.8 mg／日に到達するまで週 1 回 0.6 mg ずつ増量した。用量漸増終了後は 1.8 mg／日の用量を維持した。ロット番号：XP52720 及び AP50533。

評価基準：有効性

以下の有効性評価項目を評価した：

HbA1c、β 細胞機能〔空腹時プロインスリン、空腹時 C-ペプチド、空腹時インスリン（算出したインスリン／プロインスリン比、HOMA-B、HOMA-IR）、空腹時グルカゴン〕、空腹時血糖値（FPG）、心血管系バイオマーカー〔高感度 C 反応性タンパク質（hsCRP）、アディポネクチン、フィブリノゲン、脳性ナトリウム利尿ペプチド（BNP）〕、空腹時脂質プロファイル〔中性脂肪、コレステロール、低比重リポタンパク質コレステロール（LDL）、高比重リポタンパク質コレステロール（HDL）、超低比重リポタンパク質コレステロール（VLDL）、遊離脂肪酸（FFA）、アポリポタンパク質 A-1 及び B〕、9 点血糖値プロファイルを含む血糖自己測定、体重、ウエスト／ヒップ周囲径、血圧（収縮期及び拡張期）、インスリン投与量（IDegLira 及び IDeg）、CGM

評価基準：安全性

以下の安全性評価項目を評価した：

有害事象、身体所見、眼底検査／眼底写真、心電図、脈拍、低血糖、甲状腺摘出に関連する検査、臨床検査（例：血液学的検査、血液生化学的検査、アミラーゼ及びリパーゼ測定、尿検査、カルシトニン、アルブミン／クレアチニン比）、抗体検査、苦情

統計手法：

検出力の算出

HbA1c の変化量について、IDegLira の IDeg に対する非劣性の検出力は 94.9%及びリラグルチドに対する優越性の検出力は 98.6%であった。すなわち、主要目的を満たす同時検出力は 94.9%*98.6% = 93.6%であった。

解析対象集団

データの完全性が確認できなかったため、施設 456 に参加したすべての被験者を Per-Protocol（PP）解析対象集団から除外し、施設 956 に参加したすべての被験者をすべての解析対象集団から除外した。プライマリーエンドポイントである HbA1c、すべての検証的セカンダリーエンドポイント、重篤な有害事象及び低血糖について感度分析を実施した。その結果、これらの被験者を除外することによる全体の結論への影響は認められなかった。

- 最大の解析対象集団（FAS）：無作為割り付けされたすべての被験者を含めた。FASにおける統計的な評価はITT（intention to treat）の原則に従い、被験者はas randomisedの評価に寄与した。
- Per-Protocol（PP）解析対象集団：FASに含まれる被験者のうち以下の基準を満たすすべての被験者を含めた：いずれの選択基準にも違反していない、いずれの除外基準も満たしていない、スクリーニング又は無作為割り付け時にHbA1c測定値がある、少なくとも12週の曝露がある、12週の曝露後に少なくとも1回のHbA1c測定値がある。
- 安全性解析対象集団（SAS）：治験薬又は対照薬を少なくとも1回投与されたすべての被験者を含めた。SASに含まれる被験者はas treatedの評価に寄与した。
- 完了例の解析対象集団（CAS）：無作為割り付けされて来院28を完了したすべての被験者を含めた。CASに含まれる被験者はas randomisedの評価に寄与した。

ベースラインから投与後 26 週までの HbA1c の変化量は、標準的な共分散分析（ANCOVA）モデルを用いて解析された。主要目的は、IDegLira の IDeg に対する非劣性及びリラグルチドに対する優越性の両方が検証された場合に限り満たされることとした。

- ベースラインから投与後26週までのHbA1cの変化量の主解析を、PP解析対象集団とCASで繰り返した。これらの解析は非劣性に関する感度分析とみなした。
- IDegLiraのIDegに対する優越性を検証するために、4つの検証的セカンダリーエンドポイントを治療間で比較した。成功の要件は、IDegLiraのIDegに対する優越性の評価に用いたエンドポイントのうち少なくとも1つにおいて、多重性の調整後に統計的な有意差が示されることであった。

- ベースラインから投与後26週までの体重の変化量はFASを対象として標準的なANCOVAモデルを用いて解析された。
- 重大な又は重大でない低血糖（確定低血糖）の発現件数は、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された。本モデルには、治療、前治療の糖尿病薬、ベースラインのHbA1cの層、サブ試験参加及び国を固定効果として含めた。統計解析はFASに基づいて行った。これは、優越性の評価にあたって保守的なアプローチと考えられる。
- 増加量の$AUC_{0\text{-}4h}$（$iAUC_{0\text{-}4h}$）は、ベースライン時及び投与後26週の食事負荷試験から得られたグルコース濃度プロファイルから算出した。本エンドポイントは、食事摂取前10分に測定した値を超えるグルコース濃度曲線下面積と定義した。グルコース増加量の曲線下面積は、利用可能なグルコースの実測値及び経過時点の実測値を用いて台形法で算出し、測定時間で除した。ベースラインから投与後26週までの$iAUC_{0\text{-}4h}$の変化量は、FASを対象として標準的なANCOVAモデルを用いて解析された。
- 投与後26週の1日インスリン投与量は、FASを対象として標準的なANCOVAモデルを用いて解析された。これは、優越性の検証にあたって保守的なアプローチと考えられる。
- 仮説検定から導かれる治療効果の結論に関し、全体の第1種の過誤が増大しないことを確実にするために、4項目の比較（体重の変化量、低血糖の発現件数、食事負荷試験から得られたiAUCの変化量及び1日インスリン投与量）のp値はHolm-Bonferroni法により補正された。
- 4つの2値のエンドポイント（レスポンダー／非レスポンダー）は、被験者が投与後26週に規定されたHbA1cの目標値を達成したかどうかで定義した〔米国糖尿病学会（ADA）のHbA1cの目標値：HbA1c 7.0%未満、国際糖尿病連合（IDF）のHbA1cの目標値：HbA1c 6.5%以下〕。4つのレスポンダーエンドポイントの解析は、治療、国、ベースラインのHbA1cの層、サブ試験参加及び前治療の経口糖尿病薬を固定効果とし、ベースラインのHbA1cを共変量として含むロジスティック回帰モデルに基づいた。体重増加に関連するエンドポイントについては、ベースラインの体重を共変量としてモデルに含めた。解析結果はIDegLiraのIDeg及びリラグルチドそれぞれに対するオッズ比及び95%信頼区間で提示した。レスポンダーエンドポイントは以下のとおりであった：投与後26週に体重増加を伴わないHbA1cのレスポンダー、投与後26週に低血糖の発現がないHbA1cのレスポンダーならびに投与後26週に低血糖の発現及び体重増加を伴わないHbA1cのレスポンダー。
- ベースラインから投与後26週までの空腹時血糖値、ウエスト周囲径及びウエスト／ヒップ比の変化量は標準的なANCOVAモデルを用いて解析された。
- 投与後26週に測定された9点血糖値プロファイル（血糖自己測定）から得られた一連のエンドポイントが解析された：9点血糖値プロファイルの平均及び食後血糖増加量の平均。9点血糖値プロファイルデータを、同一被験者内の測定値に対し、無構造共分散行列を仮定する混合効果モデルにあてはめた。モデルには、治療、測定時点、前治療の糖尿病薬、ベースラインのHbA1cの層、サブ試験参加、国及び治療と測定時点の交互作用を固定効果、ベースラインの9点血糖値プロファイルの値を共変量として含めた。
- β細胞機能、血圧（収縮期及び拡張期）、心血管系バイオマーカー及び脂質は、標準的なANCOVAモデルを用いて解析された。

<u>食事負荷試験</u>

- C-ペプチド、インスリン、プロインスリン及びグルカゴンについて、ベースラインから投与後26週までの$iAUC_{0\text{-}4h}$の変化量は、投与後26週のグルコースの変化量と同様の統計モデルを用いて解析された。

<u>CGM</u>

- エンドポイントは標準的なANCOVAモデルを用いて解析された。変動及び変動係数（CV%）は、対数変換して解析された。その際、対応するベースラインの共変量も同様に対数変換を行った。

被験者背景：

<u>人口統計学的特性及びベースライン特性</u>

	IDegLira	IDeg	Lira	Total

	N (%)	N (%)	N (%)	N (%)
Number of Subjects	833	413	414	1660
Age Group				
N	833 (100.0)	413 (100.0)	413 (100.0)	1659 (100.0)
18-40 yrs	64 (7.7)	24 (5.8)	34 (8.2)	122 (7.4)
40-65 yrs	651 (78.2)	328 (79.4)	322 (78.0)	1301 (78.4)
65-75 yrs	107 (12.8)	52 (12.6)	48 (11.6)	207 (12.5)
> 75 yrs	11 (1.3)	9 (2.2)	9 (2.2)	29 (1.7)
Sex				
N	833 (100.0)	413 (100.0)	414 (100.0)	1660 (100.0)
Female	398 (47.8)	213 (51.6)	206 (49.8)	817 (49.2)
Male	435 (52.2)	200 (48.4)	208 (50.2)	843 (50.8)
Ethnicity				
N	833 (100.0)	413 (100.0)	414 (100.0)	1660 (100.0)
Hispanic or Latino	127 (15.2)	67 (16.2)	56 (13.5)	250 (15.1)
Not Hispanic or Latino	706 (84.8)	345 (83.5)	357 (86.2)	1408 (84.8)
UNKNOWN	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.1)

N = Number of Subjects, %= Percentages are based on N

ベースライン及び糖尿病特性

	IDegLira	IDeg	Lira	Total
Number of Subjects	833	413	414	1660
Age (years)				
N	833	413	413	1659
Mean (SD)	55.1 (9.9)	54.9 (9.7)	55.0 (10.2)	55.0 (9.9)
Median	55.7	55.0	55.3	55.4
Min ; Max	27.8 ; 83.8	24.0 ; 79.1	24.4 ; 81.6	24.0 ; 83.8
Height (m)				
N	833	413	414	1660
Mean (SD)	1.67 (0.10)	1.67 (0.11)	1.67 (0.10)	1.67 (0.10)
Median	1.67	1.66	1.67	1.67
Min ; Max	1.35 ; 1.94	1.43 ; 1.98	1.40 ; 2.06	1.35 ; 2.06
Body Weight (kg)				
N	833	413	414	1660
Mean (SD)	87.2 (19.0)	87.4 (19.2)	87.4 (18.0)	87.3 (18.8)
Median	85.6	86.6	87.1	86.2
Min ; Max	41.0 ; 147.1	43.5 ; 156.9	45.5 ; 143.8	41.0 ; 156.9
BMI (kg/m^2)				
N	833	413	414	1660
Mean (SD)	31.2 (5.2)	31.2 (5.3)	31.3 (4.8)	31.2 (5.1)
Median	31.3	31.0	31.3	31.2
Min ; Max	17.3 ; 45.2	16.8 ; 41.8	19.9 ; 40.5	16.8 ; 45.2
Duration of Diabetes (years)				
N	833	413	413	1659
Mean (SD)	6.62 (5.13)	6.98 (5.30)	7.15 (6.09)	6.84 (5.43)
Median	5.2	5.5	5.6	5.4
Min ; Max	0.03 ; 35.07	0.01 ; 32.34	0.01 ; 53.86	0.01 ; 53.86
HbA1c (%)				
N	833	413	414	1660
Mean (SD)	8.3 (0.9)	8.3 (1.0)	8.3 (0.9)	8.3 (0.9)
Median	8.2	8.2	8.2	8.2
Min ; Max	6.0 ; 11.0	6.6 ; 11.3	6.4 ; 12.6	6.0 ; 12.6

FPG (mmol/L)				
N	809	409	409	1627
Mean (SD)	9.2 (2.4)	9.4 (2.7)	9.0 (2.6)	9.2 (2.5)
Median	8.8	8.7	8.4	8.7
Min ; Max	2.7 ; 18.5	4.7 ; 19.4	3.1 ; 23.4	2.7 ; 23.4

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation, FPG= Fasting Plasma Glucose

有効性の結果：

全般的な血糖コントロール

- *HbA1c*：HbA1cの低下量についてIDegLiraのIDegに対する非劣性及びリラグルチドに対する優越性が検証され、IDegLiraによる血糖コントロールの効果的な改善が示された。群差の推定値は、対IDeg群（IDegLira-IDeg）で-0.47%（95%信頼区間：[-0.58; -0.36]、$p < 0.0001$）、及び対リラグルチド群（IDegLira-リラグルチド）で-0.64%（95%信頼区間：[0.75; -0.53]、$p < 0.0001$）であった。HbA1cの変化量はIDegLiraで-1.91%、IDeg群で-1.44%及びリラグルチド群で-1.28%であった。投与後26週のHbA1cはIDegLira群で6.4%、IDeg群で6.9%及びリラグルチド群で7.0%であった。
- *HbA1cのレスポンダー*：投与後26週のHbA1cが7%未満に到達した被験者の割合は、IDeg群で65.1%及びリラグルチド群で60.4%であったのに対し、IDegLira群では80.6%であった。IDegLira群のIDeg群及びリラグルチド群に対するオッズ比の推定値は、それぞれ2.38（95%信頼区間：[1.78; 3.18]、$p < 0.0001$）及び3.26（95%信頼区間：[2.45; 4.33]、$p < 0.0001$）であった。同様に、投与後26週のHbA1cが6.5%以下に到達した被験者の割合は、IDegLira群（69.7%）で最も高く、IDeg群（47.5%）及びリラグルチド群（41.1%）が続いた。IDegLira群のIDeg群及びリラグルチド群に対するオッズ比の推定値は、それぞれ2.82（95%信頼区間：[2.17; 3.67]、$p < 0.0001$）及び3.98（95%信頼区間：[3.05; 5.18]、$p < 0.0001$）であった。以上の結果から、HbA1cの目標値である7%未満又は6.5%以下に到達する可能性は、IDeg群及びリラグルチド群と比較してIDegLira群で統計的に有意に高いことが示されている。
- *投与量調節のための朝食前血糖値（血糖自己測定）*：投与後26週の朝食前血糖値（血糖自己測定）の平均は、投与量調節が可能な2群のいずれにおいても目標値に近かった〔IDegLira群：5.6 mmol/L（101 mg/dL）、IDeg群：5.4 mmol/L（97 mg/dL）〕。朝食前血糖値が同様であることは、これら2群で同様に投与量調節が行われたことを示している。
- *インスリン投与量*：投与後26週の1日インスリン投与量について、IDegLiraのIDegに対する優越性が検証された。群差（IDegLira-IDeg）の推定値は、-14.90単位（95%信頼区間：[-17.14; -12.66]、$p < 0.0001$）であった。投与後26週の1日インスリン投与量はIDegLira群で38単位及びIDeg群で53単位であった。投与後26週におけるインスリン投与量の比（IDegLira/IDeg）は0.72であり、インスリン投与量はIDeg群と比較してIDegLira群で28%少ないことが示された。

血糖コントロールに寄与した主な項目

- *空腹時血糖値*：空腹時血糖値は試験期間中にIDegLira群で3.62 mmol/L（65 mg/dL）、IDeg群で3.61 mmol/L（65 mg/dL）及びリラグルチド群で1.75 mmol/L（32 mg/dL）低下した。投与後26週の変化量にIDegLira群とIDeg群との間に統計的な有意差は認められなかった。空腹時血糖値の低下量はリラグルチド群と比較してIDegLira群で統計的に有意に大きかった〔群差の推定値：-1.76 mmol/L（95%信頼区間：[-2.00; -1.53]、$p < 0.0001$）〕。
- *9点血糖値プロファイル（血糖自己測定）*：9点血糖値プロファイル（血糖自己測定）の平均の低下量は、IDeg群〔群差の推定値：-0.30 mmol/L（95%信頼区間：[-0.50; -0.09]、$p = 0.0040$）〕及びリラグルチド群〔群差の推定値：-0.93 mmol/L（95%信頼区間：[-1.13; -0.73]、$p < 0.0001$）〕と比較してIDegLira群で統計的に有意に大きかった。
  食後血糖増加量（すべての食事の平均）は、IDeg群と比較してIDegLira群で統計的に有意に小さく〔群差（IDegLira-IDeg）の推定値：-0.45 mmol/L（95%信頼区間：[-0.63; -0.28]、$p < 0.0001$）〕、IDegLira群とリラグルチド群との間では同様であった（統計的な有意差なし）。
- *食事負荷試験 - 食後血糖増加量（サブ集団）*：投与後26週の食後血糖増加量（$iAUC_{0\text{-}4h}$）についてIDegLiraのIDegに対する優越性が検証された〔群差（IDegLira-IDeg）の推定値：-0.71 mmol/L（95%信

頼区間：[-1.17; -0.26]、p = 0.0023）〕。投与後26週において、IDegLira群とリラグルチド群との間で統計的な有意差は認められなかった〔群差の推定値：-0.09 mmol/L（95%信頼区間：[-0.56; 0.37]、p = 0.7399）〕。

- *低血糖*：26週間の確定低血糖の発現件数についてIDegLiraのIDegに対する優越性が検証された。群の比（IDegLira/IDeg）の推定値は0.68（95%信頼区間：[0.53; 0.87]、p = 0.0023）であり、低血糖の単位時間あたりの発現件数はIDegLira群で32%少ないことが示された。投与期間中に確定低血糖を発現した被験者の割合は、IDeg群（38.6%）と比較してIDegLira群（31.9%）で低かった。同様に、確定低血糖の単位時間あたりの発現件数は少なかった（IDegLira群：180件／100人・年、IDeg群：257件／100人・年）。確定低血糖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リラグルチド群（6.8%、22件／100人・年）で最も低かった。
- *体重*：投与後26週の体重についてIDegLiraのIDegに対する優越性が検証された。群差の推定値（IDegLira-IDeg）は-2.22 kg（95%信頼区間：[-2.64; -1.80]、p < 0.0001）であった。投与後26週の体重の変化量はIDegLira群で-0.5 kg、IDeg群で+1.6 kg及びリラグルチド群で-3.0 kgであった。

安全性の結果：

本試験における投与後 26 週の IDegLira、IDeg 及びリラグルチドの安全性についての結論は以下のとおりであった：IDegLira、IDeg 及びリラグルチドの忍容性は概して良好であった。IDeg 群及びリラグルチド群の有害事象及び忍容性プロファイルは過去の結果と一致していた。IDegLira 群の安全性プロファイルは IDeg 群及びリラグルチド群でみられた結果と一致していた。

検討した各領域における安全性の結果を以下に要約する：

<u>全般的な有害事象プロファイル（低血糖以外）</u>

- 1件の死亡（IDegLira群）が報告された。死因は不明であった（その後、心血管死と判定された）。
- 有害事象の単位時間あたりの発現件数（件／100人・年）は、IDegLira群とIDeg群との間では同様であったが、リラグルチド群との比較ではIDegLira群で少なかった（IDegLira群：482.8件／100人・年、IDeg群：430.0件／100人・年、リラグルチド群：640.5件／100人・年）。いずれの投与群においても、有害事象の大部分は重症度が軽度であり、治験責任医師により治験薬との関連は「なし」と判定された。
- 最も高頻度に報告された有害事象は頭痛であり、被験者の9.2～11.9%で発現し、単位時間あたりの発現件数は41.4～50.7件／100人・年であった。その他の高頻度に報告された有害事象は胃腸障害（悪心、下痢及び嘔吐）であった。これらの事象を合わせた単位時間あたりの発現件数は、IDeg群と比較してIDegLira群で多かったが、リラグルチド群との比較ではIDegLira群で少なかった（IDegLira群：55件／100人・年、IDeg群：22件／100人・年、リラグルチド群：118件／100人・年）。
- 被験者の1%以上で報告された重篤な有害事象は認められず、重篤な有害事象の大部分は治験薬との因果関係は「なし」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」と判定された重篤な有害事象は6件（6例）であった。その内訳は、IDegLira群で3件（重大な低血糖、低血糖性意識消失及び悪性黒色腫）及びリラグルチド群で3件（胃炎、急性心筋梗塞及び嘔吐）であった。
- 試験全体では2.5%（42/1663例）の被験者が有害事象の発現により試験を中止した。この割合が最も高かったのはリラグルチド群であった（5.8%、大部分は悪心又は嘔吐による中止）。6例を除くすべての被験者でこれらの事象の転帰は回復又は軽快であった。

<u>事前に規定した注目すべき安全性領域の有害事象</u>

- 確定された心血管系事象の単位時間あたりの発現件数はIDegLira群、IDeg群及びリラグルチド群でそれぞれ0.3件／100人・年、2.1件／100人・年及び1.1件／100人・年であった。14例18件の心血管系事象（1件の死亡を含む）が判定対象とされ、そのうち8件（5例）が心血管系事象と確定された（治験薬投与下でない1件の有害事象を含む）。そのうち3件は主要な心血管イベント（各群1件）であった。
- 24件の不整脈（21例）が報告され、単位時間あたりの発現件数は、IDegLira群、IDeg群及びリラグルチド群でそれぞれ2.3件／100人・年、3.1件／100人・年及び4.8件／100人・年であった。
- 18件の膵炎又は膵炎の疑いが判定対象とされ、そのうち1件（リラグルチド群）が急性膵炎と確定された。

- 投薬過誤が認められた被験者は少なく、重度と判定されたものはなかった。すべての被験者は回復した。群間で明らかな違いは認められなかった。
- 85例109件のリパーゼ増加又はアミラーゼ増加が報告され、リパーゼ増加、アミラーゼ増加又はその両方を発現した被験者の割合は、IDeg群（3.6%）と比較してIDegLira群（5.6%）及びリラグルチド群（5.8%）で高かった。大部分は無症候性であり、増加は一時的なものであった。
- 26件の新生物（24例）が判定対象とされ、そのうち12件（11例）が新生物と確定された。すべての新生物及び確定された新生物について、単位時間あたりの発現件数は群間で同様であった。
- 甲状腺切除を要する甲状腺疾患及び甲状腺新生物が判定された。7件の甲状腺に関連する有害事象（7例）が報告された（IDegLira群：3件、IDeg群：1件、リラグルチド群：3件）。これらの事象のうち1件（甲状腺腫、EAC判定はnot-confirmed）が甲状腺の事象の判定対象とされた。甲状腺髄様癌は報告されなかった。
- カルシトニンの継続的なモニタリングから15例15件のカルシトニン値の増加（20 ng/L以上）が有害事象として報告されたが、いずれも臨床症状は認められなかった。
- 腎機能の悪化、高血糖又はアレルギー反応については、報告件数は少なく、群間で違いは認められなかった。
- 注射部位反応の単位時間あたりの発現件数は、IDegLira群とリラグルチド群で同様であり（11.9件／100人・年）、IDeg群で少なかった（6.2件／100人・年）。最も高頻度に報告された有害事象は注射部位血腫であった。

<u>低血糖</u>

- 確定低血糖の発現件数は、本試験における有効性の検証的エンドポイントであった。前述の有効性の結果を参照のこと。
- ADAの分類に基づく低血糖についても、単位時間あたりの発現件数は確定低血糖と同様の傾向が認められ、IDeg群と比較してIDegLira群で少なく、リラグルチド群で非常に少なかった（IDegLira群：1617件／100人・年、IDeg群：1815件／100人・年、リラグルチド群：160件／100人・年）。ADAの分類に基づく低血糖の大部分は無症候性低血糖（asymptomatic hypoglycaemia）又は確定症候性低血糖（documented symptomatic hypoglycaemia）であった。
- 確定夜間低血糖の単位時間あたりの発現件数はIDegLira群（22.4件／100人・年）とIDeg群（27.9件／100人・年）で概ね同様であり、リラグルチド群（2.7件／100人・年）で少なかった。
- 重大な低血糖は26週の投与期間中に4件報告された（IDegLira群：2件、IDeg群：2件）。

<u>脈拍数</u>

- IDegLira群（2.8拍／分）及びリラグルチド群（2.6拍／分）では、脈拍数の増加が認められたが、IDeg群では脈拍数は一定であった。脈拍数の増加量は、IDeg群と比較してIDegLira群で統計的に有意に大きかったが、IDegLira群とリラグルチド群との間では同様であった。

<u>臨床検査評価</u>

- 血液学的検査又は血液生化学的検査のパラメータについては、いずれの投与群においてもベースラインから投与終了時までに臨床的に問題のある変化は認められなかった。
- リパーゼは、ベースラインから投与終了時までにIDegLira群（11.4 U/L）及びリラグルチド群（15.3 U/L）で増加したが、IDeg群（-6.8 U/L）では減少した。同様に、アミラーゼについても顕著ではないがIDegLira群及びリラグルチド群で増加した。臨床的な影響については現在のところ不明である。
- 最も高頻度に報告された臨床検査に関する有害事象はリパーゼ増加であり、IDegLira群の5.0%、IDeg群の3.4%及びリラグルチド群の5.3%の被験者で認められた。
- カルシトニンについては、臨床的に問題となる群間の違いは認められなかった。
- 尿アルブミン／クレアチニン比については、IDegLira群とIDeg群又はリラグルチド群との間で統計的な有意差は認められなかった。

<u>身体所見、眼底検査／眼底写真及び心電図</u>

- 投与後26週の身体所見、眼底検査／眼底写真又は心電図の結果については、臨床的に問題となる群間の違いは認められなかった。

抗体検査 • 26週の投与期間中、問題となるIDeg特異抗体産生はIDegLira群及びIDeg群のいずれでも認められなかった。2群の中でヒトインスリンとの交叉抗体がみられた被験者は非常に少なく、IDegLira群とIDeg群との間で違いは認められなかった。 • 抗リラグルチド抗体産生は非常に限られていた。投与後26週に抗体陽性であった被験者はIDegLira群又はリラグルチド群の1%未満であり、そのうち内因性GLP-1との交叉抗体が認められた被験者は1例のみであった。
全体の結論： • 血糖コントロールについての有効性が確認された：ベースラインから投与後26週までのHbA1cの変化量について、IDegLiraのIDegに対する非劣性及びリラグルチドに対する優越性が示された。 • 投与後26週において、IDegLiraでは、IDegと比較して、少ないインスリン投与量で低いHbA1cに到達し、食後の血糖コントロールは改善し、低血糖の発現件数は少なかった。さらに、IDegLiraの投与による体重の増加は認められなかった。 • 空腹時血糖値の低下量は、リラグルチドと比較してIDegLiraで大きかった。 • IDeg及びリラグルチドにおける個々の有効性プロファイルは概して過去の結果と一致していた。 • IDeg及びリラグルチドにおける有害事象及び忍容性プロファイルは過去の結果と一致していた。IDegLiraの安全性プロファイルはIDeg及びリラグルチドでみられた結果と一致していた。
本試験は、ヘルシンキ宣言の精神及びICH-GCPを遵守して実施された。

ここに提示する結果は、2012年7月17日の時点での臨床データベースに基づいている。本データベースは、安全性及び有効性の重要な情報を更新するためにロックを解除された。

2.7.6.7 NN9068-3697

2.7.6.7.1 臨床試験概要

Trial Registration ID-number： NCT01336023	UTN：U1111-1119-1174 IND number：109/121 EudraCT number：2010-021560-15

治験の標題：

DUAL I‐2 型糖尿病患者におけるリラグルチド及びインスリン デグルデクの Dual Action：2 型糖尿病患者を対象としたインスリン デグルデク／リラグルチド、インスリン デグルデク及びリラグルチドの有効性及び安全性を比較する試験

1～2 種類の経口糖尿病薬で治療中の 2 型糖尿病患者を対象とした、インスリン デグルデクとリラグルチドの固定比率の配合剤と、インスリン デグルデク又はリラグルチドの単剤とを比較する 26 週間（+26 週間の延長期間）、無作為割り付け、3 群並行、非盲検、多施設、国際共同、treat-to-target 試験

本治験総括報告書には、本試験における 52 週間の全治療期間について記載する。

治験責任医師名：

19 ヵ国で計 286 名の治験責任医師が任命された。以下の治験責任医師が治験総括報告書の内容を確認し、署名する「治験総括報告書への署名責任を有する医師（Signatory Investigator）」に任命された：

Professor [redacted]

治験実施施設：

以下の 19 ヵ国 271 施設において被験者の無作為割り付けが実施された：オーストラリア（7 施設）、カナダ（14 施設）、フィンランド（5 施設）、ドイツ（12 施設）、ハンガリー（6 施設）、インド（23 施設）、アイルランド（2 施設）、イタリア（6 施設）、マレーシア（5 施設）、メキシコ（2 施設）、ロシア（11 施設）、シンガポール（3 施設）、スロバキア（5 施設）、南アフリカ共和国（13 施設）、スペイン（8 施設）、台湾（3 施設）、タイ（4 施設）、英国（16 施設）及び米国（126 施設）

公表文献（引用文献）：

本治験総括報告書作成時点でなし

治験期間：	**開発のフェーズ**：
開始日：2011 年 5 月 23 日 終了日：2012 年 11 月 22 日	第 3a 相

目的：

治験実施計画書及びその改訂版に記載のとおり、26 週間の主要期間及び 52 週間の全治療期間（延長期間終了までの期間、イタリック体で以下に示す）の目的は：

主要目的：

- 2型糖尿病患者を対象として、インスリン デグルデク／リラグルチド（IDegLira）の血糖コントロールにおける有効性を検証する。

副次的目的：

- 投与後26週までの体重管理、低血糖、食事に関連する血糖コントロール及びインスリン デグルデク（IDeg）の1日投与量により間接的に評価される血糖コントロールについて、IDegLiraのIDegに対する優越性を検証する。
- *2型糖尿病患者を対象として、投与後52週における血糖コントロールについてIDegLiraの有効性を検証*

する。

- *投与後26週及び52週におけるIDegLira、IDeg及びリラグルチドの全般的な有効性及び安全性を比較検討する。*
  - 当初の副次的目的は投与後26週のみの有効性及び安全性を検討することであった。しかしながら、本試験に26週間の延長期間を追加し（amendment 2）、52週間の全期間について記載する本治験総括報告書で投与後52週における検討を副次的目的に含めた。

薬物動態の目的：

- 母集団薬物動態解析を用いて、26週間のIDegLiraと各有効成分単剤（個別投与）の臨床用量での薬物動態を比較する。また、事前に規定した共変量の血漿中IDegLira濃度への影響を検討する。
  結果は別の治験総括報告書で示している。

治験方法：

- 本試験は、1～2種類の経口糖尿病薬（メトホルミン単剤又はメトホルミンとピオグリタゾンとの併用）による治療で十分な血糖コントロールが得られていない2型糖尿病患者を対象とした、26週間（+26週間の延長期間）、無作為割り付け、実薬対照、3群並行、非盲検、多施設、国際共同、treat-to-target試験であり、IDegLiraと各有効成分単剤（IDeg及びリラグルチド）の1日1回投与の有効性及び安全性を比較検討した。HbA1cが7.0%以上、10.0%以下を「十分な血糖コントロールが得られていない」とした。
- 適格と判断された被験者をIDegLira、IDeg又はリラグルチドの1日1回投与からなる3つの治療群のいずれかに2：1：1の割合で無作為に割り付けた。メトホルミン単剤又はメトホルミンとピオグリタゾンとの併用による治療は試験開始前の用法・用量で継続した。前治療（メトホルミン単剤及びメトホルミンとピオグリタゾンとの併用）及びベースラインのHbA1c（8.3%以下、8.3%超）ごとに被験者を層別した。すべての治療は非盲検下で行われた。
- リラグルチド群では、規定の用量漸増法に従い、目標用量の1.8 mgに到達するまで1週間に1回0.6 mgずつ増量した。IDegLira群及びIDeg群では、それぞれ10用量ステップ及び10単位で投与を開始し、朝食前血糖値に基づき、事前に規定したアルゴリズムに従い1週間に2回投与量調節を行った。
- 選択された治験実施医療機関では、持続血糖測定（CGM）及び食事負荷試験のサブ試験を行った。
- 無作為割り付け後26週時点ですべての被験者に追加の26週間の投与期間への参加を提案した。被験者は同じ治療〔同じ投与量（リラグルチド群）又は同じ投与方法（IDeg群及びIDegLira群）〕を継続することとした。

計画及び解析された被験者数：

計画された被験者数は、IDegLira 群で 830 例、IDeg 群及びリラグルチド群で各 415 例であり、無作為割り付け予定被験者数は計 1660 例であった。サブ試験の予定被験者数は 256 例であった。

	IDegLira N (%)	IDeg N (%)	Lira N (%)	Total N (%)
Screened				3004
Screening Failures				1341
Withdrawn before Randomisation				0
Randomised	834 (100.0)	414 (100.0)	415 (100.0)	1663(100.0)
Exposed	826 (99.0)	413 (99.8)	413 (99.5)	1652(99.3)
Completed Main Trial	734 (88.0)	366 (88.4)	342 (82.4)	1442(86.7)
Withdrawn at/after Randomisation and Before extension	100 (12.0)	48 (11.6)	73 (17.6)	221(13.3)
Adverse Event	11 (1.3)	8 (1.9)	24 (5.8)	43(2.6)
Ineffective Therapy	1 (0.1)	0 (0.0)	0 (0.0)	1(0.1)
Non-Compliance	2 (0.2)	1 (0.2)	0 (0.0)	3(0.2)

Withdrawal Criteria	70 (8.4)	34 (8.2)	40 (9.6)	144(8.7)
Other	16 (1.9)	5 (1.2)	9 (2.2)	30(1.8)
Completed Main Trial Not Screened for Extension	69 (8.3)	33 (8.0)	29 (7.0)	131(7.9)
Completed Main Trial Screening Failure in Extension	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)
Included in Extension	665 (79.7)	333 (80.4)	313 (75.4)	1311(78.8)
Withdrawn during extension	44 (5.3)	28 (6.8)	28 (6.7)	100(6.0)
Adverse Event	5 (0.6)	1 (0.2)	2 (0.5)	8(0.5)
Ineffective Therapy	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)
Non-Compliance	2 (0.2)	0 (0.0)	1 (0.2)	3 0.2)
Withdrawal Criteria	19 (2.3)	14 (3.4)	16 (3.9)	49(2.9)
Other	18 (2.2)	13 (3.1)	9 (2.2)	40(2.4)
Completed Extension	621 (74.5)	305 (73.7)	285 (68.7)	1211(72.8)
Full Analysis Set	833 (99.9)	413 (99.8)	414 (99.8)	1660(99.8)
PP Analysis Set	755 (90.5)	374 (90.3)	362 (87.2)	1491(89.7)
Safety Analysis Set	825 (98.9)	412 (99.5)	412 (99.3)	1649(99.2)
Extension Trial Set	665 (79.7)	332 (80.2)	313 (75.4)	1310(78.8)

N: Number of subjects
%: Proportion of randomised subjects, PP: Per Protocol

診断及び主要な組入れ基準：

主な選択基準

性別不問、年齢 18 歳以上〔シンガポール：21 歳以上、台湾（施設 653）：20 歳以上〕の 2 型糖尿病患者。HbA1c 7.0%以上、10.0%以下の被験者で中央値が 8.3%となることを目標とする。HbA1c 8.3%超の被験者の割合が無作為割り付け予定被験者数の約 50%となった場合には、残りの割り付けられる被験者の HbA1c はすべて 8.3%以下でなければならない。また、HbA1c 8.3%以下の被験者の割合が無作為割り付け予定被験者数の約 50%となった場合には、残りの割り付けられる被験者の HbA1c はすべて 8.3%超でなければならない。スクリーニングの 90 日以上前から、1～2 種類の経口糖尿病薬〔メトホルミン単剤（1500 mg 以上又は最大耐用量）又はメトホルミン（1500 mg 以上又は最大耐用量）とピオグリタゾン（30 mg 以上）との併用〕による安定した（1 日投与量が安定）治療を受けている被験者。BMI（kg/m^2）が 40 以下の被験者。治験実施計画書に従った血糖自己測定、被験者日誌への記録ならびにペン型注入器又はフレックスペン®の使用を受け入れられる被験者。

主な除外基準

インスリン治療歴を有する被験者（ただし、併発疾患のための短期間のインスリン投与については可とする：治験責任医師の判断による）。試験開始前 90 日以内に GLP-1 受容体作動薬、スルホニルウレア薬又はジペプチジルペプチダーゼ 4 阻害薬（DPP-4 阻害薬）の投与を受けた被験者。消化器系、呼吸器系、神経系、泌尿生殖器系又は血液系の臨床的に問題となる活動性（過去 12 ヵ月以内）の疾患を有する被験者。肝機能障害（アラニンアミノトランスフェラーゼが基準範囲上限の 2.5 倍以上）を有する被験者。腎機能障害〔血清クレアチニンが男性で 133 μmol/L 以上（1.5 mg/dL 以上）、女性で 125 μmol/L 以上（1.4 mg/dL 以上）〕を有する被験者。スクリーニング時のカルシトニン濃度が 50 ng/L 以上である被験者。

主な中止・脱落基準

糖代謝又は脂質代謝に影響を及ぼすと考えられる薬剤の全身投与を開始する場合（治験責任医師の判断による）、被験者が妊娠した又は妊娠を希望する場合、高血糖（確定）が発現した場合、急性膵炎と診断された場合、被験者は試験を中止しなければならない。

被験薬、用量及び投与方法、ロット番号：

IDegLira

1 mL あたり IDeg 100 単位とリラグルチド 3.6 mg の固定比率の配合剤、ペン型注入器（フレックスペン

®、3 mL）と一体化したプレフィルド製剤として提供された。
IDegLira は 1 日 1 回、毎日同時刻に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。10 用量ステップ（IDeg：10 単位、リラグルチド：0.36 mg に相当）で投与を開始した。各投与量調節日前の連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき、1 週間に 2 回投与量調節を行った。朝食前血糖値 4.0～5.0 mmol/L（72～90 mg/dL）を目標として、2 用量ステップ（IDeg：2 単位、リラグルチド：0.072 mg）ずつ投与量調節を行った。最高用量は 50 用量ステップ（IDeg：50 単位、リラグルチド：1.8 mg）であった。ロット番号：AP50043、YP52274、AP50044 及び AP50017。

投与期間：
26 週間（主要期間）＋26 週間（延長期間）

対照薬、用量及び投与方法、ロット番号：
IDeg
100 単位/mL、ペン型注入器（フレックスペン®、3 mL）と一体化したプレフィルド製剤として提供された。IDeg は 1 日 1 回、毎日同時刻に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。10 単位で投与を開始し、前述の IDegLira と同様に、連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均に基づき、4.0～5.0 mmol/L（72～90 mg/dL）を目標として、1 週間に 2 回投与量調節を行った。最高用量は設定しなかった。ロット番号：YP52252 及び AP51402。
リラグルチド
6 mg/mL、ペン型注入器（3 mL）と一体化したプレフィルド製剤として提供された。リラグルチドは 1 日 1 回、毎日同時刻に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。0.6 mg／日で投与を開始し、以降は最高用量 1.8 mg／日に到達するまで週 1 回 0.6 mg ずつ増量した。用量漸増終了後は 1.8 mg／日の用量を維持した。ロット番号：XP52720 及び AP50533。

評価基準：有効性
以下の有効性評価項目を評価した：
HbA1c、β 細胞機能〔空腹時プロインスリン、空腹時 C-ペプチド、空腹時インスリン（算出したインスリン／プロインスリン比、HOMA-B、HOMA-IR）、空腹時グルカゴン〕、空腹時血糖値（FPG）、心血管系バイオマーカー〔高感度 C 反応性タンパク質（hsCRP）、アディポネクチン、フィブリノゲン、脳性ナトリウム利尿ペプチド（BNP）、プラスミノーゲン活性化抑制因子（PAI-1）〕、空腹時脂質プロファイル〔中性脂肪、コレステロール、低比重リポタンパク質コレステロール（LDL）、高比重リポタンパク質コレステロール（HDL）、超低比重リポタンパク質コレステロール（VLDL）、遊離脂肪酸（FFA）、アポリポタンパク質 A-1 及び B〕、9 点血糖値プロファイルを含む血糖自己測定、体重、ウエスト／ヒップ周囲径、血圧（収縮期及び拡張期）、インスリン投与量（IDegLira 及び IDeg）、CGM（サブ試験のみ）

評価基準：安全性
以下の安全性評価項目を評価した：
有害事象、身体所見、眼底検査／眼底写真、心電図、脈拍数、低血糖、甲状腺摘出に関連する検査、臨床検査（例：血液学的検査、血液生化学的検査、アミラーゼ及びリパーゼ測定、尿検査、カルシトニン、アルブミン／クレアチニン比）、抗体検査、苦情

統計手法：
検出力の算出
本試験では投与後 26 週（主要期間）の HbA1c の変化量について、IDegLira の IDeg に対する非劣性及びリラグルチドに対する優越性の検出力を算定した。投与後 26 週の HbA1c の変化量について、IDegLira の IDeg に対する非劣性を示す検出力は 94.9%及びリラグルチドに対する優越性を示す検出力は 98.6%であった。すなわち、主要目的を満たす同時検出力は 94.9%*98.6% = 93.6%であった。
解析対象集団
データの完全性が確認できなかったため、施設 456 に参加したすべての被験者を Per-Protocol（PP）解析対象集団から除外し、施設 956 に参加したすべての被験者をすべての解析対象集団から除外した。
HbA1c、重篤な有害事象及び低血糖についての感度分析を実施した。その結果、全体の結論への影響は認

められなかった。

- 最大の解析対象集団（FAS）：無作為割り付けされたすべての被験者を含めた。FASにおける統計的な評価はITT（intention to treat）の原則に従い、被験者はas randomisedの評価に寄与した。
- Per-Protocol（PP）解析対象集団：FASに含まれる被験者のうち以下の基準を満たすすべての被験者を含めた：いずれの選択基準にも違反していない、いずれの除外基準も満たしていない、スクリーニング又は無作為割り付け時にHbA1c測定値がある、少なくとも12週の曝露がある、12週の曝露後に少なくとも1回のHbA1c測定値がある。
- 安全性解析対象集団（SAS）：治験薬又は対照薬を少なくとも1回投与されたすべての被験者を含めた。SASに含まれる被験者はas treatedの評価に寄与した。
- 延長期間解析対象集団（ETS）：延長期間に参加して来院30以降の来院があったすべての被験者を含めた。
- 完了例の解析対象集団（CAS）：無作為割り付けされ来院55を完了し、全投与期間を完了したすべての被験者を含めた。CASに含まれる被験者はas randomisedの評価に寄与した。
  ベースラインから投与後52週までのHbA1cの変化量は、FASを対象として標準的な共分散分析（ANCOVA）モデルを用いて解析された。感度分析を、PP解析対象集団、ETS及びCASで繰り返した。
- 投与後52週における有効性のすべての解析は探索的位置づけであり、多重性の調整は行わなかった。
- ベースラインから投与後52週までの体重の変化量はFASを対象として標準的なANCOVAモデルを用いて解析された。
- 重大な又は重大でない低血糖（確定低血糖）の発現件数は、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された。本モデルには、治療、前治療の糖尿病薬、ベースラインのHbA1cの層、サブ試験参加及び国を固定効果として含めた。統計解析はFASに基づいて行った。
- 増加量の$AUC_{0\text{-}4h}$（$iAUC_{0\text{-}4h}$）は、ベースライン時及び投与後52週の食事負荷試験から得られたグルコース濃度プロファイルから算出した。本エンドポイントは、食事摂取前10分に測定した値を超えるグルコース曲線下面積と定義した。グルコース増加量の曲線下面積は、利用可能なグルコースの実測値及び関連する経過時点の実測値を用いて台形法により算出し、測定時間で除した。ベースラインから投与後52週までの$iAUC_{0\text{-}4h}$の変化量は、FASを対象として標準的なANCOVAモデルを用いて解析された。
- 投与後52週の1日インスリン投与量は、FASを対象として標準的なANCOVAモデルを用いて解析された。
- 8つの2値のエンドポイント（レスポンダー／非レスポンダー）は、被験者が投与後52週に規定されたHbA1cの目標値を達成したかどうかで定義された〔米国糖尿病学会（ADA）のHbA1cの目標値：HbA1c 7.0%未満、国際糖尿病連合（IDF）のHbA1cの目標値：HbA1c 6.5%以下〕。8つのレスポンダーエンドポイントの解析は、治療、地域、ベースラインのHbA1cの層、サブ試験参加及び前治療の経口糖尿病薬を固定効果とし、ベースラインのHbA1cを共変量として含むロジスティック回帰モデルに基づいた。体重増加に関連するエンドポイントについては、ベースラインの体重を共変量としてモデルに含めた。解析結果はIDegLiraのIDeg及びリラグルチドそれぞれに対するオッズ比及び95%信頼区間で提示した。レスポンダーエンドポイントは以下のとおりであった：投与後52週に体重増加を伴わないHbA1cのレスポンダー、投与後52週に低血糖の発現がないHbA1cのレスポンダーならびに投与後52週に低血糖の発現及び体重増加を伴わないHbA1cのレスポンダー。
- ベースラインから投与後52週までの空腹時血糖値、ウエスト周囲径及びウエスト／ヒップ比の変化量は標準的なANCOVAモデルを用いて解析された。
- 投与後52週に得られた9点血糖値プロファイル（血糖自己測定）から得られた一連のエンドポイントが解析された：9点血糖値プロファイルの平均及び食後血糖増加量の平均。9点血糖値プロファイルデータを、同一被験者内の測定値に対し、無構造共分散行列を仮定する混合効果モデルにあてはめた。モデルには、治療、測定時点、前治療の糖尿病薬、ベースラインのHbA1cの層、サブ試験参加、国及び治療と測定時点の交互作用を固定効果、ベースラインの9点血糖値プロファイルの値を共変量とし

て含めた。
- β細胞機能、血圧（収縮期及び拡張期）、心血管系バイオマーカー及び脂質は、標準的なANCOVAモデルを用いて解析された。

食事負荷試験
- C-ペプチド、インスリン、プロインスリン及びグルカゴンについて、ベースラインから投与後52週までの$iAUC_{0-4h}$の変化量は、サブ試験参加の因子を除いて標準的なANCOVAモデルを用いて解析された。

CGM
- エンドポイントはサブ試験参加の因子を除いて標準的なANCOVAモデルを用いて解析された。変動及び変動係数（CV%）は、対数変換して解析された。その際対応するベースラインの共変量も同様に対数変換を行った。
- 投与後52週における安全性及び忍容性は、以下の安全性評価項目を対象としたデータの要約を用いて評価した：
  - 有害事象
  - 治験薬投与下で発現した低血糖の発現件数
  - 治験薬投与下で発現した夜間低血糖の発現件数
  - ベースラインからの脈拍数の変化量
  - 臨床評価（身体所見、眼底検査／眼底写真及び心電図）
  - 臨床検査評価（血液生化学的検査、血液学的検査、尿検査、カルシトニン、リパーゼ及びアミラーゼ検査及びアルブミン／クレアチニン比）
  - 抗IDeg抗体及び抗リラグルチド抗体

被験者背景：

人口統計学的特性及びベースライン特性

	IDegLira N (%)	IDeg N (%)	Lira N (%)	Total N (%)
Number of Subjects	833	413	414	1660
Age Group				
N	833 (100.0)	413 (100.0)	414 (100.0)	1660 (100.0)
18-40 yrs	64 (7.7)	24 (5.8)	34 (8.2)	122 (7.3)
40-65 yrs	651 (78.2)	328 (79.4)	323 (78.0)	1302 (78.4)
65-75 yrs	107 (12.8)	52 (12.6)	48 (11.6)	207 (12.5)
> 75 yrs	11 (1.3)	9 (2.2)	9 (2.2)	29 (1.7)
Sex				
N	833 (100.0)	413 (100.0)	414 (100.0)	1660 (100.0)
Female	398 (47.8)	213 (51.6)	206 (49.8)	817 (49.2)
Male	435 (52.2)	200 (48.4)	208 (50.2)	843 (50.8)
Ethnicity				
N	833 (100.0)	413 (100.0)	414 (100.0)	1660 (100.0)
Hispanic or Latino	127 (15.2)	67 (16.2)	56 (13.5)	250 (15.1)
Not Hispanic or Latino	706 (84.8)	345 (83.5)	357 (86.2)	1408 (84.8)
Not Applicable	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.1)

N = Number of Subjects, %= Percentages are based on N

ベースライン及び糖尿病特性

	IDegLira N (%)	IDeg N (%)	Lira N (%)	Total N (%)
Age (years)				
N	833	413	414	1660
Mean (SD)	55.1 (9.9)	54.9 (9.7)	55.0 (10.2)	55.0 (9.9)

Median	55.7	55.0	55.3	55.4
Min ; Max	27.8 ; 83.8	24.0 ; 79.1	24.4 ; 81.6	24.0 ; 83.8
Height (m)				
N	833	413	414	1660
Mean (SD)	1.67 (0.10)	1.67 (0.11)	1.67 (0.10)	1.67 (0.10)
Median	1.67	1.66	1.67	1.67
Min ; Max	1.35 ; 1.94	1.43 ; 1.98	1.40 ; 2.06	1.35 ; 2.06
Body Weight (kg)				
N	833	413	414	1660
Mean (SD)	87.2 (19.0)	87.4 (19.2)	87.4 (18.0)	87.3 (18.8)
Median	85.6	86.6	87.1	86.2
Min ; Max	41.0 ; 147.1	43.5 ; 156.9	45.5 ; 143.8	41.0 ; 156.9
BMI (kg/m^2)				
N	833	413	414	1660
Mean (SD)	31.2 (5.2)	31.2 (5.3)	31.3 (4.8)	31.2 (5.1)
Median	31.3	31.0	31.3	31.2
Min ; Max	17.3 ; 45.2	16.8 ; 41.8	19.9 ; 40.5	16.8 ; 45.2
Duration of Diabetes (years)				
N	833	413	413	1659
Mean (SD)	6.63 (5.13)	6.99 (5.31)	7.15 (6.09)	6.85 (5.43)
Median	5.2	5.5	5.6	5.4
Min ; Max	0.03 ; 35.07	0.01 ; 32.34	0.01 ; 53.86	0.01 ; 53.86
HbA1c (%)				
N	833	413	414	1660
Mean (SD)	8.3 (0.9)	8.3 (1.0)	8.3 (0.9)	8.3 (0.9)
Median	8.2	8.2	8.2	8.2
Min ; Max	6.0 ; 11.0	6.6 ; 11.3	6.4 ; 12.6	6.0 ; 12.6
FPG (mmol/L)				
N	809	409	409	1627
Mean (SD)	9.2 (2.4)	9.4 (2.7)	9.0 (2.6)	9.2 (2.5)
Median	8.8	8.7	8.4	8.7
Min ; Max	2.7 ; 18.5	4.7 ; 19.4	3.1 ; 23.4	2.7 ; 23.4

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation, FPG= Fasting Plasma Glucose

有効性の結果：

投与後 26 週に認められた IDeg 又はリラグルチドに対する IDegLira の有益な効果は、投与後 52 週においても経口糖尿病薬の併用下における IDegLira、IDeg 及びリラグルチドで維持された。投与後 52 週の結論は以下のとおりであった：

全般的な血糖コントロール

- *HbA1c*：IDegLiraによる血糖コントロールの効果的な改善が示された。群差の推定値は、対IDeg群（IDegLira-IDeg）で-0.46%（95%信頼区間：-0.57; -0.34、p < 0.0001）、及び対リラグルチド群（IDegLira-リラグルチド）で -0.65%（95%信頼区間：-0.76; -0.53、p < 0.0001）であった。HbA1cの変化量はIDegLira群で-1.84%、IDeg群で-1.40%及びリラグルチド群で-1.21%であった。投与後52週のHbA1cはIDegLira群で6.4%、IDeg群で6.9%及びリラグルチド群で7.1%であった。
- *HbA1cのレスポンダー*：投与後52週のHbA1cが7%未満に到達した被験者の割合は、IDeg群で62.5%及びリラグルチド群で56.5%であったのに対し、IDegLira群では78.2%であった。IDegLira群のIDeg群及びリラグルチド群に対するオッズ比の推定値は、それぞれ2.35（95%信頼区間：1.77; 3.13、p < 0.0001）及び3.42（95%信頼区間：2.58; 4.54、p < 0.0001）であった。同様に、投与後52週のHbA1cが6.5%以下に到達した被験者の割合は、IDegLira群（66.9%）で最も高く、IDeg群（49.2%）及びリラグルチド群（38.2%）が続いた。IDegLira群のIDeg群及びリラグルチド群に対するオッズ比の推定値は、それぞれ2.26（95%信頼区間：1.74; 2.93、p < 0.0001）及び3.94（95%信頼区間：3.02; 5.14、p < 0.0001）であった。以上の結果から、HbA1cの目標値である7%未満又は6.5%以下に到達する可能

性は、IDeg群及びリラグルチド群と比較してIDegLira群で統計的に有意に高いことが示されている。

- *投与量調節のための朝食前血糖値（血糖自己測定）*：投与後52週の朝食前血糖値（血糖自己測定）は、投与量調節が可能な2群のいずれにおいても目標値に近かった〔IDegLira群：5.6 mmol/L（101 mg/dL）、IDeg群：5.4 mmol/L（97 mg/dL）〕。朝食前血糖値が同様であることは、これら2群で同様に投与量の調節が行われたことを示している。
- *インスリン投与量*：投与後52週の1日インスリン投与量はIDeg群と比較してIDegLira群で統計的に有意に少なかった。群差（IDegLira-IDeg）の推定値は、-23.38単位（95%信頼区間：-26.44; -20.31、$p < 0.0001$）であった。投与後52週の1日インスリン投与量はIDegLira群で39単位及びIDeg群で62単位であった。投与後52週におけるインスリン投与量の比（IDegLira/IDeg）は0.63であり、インスリン投与量はIDeg群と比較してIDegLira群で37%少ないことが示された。

血糖コントロールに寄与した主な項目

- *空腹時血糖値*：空腹時血糖値は試験期間中にIDegLira群で3.45 mmol/L（62.1 mg/dL）、IDeg群で3.40 mmol/L（61.2 mg/dL）及びリラグルチド群で1.67 mmol/L（30.2 mg/dL）低下した。投与後52週の空腹時血糖値の低下量はIDegLira群とIDeg群で同様であった〔群差の推定値：-0.20 mmol/L（95%信頼区間：-0.45; 0.05、$p = 0.1107$）〕。リラグルチド群と比較してIDegLira群で統計的に有意に大きかった〔群差の推定値：-1.67 mmol/L（95%信頼区間：-1.92; -1.42、$p < 0.0001$）〕。
- *9点血糖値プロファイル（血糖自己測定）*：9点血糖値プロファイル（血糖自己測定）の平均の低下量は、IDeg群〔群差の推定値：-0.30 mmol/L（95%信頼区間：-0.50; -0.11、$p = 0.0025$）〕及びリラグルチド群〔群差の推定値：-0.99 mmol/L（95%信頼区間：-1.19 ; -0.80、$p < 0.0001$）〕と比較してIDegLira群で統計的に有意に大きかった。
  食後血糖増加量（すべての食事の平均）は、IDeg群と比較してIDegLira群で統計的に有意に小さく〔群差（IDegLira-IDeg）の推定値：-0.39 mmol/L（95%信頼区間：-0.57; -0.21、$p < 0.0001$）〕、IDegLira群とリラグルチド群との間では同様であった〔群差の推定値：0.10 mmol/L（95%信頼区間： -0.08; 0.27、$p = 0.2924$）〕。
- *食事負荷試験 - 食後血糖増加量（サブ集団）*：投与後52週の食後血糖増加量（$iAUC_{0\text{-}4h}$）はIDeg群と比較してIDegLira群で統計的に有意に小さかった〔群差（IDegLira-IDeg）の推定値：-0.64 mmol/L（95%信頼区間：-1.11; -0.17、$p = 0.0073$）〕。投与後52週において、IDegLira群とリラグルチド群との間で統計的な有意差は認められなかった〔群差の推定値：0.05 mmol/L（95%信頼区間：-0.43; 0.53、$p = 0.8417$）〕。
- *体重に対する効果*：投与後52週の体重の変化量はIDegLira群で-0.4 kg、IDeg群で+2.3 kg及びリラグルチド群で-3.0 kgであった。投与後52週の体重はIDeg群と比較してIDegLira群で統計的に有意に少なかった。群差の推定値（IDegLira-IDeg）は-2.80 kg（95%信頼区間：-3.34; -2.27、$p < 0.0001$）であった。

安全性の結果：

本試験における投与後 52 週の IDegLira、IDeg 及びリラグルチドの安全性について結論は以下のとおりであった：IDegLira、IDeg 及びリラグルチドの忍容性は概して良好であった。IDeg 及びリラグルチドの有害事象及び忍容性プロファイルは過去の結果と一致していた。IDegLira では新規の有害事象又は忍容性の懸念は認められず、IDegLira の安全性プロファイルは IDeg 及びリラグルチドでみられた結果と一致していた。

検討した各領域における安全性の結果を以下に要約する：

全般的な有害事象プロファイル（低血糖以外）

- 2件の治験薬投与下の死亡（IDegLira群）が報告された（死因について1件は自然死、1件は尿路感染及び敗血症ショックによる死亡）。両事象ともに、イベント判定委員会により心血管死と判定された。さらに、治験薬投与下でない1件の死亡（IDegLira群：銃創）が報告された
- 有害事象の単位時間あたりの発現件数（件／100人・年）は、IDegLira群とIDeg群との間では同様であったが、リラグルチド群との比較ではIDegLira群で少なかった（IDegLira群：407.9件／100人・年、IDeg群：383.3件／100人・年、リラグルチド群：507.3件／100人・年）。いずれの投与群においても、有害事象の大部分は重症度が軽度であり、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。

- 最も高頻度に報告された有害事象は頭痛、悪心、下痢、嘔吐、鼻咽頭炎及び上気道感染であった。悪心、下痢及び嘔吐を合わせた単位時間あたりの発現件数は、IDeg群と比較してIDegLira群で多かったが、リラグルチド群との比較ではIDegLira群で少なかった（IDegLira群：41件／100人・年、IDeg群：18件／100人・年、リラグルチド群：80件／100人・年）。鼻咽頭炎及び上気道感染の単位時間あたりの発現件数に群差は認められなかった。
- 被験者の1%以上で報告された重篤な有害事象は認められず、重篤な有害事象の大部分は治験薬との因果関係は「なし」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」と判定された重篤な有害事象は10件（9例）であった。その内訳は、IDegLira群で4件（重大な低血糖、低血糖性意識消失、悪性黒色腫及び穿孔性虫垂炎）、IDeg群で1件（胆嚢炎）及びリラグルチド群で5件（急性心筋梗塞、狭心症、胃炎、嘔吐及び胃腸炎）であった。
- 試験全体では3.0%（49例）の被験者が有害事象の発現により試験を中止した。この割合が最も高かったのはリラグルチド群であった（6.3%、大部分は悪心又は嘔吐による中止・脱落）。6例を除くすべての被験者でこれらの事象の転帰は回復又は軽快であった。

<u>事前に規定した注目すべき安全性領域の有害事象</u>

- 24例38件の治験薬投与下の心血管系事象（2件の死亡を含む）が判定対象とされ、そのうち19件（13例）が心血管系事象と確定された。そのうち6件は主要な心血管イベントであった（IDegLira群：4件、IDeg群：1件、リラグルチド群：1件）。確定された心血管系事象の単位時間あたりの発現件数はIDegLira群、IDeg群及びリラグルチド群でそれぞれ1.1件／100人・年、2.3件／100人・年及び1.2件／100人・年であった。37件の不整脈（32例）が報告され、単位時間あたりの発現件数は、IDegLira群、IDeg群及びリラグルチド群でそれぞれ2.1件／100人・年、2.6件／100人・年及び3.9件／100人・年であった。
- 18件の治験薬投与下の膵炎又は膵炎の疑いが判定対象とされ、そのうち2件（リラグルチド群）がイベント判定委員会により急性膵炎と確定された。また、治験薬投与下でない1件の事象（IDeg群）が急性膵炎と確定された。
- 111例152件のリパーゼ増加又はアミラーゼ増加が報告され、これらの事象を合わせた単位時間あたりの発現件数は、IDegLira群、IDeg群及びリラグルチド群でそれぞれ10.6件／100人・年、8.0件／100人・年及び14.7件／100人・年であった。大部分は無症状であった。
- 45件の治験薬投与下の新生物に関連する可能性がある有害事象（41例）が判定対象とされ、そのうち21件（18例）が新生物と確定された。確定された新生物の単位時間あたりの発現件数は、IDegLira群、IDeg群及びリラグルチド群でそれぞれ1.8件／100人・年、1.4件／100人・年及び0.9件／100人・年であった。IDegLira群において、最も高頻度に報告された確定された新生物は基底細胞癌（3例4件、0.6件／100人・年）であり、そのうちすべてが治験薬との因果関係は「なし」と判定され、すべての被験者が試験終了時には回復していた。また、治験薬投与下でない1件の事象がイベント判定委員会により乳癌（IDegLira群）と確定された。
- 甲状腺切除を要する甲状腺疾患及び甲状腺新生物の疑いが判定された。1件の甲状腺摘出が実施された。本事象（甲状腺腫）はイベント判定委員会により甲状腺新生物ではなく、甲状腺に関連する有害事象と確定された。甲状腺髄様癌は報告されなかった。
- カルシトニンの継続的なモニタリングから18例22件の血中カルシトニン増加（20 ng/L以上）が有害事象として報告されたが〔IDegLira群：9例（1.1%）、IDeg群：8例（1.9%）、リラグルチド群：1例（0.2%）〕、いずれも臨床症状は認められなかった。
- 腎機能の悪化、高血糖又は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はIDeg群及びリラグルチド群と比較してIDegLira群でわずかに少なく、報告件数は少なかった。
- 注射部位反応の単位時間あたりの発現件数は、IDegLira群とリラグルチド群で同様であり（IDegLira群：9.2件／100人・年、リラグルチド群：7.8件／100人・年）、IDeg群で少なかった（4.3件／100人・年）。最も高頻度に報告された有害事象は注射部位血腫であった。
- 投薬過誤に関連する有害事象は少なく、重度と判定されたものはなかった。すべての被験者は回復し

た。有害事象又は低血糖と関連していたのは、2例の偶発的過量投与のみであった。

低血糖

- 確定低血糖の単位時間あたりの合計発現件数は、IDeg群と比較してIDegLira群で少なかったが、リラグルチド群と比較してIDegLira群で多かった（IDegLira群：176.7件／100人・年、IDeg群：279.1件／100人・年、リラグルチド群：19.1件／100人・年）。単位時間あたりの発現件数の比の推定値は、IDeg群に対するIDegLira群で0.63（95%信頼区間：0.50; 0.79、$p < 0.0001$）及びリラグルチド群に対するIDegLira群で8.52（95%信頼区間：6.09; 11.93、$p < 0.0001$）であった。
- ADAの分類に基づく低血糖の大部分は無症候性低血糖（asymptomatic hypoglycaemia）又は確定症候性低血糖（documented symptomatic hypoglycaemia）であった。
- 確定夜間低血糖の単位時間あたりの発現件数はIDegLira群とIDeg群で概ね同様であり、リラグルチド群で少なかった（IDegLira群：22.3件／100人・年、IDeg群：36.6件／100人・年、リラグルチド群：1.8件／100人・年）。
- 重大な低血糖は52週間の投与期間中に7件報告された（IDegLira群：3件、IDeg群：2件、リラグルチド群：2件）。

脈拍数

- IDegLira群（1.8拍／分）及びリラグルチド群（1.4拍／分）では、脈拍数の増加が認められたが、IDeg群では脈拍数は一定であった。脈拍数の増加量は、IDeg群と比較してIDegLira群で統計的に有意に大きかったが、IDegLira群とリラグルチド群との間では同様であった。

臨床検査評価

- アミラーゼ及びリパーゼ測定を除き血液学的検査又は血液生化学的検査のパラメータについては、ベースラインから投与終了時までにいずれの投与群においても臨床的に問題のある変化は認められなかった。
- ベースラインから投与終了時までのリパーゼは、IDegLira群（8.3 U/L）及びリラグルチド群（12.5 U/L）で増加した一方、IDeg群（-7.1 U/L）では減少した。アミラーゼについても顕著ではないが同様にIDegLira群及びリラグルチド群で増加した。臨床的に問題のある結果であるか否かは現在のところ不明である。
- カルシトニンについては、臨床的に問題となる群間の違いは認められなかった。
- 尿アルブミン／クレアチニン比については、IDegLira群とIDeg群又はリラグルチド群との間で統計的な有意差は認められなかった。
- 最も高頻度に報告された臨床検査に関する有害事象はリパーゼ増加及びアミラーゼ増加であり、IDegLira群の6.4%、IDeg群の5.1%及びリラグルチド群の9.0%の被験者で認められた。

身体所見、眼底検査／眼底写真及び心電図検査

- 投与後52週の身体所見、眼底検査／眼底写真又は心電図の結果については、臨床的に問題となる群間の違いは認められなかった。

抗体検査

- 52週の投与期間中、IDegLira群及びIDeg群のいずれでも少数の被験者で低い値のIDeg特異抗体産生がみられたが、臨床的に問題があるものとはみなされていない。2群の中でヒトインスリンとの交叉抗体がみられた被験者は非常に少なく、IDegLira群とIDeg群との間で違いは認められなかった。
- 抗リラグルチド抗体産生は非常に限られていた。投与後52週に抗体陽性であった被験者はIDegLira群の2.6%及びリラグルチド群の3.8%であり、そのうち内因性GLP-1との交叉抗体を保有する被験者は認められなかった。リラグルチドに対する*in vitro*での中和作用は、27例中5例において53週目のウォッシュアウト期間後に認められた。

全体の結論：

- 血糖コントロールの有効性は投与後52週も維持された：ベースラインから投与後52週までのHbA1cの低下量はIDeg及びリラグルチドと比較してIDegLiraで統計的に有意に良好であった。
- 投与後52週において、IDegLiraでは、IDegと比較して少ないインスリン投与量で低いHbA1cに到達し食後の血糖コントロールは改善し、低血糖の発現リスクは有意に低くなった。さらに、IDegLiraの投与による体重の増加は認められなかった。
- 空腹時血糖値の低下量はリラグルチドと比較してIDegLiraで大きく、IDegLiraによるHbA1cの低下を説明するものであった。
- IDeg及びリラグルチドにおける有害事象及び忍容性プロファイルは過去の結果と一致していた。IDegLiraの安全性プロファイルはIDeg及びリラグルチドでみられた結果と一致していた。
- 投与後26週に認められたIDegLiraの有益な効果は、投与後52週においても概ね維持された。

本試験は、ヘルシンキ宣言の精神及び ICH-GCP を遵守して実施された。

ここに提示する結果は、2013 年 1 月 15 日の時点での臨床データベースに基づいている。本データベースは、安全性及び有効性の重要な情報を更新するために以下の日にロックを解除された：2013 年 2 月 4 日（薬物動態の値に関する訂正）、2013 年 3 月 4 日（カルシトニンの基準範囲に関する訂正）、2013 年 3 月 11 日（当初陰性と報告された中和抗体の結果に関する訂正）。

2.7.6.8 NN9068-3912

2.7.6.8.1 臨床試験概要

Trial Registration ID-number： NCT01392573	UTN：U1111-1121-4897 IND number：109121 EudraCT number：2011-002336-72
治験の標題： DUAL™ II：2 型糖尿病患者を対象としたインスリン デグルデク／リラグルチド（IDegLira）及びインスリン デグルデク（IDeg）の有効性及び安全性の比較試験 ‐2 型糖尿病患者を対象としたインスリン デグルデグ／リラグルチド及びインスリン デグルデグ（用量比固定）を比較する 26 週間、無作為割り付け、2 群並行、二重盲検、多施設、国際共同、treat-to-target 試験‐	
治験責任医師名： 計 7 ヵ国で計 75 名の治験責任医師が任命された。以下の治験責任医師が「治験総括報告書への署名責任を有する医師（signatory investigator）」に任命された： Dr. [redacted]	
治験実施施設： 計 7 ヵ国 75 施設において実施した：ブルガリア（6 施設）、スイス（2 施設）、デンマーク（3 施設）、ハンガリー（3 施設）、インド（6 施設）、スロヴェニア（3 施設）及び米国（52 施設）	
公表文献（引用文献）： 本治験総括報告書作成時点でなし	
治験期間： 開始日：2011 年 11 月 28 日 終了日：2012 年 10 月 04 日	**開発のフェーズ**： 第 3a 相
目的： 治験実施計画書及びその改訂版に記載のとおり、本試験の目的は： 主要目的： 2 型糖尿病患者を対象として、血糖コントロールについて、IDegLira の IDeg に対する優越性を検証する。 副次的目的： 投与後 26 週における IDegLira 及び IDeg の全般的な有効性及び安全性を比較検討する。	
治験方法： 本試験は、メトホルミン単剤と Basal インスリンの併用又はメトホルミンとスルホニルウレア薬（SU）又はグリニドと Basal インスリンとの併用で十分な血糖コントロールが得られていない 2 型糖尿病患者を対象とした、26 週間、無作為割り付け、2 群並行、二重盲検、多施設、国際共同、treat-to-target 試験であり、メトホルミン併用下における IDegLira 及び IDeg（いずれも 1 日 1 回投与）の有効性及び安全性を比較した。 「十分な血糖コントロールが得られていない 2 型糖尿病患者」とは、HbA1c が 7.5%以上 10.0%以下の患者と定義した。 適格例は、メトホルミンと併用する IDegLira 群又は IDeg 群（いずれも 1 日 1 回投与）のいずれかに 1：1 の割合で無作為割り付けされた。前治療の Basal インスリン、SU 及びグリニド投与は来院 2 時に中止した。メトホルミンによる治療は、試験期間を通して、無作為割り付け前と同じ用量・用法による安定した治療を継続した（ただし安全性上の理由での用量調整は可とした）。 IDegLira の開始用量は 16 用量ステップ（IDeg 16 単位／リラグルチド 0.6 mg）、IDeg の開始用量は 16 単位	

とした。IDegLira の開始用量である 16 用量ステップに含まれるリラグルチドは、ビクトーザ®の推奨開始用量である 0.6 mg／日に従って設定した。その後は treat-to-target 法を用い、空腹時血糖値の目標が 4.0～5.0 mmol/L（72～90 mg/dL）となるように投与量を調節した。1 週間に 2 回、直前の連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均値に基づいて規定の投与量調節アルゴリズムに従って投与量調節を行った。最高用量は、IDegLira では 50 用量ステップ（IDeg 50 単位／リラグルチド 1.8 mg）、IDeg では 50 単位であった。被験者は試験期間を通して空腹時血糖値の自己測定を行うこととし、来院 3 以降、投与量調節日までの 3 日間における測定日、測定時間及び投与量を被験者日誌に記録することとした。

被験者の内訳

	IDegLira N (%)	IDeg N (%)	Total N (%)
Screened			831
Screening Failures			418
Withdrawn before Randomisation			0
Randomised	207 (100.0)	206 (100.0)	413 (100.0)
Exposed	207 (100.0)	206 (100.0)	413 (100.0)
Withdrawn at/after Randomisation	32 (15.5)	35 (17.0)	67 (16.2)
Adverse Event	1 (0.5)	3 (1.5)	4 (1.0)
Ineffective Therapy	1 (0.5)	2 (1.0)	3 (0.7)
Non-Compliance With Protocol	0 (0.0)	2 (1.0)	2 (0.5)
Withdrawal Criteria	13 (6.3)	15 (7.3)	28 (6.8)
Other	17 (8.2)	13 (6.3)	30 (7.3)
Completed	175 (84.5)	171 (83.0)	346 (83.8)
Full Analysis Set	199 (96.1)	199 (96.6)	398 (96.4)
Safety Analysis Set	199 (96.1)	199 (96.6)	398 (96.4)

計画及び解析された被験者数：

IDegLira 群及び IDeg 群でそれぞれ 191 例ずつ、合計 382 例の無作為割り付け予定症例数を計画した。最大の解析対象集団及び安全性解析対象集団ではそれぞれ 199 例が含まれた。

診断及び主要な組入れ基準：

主な選択基準：

性別不問、年齢 18 歳以上、HbA1c 7.5%以上 10.0%以下の 2 型糖尿病患者。スクリーニングの 90 日以上前から安定した投与量での、Basal インスリン（例：インスリン グラルギン、インスリン デテミル又は NPH インスリン）（スクリーニングの前 90 日間は 1 日総インスリン投与量：20～40 単位、かつ投与量の変動±10%以内）を実施中で、メトホルミン（1500 mg 以上又は最大耐用量）単剤、もしくはメトホルミンに加えて SU 又はグリニド（いずれも各国で承認されている最高用量の半分以上）の治療をしている被験者。BMI（kg/m^2）が 27 以上の被験者。治験実施計画書に従った血糖自己測定及び被験者日誌への記録を行う意思があり、かつ実施可能である被験者、ペン型注入器又は FlexPen®（フレックスペン®）を使用する意思がある被験者。治験に関連する何らかの手順を実施する前に同意を取得することとした。

主な除外基準：

血糖値に影響を及ぼすと治験責任医師が判断した薬剤（Basal インスリン、メトホルミン、SU、グリニドを除く。副腎皮質ステロイド剤の全身投与等）を使用した被験者、スクリーニング前 90 日以内に GLP-1 受容体作動薬（エキセナチド、リラグルチド等）又はジペプチジルペプチダーゼ 4 阻害薬（DPP-4 阻害薬）及び／又はチアゾリジン薬（TZD）の投与を受けた被験者、消化器系、呼吸器系、神経系、内分泌系（2 型糖尿病を除く）、神経系、泌尿生殖器系又は血液系（2 型糖尿病に伴う疾患を除く）の臨床的に問題となる活動性（過去 12 ヵ月以内）の疾患（試験結果に影響を及ぼす又は治験薬投与によるリスク増大の可能性があると治験責任医師が判断する場合）を有する被験者。肝機能障害（ALAT アラニンアミノトランスフェラーゼ

が正常範囲上限の 2.5 倍以上）のある被験者。腎機能障害〔血清クレアチニンが男性：133 μmol/L（1.5 mg/dL）以上 、女性：125 μmol/L（1.4 mg/dL）以上〕のある被験者。スクリーニング時のカルシトニン濃度が 50 ng/L 以上の被験者。 **主な中止・脱落基準**： 糖代謝又は脂質代謝に影響を及ぼすと治験責任医師が判断した薬剤の全身投与を開始した場合、女性被験者が妊娠した場合、妊娠を希望する場合、高血糖状態（試験過程に応じて 11.1～15.0 mmol/L 超と設定）が繰り返し認められる場合、又は急性膵炎と診断された場合、試験を中止することとする。
被験薬及び使用機器、用量及び投与方法、ロット番号： IDegLira：IDeg 100 単位/mL＋リラグルチド 3.6 mg/mL（IDeg／リラグルチドの用量比は固定）が 3 mL プレフィルドペン型注入器のフレックスペン®に充填された状態で提供された。大腿部、上腕部（三角筋部）又は腹部のいずれかに 1 日 1 回、毎日同じ時刻に皮下投与した。16 用量ステップ（IDeg 16 単位／リラグルチド 0.6 mg に相当）から投与を開始し、各投与量調節日前の連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき、1 週間に 2 回投与量調節を行った。朝食前血糖値の目標が 4.0～5.0 mmol/L（72～90 mg/dL）に到達するまで 2 用量ステップ（IDeg 2 単位／リラグルチド 0.072 mg）ずつ投与量を調節した。最高用量は 50 用量ステップ（IDeg 50 単位／リラグルチド 1.8 mg）であった。ロット番号：AP51384
投与期間： 26 週間
対照薬及び使用機器、用量及び投与方法、ロット番号： IDeg：100 単位/mL が 3 mL プレフィルドペン型注入器のフレックスペン®に充填された状態で提供された。大腿部、上腕部（三角筋部）又は腹部のいずれかに 1 日 1 回、毎日同じ時刻に皮下投与した。16 単位から投与を開始し、前述の IDegLira と同様に、連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均に基づき、4.0～5.0 mmol/L（72～90 mg/dL）を目標として、1 週間に 2 回投与量調節を行った。最高用量は 50 単位であった。ロット番号：AP51397
評価基準：有効性 以下の項目の有効性を評価した： HbA1c、HbA1c のレスポンダー〔（HbA1c 7%未満又は 6.5%以下）＋（体重増加がない、低血糖の発現がない、又は低血糖の発現及び体重増加がない）〕、β 細胞機能〔空腹時プロインスリン、空腹時 C-ペプチド、空腹時インスリン（及び算出したプロインスリン／インスリン比）、空腹時グルカゴン、空腹時血糖値（FPG）〕、治験薬の効果不十分を理由に試験を中止した被験者の割合、心血管系バイオマーカー〔高感度 C-反応性タンパク（hsCRP）、PAI-l、アディポネクチン、フィブリノゲン、脳性ナトリウム利尿ペプチド（BNP）〕、空腹時脂質プロファイル〔トリグルセリド、コレステロール、低比重リポタンパク（LDL）コレステロール、高比重リポタンパク（HDL）コレステロール、超低比重リポタンパク（VLDL）コレステロール、遊離脂肪酸（FFA）、アポリポタンパク（A-I 及び B）〕、9 点血糖値プロファイルを含めた血糖自己測定による血糖値、体重、ウエスト周囲径、収縮期血圧、拡張期血圧及びインスリン投与量（IDegLira 及び IDeg）
評価基準：安全性 以下の項目の安全性を評価した： 有害事象、低血糖、身体所見、眼検査、心電図、脈拍数、臨床検査項目（血液学的検査、血液生化学的検査、リパーゼ、アミラーゼ、カルシトニン等）、尿検査、抗体検査及びアルブミン／クレアチニン比。

統計手法：

- 検出力の算出：HbA1cの変化量について、IDegに対するIDegLiraの優越性を結論付けるための検出力は90.0%であった。
- 解析対象集団：データの完全性が確認できなかったため、施設105のすべての被験者を以下3つの解析対象集団から除外した。プライマリーエンドポイントであるHbA1cならびに重篤な有害事象及び低血糖に対して感度分析を行い、施設105を含めた解析結果及び含めなかった解析結果を比較した。
    - 最大の解析対象集団（FAS）：FASには無作為割り付けされたすべての被験者が含まれた。例外的に被験者をFASから除外することがあった。除外する場合には正当な理由を示し文書化することとした。FASの統計的評価はintention-to-treatの原則に従い、FASの被験者はas randomisedの評価に寄与した。
    - 安全性解析対象集団（SAS）：SASには治験薬又は対照薬の投与を少なくとも1回受けたすべての被験者が含まれた。SASの被験者はas treatedの評価に寄与した。
    - 完了例の解析対象集団（CAS）：CASには無作為割り付けされて来院33を完了したすべての被験者が含まれた。CASの被験者はas randomisedの評価に寄与した。
- ベースラインから投与後26週までのHbA1cの変化量について、標準的な共分散分析（ANCOVA）モデルを用いて解析した。モデルには治療、前治療の糖尿病薬及び国を固定効果、ベースライン値を共変量として含めた。IDegに対するIDegLiraの優越性が検証されたときにのみ主要目的が達成されることとした。
- 感度分析として、ベースラインから投与後26週までのHbA1cの変化量に関する主要解析をCASで繰り返し実施した。
- 重大な又は重大でない低血糖（確定低血糖）の発現件数について、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。モデルには治療、前治療の糖尿病薬及び地域を固定効果として含めた。
- 投与後26週における1日インスリン投与量について、FASを用いて標準的なANCOVAモデルで解析した。モデルには治療、前治療の糖尿病薬及び国を固定効果、ベースラインのHbA1c及びベースラインのインスリン投与量を共変量として含めた。
- 2つの2値のエンドポイント（レスポンダー／非レスポンダー）は、被験者が投与後26週に規定のHbA1c目標値を達成したかどうかで定義された。目標値とは、米国糖尿病学会（ADA）ではHbA1c 7%未満、国際糖尿病連合（IDF）ではHbA1c 6.5%以下である。この2つのレスポンダーエンドポイントの解析は、治療、地域及び前治療の糖尿病薬を固定効果、ベースラインのHbA1cを共変量として含めたロジスティック回帰モデルに基づいて行った。また、以下のエンドポイントを定義づけた：投与後26週に体重増加がないHbA1cレスポンダー、投与後26週に低血糖の発現がないHbA1cレスポンダー、投与後26週に低血糖の発現及び体重増加がないHbA1cレスポンダー
- 空腹時血糖値、体重、ウエスト周囲径のベースラインから投与後26週までの変化量について、標準的なANCOVAモデルを用いて解析した。
- 9点血糖値プロファイル（血糖自己測定による）の平均及び食後血糖増加量のエンドポイントのベースラインから投与後26週までの変化量について、標準的なANCOVAモデルを用いて別々に解析した。ベースライン時のエンドポイントは共変量として用いた。
- β細胞機能、収縮期血圧及び拡張期血圧、心血管系バイオマーカー（PAI-1除く）及び脂質を対数変換し標準的なANCOVAモデルを用いて解析した。PAI-1は投与後26週における値を対数変換し、治療、国及び前治療の糖尿病薬を固定効果としたANCOVAモデルを用いて解析した（当解析は実測値に基づく）。
- 治験薬の効果不十分を理由に試験を中止した被験者の割合については、治療、国及び前治療の糖尿病薬を固定効果、ベースラインのHbA1cを共変量としたロジスティック回帰モデルを用いて解析した。
- 安全性に関するエンドポイントは記述的に要約した。

被験者背景：
被験者のベースライン時の背景及び特性は両投与群で概ね同様であった。
被験者の約 75%が 40～65 歳未満であり、21.8%が 65 歳以上であった。HbA1c の平均値は IDegLira 群で 8.7%、IDeg 群で 8.8%であった。糖尿病の罹病期間は IDegLira 群で約 10 年、IDeg 群で約 11 年であった。

被験者背景及びベースライン特性

	IDegLira N (%)	IDeg N (%)	Total N (%)
Number of Subjects	199	199	398
Age Group			
N	199 (100.0)	199 (100.0)	398 (100.0)
18-40 yrs	5 (2.5)	11 (5.5)	16 (4.0)
40-65 yrs	156 (78.4)	139 (69.8)	295 (74.1)
65-75 yrs	34 (17.1)	43 (21.6)	77 (19.3)
> 75 yrs	4 (2.0)	6 (3.0)	10 (2.5)
Sex			
N	199 (100.0)	199 (100.0)	398 (100.0)
Female	87 (43.7)	93 (46.7)	180 (45.2)
Male	112 (56.3)	106 (53.3)	218 (54.8)
Ethnicity			
N	199 (100.0)	199 (100.0)	398 (100.0)
Hispanic or Latino	16 (8.0)	24 (12.1)	40 (10.1)
Not Hispanic or Latino	183 (92.0)	175 (87.9)	358 (89.9)
Race			
N	199 (100.0)	199 (100.0)	398 (100.0)
White	157 (78.9)	151 (75.9)	308 (77.4)
Black or African American	9 (4.5)	10 (5.0)	19 (4.8)
Asian Indian	31 (15.6)	34 (17.1)	65 (16.3)
Asian non-Indian	2 (1.0)	2 (1.0)	4 (1.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Oth. Pacific Islander	0 (0.0)	1 (0.5)	1 (0.3)
Other	0 (0.0)	1 (0.5)	1 (0.3)

N = Number of Subjects, %= Percentages are based on N

ベースライン特性及び糖尿病特性

	IDegLira N (%)	IDeg N (%)	Total N (%)
Age (years)			
N	199	199	398
Mean (SD)	56.8 (8.9)	57.5 (10.5)	57.2 (9.7)
Median	56.2	58.2	57.4
Min ; Max	31.4 ; 76.9	29.5 ; 85.8	29.5 ; 85.8
Height (m)			
N	199	199	398
Mean (SD)	1.68 (0.11)	1.66 (0.10)	1.67 (0.11)
Median	1.68	1.66	1.67
Min ; Max	1.41 ; 1.97	1.44 ; 1.95	1.41 ; 1.97
Body Weight (kg)			
N	199	199	398
Mean (SD)	95.4 (19.4)	93.5 (20.0)	94.5 (19.7)
Median	93.5	90.3	92.3
Min ; Max	57.5 ; 171.5	58.9 ; 191.9	57.5 ; 191.9
BMI (kg/m^2)			
N	199	199	398
Mean (SD)	33.6 (5.7)	33.8 (5.6)	33.7 (5.7)
Median	32.3	32.8	32.6
Min ; Max	26.5 ; 56.5	25.8 ; 54.7	25.8 ; 56.5
Duration of Diabetes (years)			
N	199	199	398
Mean (SD)	10.30 (6.01)	10.91 (7.04)	10.60 (6.54)
Median	8.7	9.5	9.1
Min ; Max	0.79 ; 30.42	0.76 ; 40.42	0.76 ; 40.42
HbA1c (%)			
N	199	199	398
Mean (SD)	8.7 (0.7)	8.8 (0.7)	8.8 (0.7)
Median	8.6	8.9	8.7
Min ; Max	7.2 ; 12.3	7.3 ; 10.9	7.2 ; 12.3
FPG (mmol/L)			
N	198	199	397
Mean (SD)	9.7 (2.9)	9.6 (3.1)	9.6 (3.0)
Median	9.5	9.3	9.4
Min ; Max	3.0 ; 19.1	4.2 ; 29.9	3.0 ; 29.9

N = Number of Subjects, % = Percentages are based on N
18-40 yrs = age range from 18 to less than 40
40-65 yrs = age range from 40 to less than 65
65-75 yrs = age range from 65 to less than 75
> 75 yrs = age range from 75
yrs = years, BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation, FPG= Fasting Plasma Glucose

有効性の結果：

IDegLira 及び IDeg（いずれもメトホルミンとの併用）による 26 週間の治療について、以下の結論を得た。

<u>全般的な血糖コントロール</u>

HbA1c

- IDegLiraにより血糖コントロールが効果的に改善され、HbA1cの低下について、同量のインスリン投与量（IDegLira：45用量ステップ、IDeg：45単位）でIDegLiraのIDegに対する優越性が検証された。投与後26週におけるHbA1c（実測値）は、IDegLira群ではベースラインから1.09%低下して6.9%となり、IDeg群ではベースラインから0.89%低下して8.0%となった。群差（IDegLira群－IDeg群）の推定値は、-1.05%

（95%信頼区間：[-1.25; -0.84]）（p<0.0001）であった。これらの結果から、リラグルチドが全般的な血糖コントロールの改善に有意に寄与していることが示唆された。

HbA1c レスポンダー

- 投与後26週にHbA1c 7%未満を達成した被験者の割合は、IDegLira群で60.3%であったのに対し、IDeg群では23.1%であった。同様に、投与後26週にHbA1c 6.5%以下を達成した被験者の割合は、IDeg群（13.1%）と比較してIDegLira群（45.2%）で高かった。これらの達成率について、オッズ比（IDegLira群／IDeg群）の推定値から、IDegLiraで統計的に有意に高いことが示された。

血糖コントロールに寄与した主な項目

空腹時血糖値

- 試験期間中の空腹時血糖値は、IDegLira群で3.46 mmol/L（62.4 mg/dL）、IDeg群で2.58 mmol/L（46.4 mg/dL）低下した。空腹時血糖値の低下は、IDeg群と比較してIDegLira群で統計的に有意に大きかった。群差（IDegLira群－IDeg群）の推定値は-0.73 mmol/L（95%信頼区間：[-1.19; -0.27]）（p = 0.0019）であった。

9 点血糖値プロファイル

- 9点血糖値プロファイルの平均は、IDeg群と比較してIDegLira群で統計的に有意に低下した。群差の推定値は-1.07 mmol/L（95%信頼区間：[-1.44; -0.70]）（p < 0.0001）であった。すべての食事の食後血糖増加量（9点血糖値プロファイルから算出）のベースラインから投与後26週までの変化量は、IDeg群と比較してIDegLira群で統計的に有意に小さく、群差（IDegLira群－IDeg群）の推定値は-0.37 mmol/L（95%信頼区間：-0.69; -0.04）（p = 0.0260）であった。

体重

- 投与後26週における体重の変化量（実測値）は、IDegLira群で-2.7 kg及びIDeg群で0.0 kgであった。BMI及びウエスト周囲径は体重の変化に比例して変化した。体重の減少は、IDeg群と比較してIDegLira群で統計的に有意に大きかった。群差（IDegLira群－IDeg群）の推定値は-2.51 kg（95%信頼区間：[-3.21; -1.82]）（p < 0.0001）であった。

安全性の結果：

投与後 26 週において、本試験の IDegLira 及び IDeg の安全性に関して以下のとおり結論づけられた。

概して、IDegLira 及び IDeg の忍容性は高く、IDegLira の投与において新規の有害事象の発現や忍容性に関する問題は認められなかった。検討した各領域における安全性の結果を以下に要約する：

全体的な有害事象プロファイル

- 死亡は報告されなかった。
- 有害事象の単位時間あたりの発現件数は、IDegLira群（398.1件／100人・年）とIDeg群（355.5件／100人・年）で同様であった。有害事象の大部分（686件中521件）は軽度であり、また事象の大部分（686件中556件）が治験責任医師により治験薬との因果関係が「なし」と判定された。
- IDegLira群で最も高頻度で報告された有害事象は胃腸障害（下痢及び悪心）ならびに頭痛であった。これは被験者の6.0～6.5%で発現し、単位時間あたりの発現件数は21.8～25.0件／100人・年であった。IDeg群で最も高頻度で報告された有害事象は鼻咽頭炎であり、被験者の6.0%で発現し、単位時間あたりの発現件数は15.6件／100人・年であった。
- 18例で24件の重篤な有害事象が報告された。被験者の1%以上で発現した重篤な有害事象はなく、重篤な有害事象の大部分は治験薬との因果関係が「なし」と判定された。2例2件（IDegLira群で1件の低血糖、IDeg群で1件の痙攣）の重篤な有害事象が治験薬との因果関係が「あり」又は「可能性あり」と判定された。
- 被験者の1.0%（398例中4例）が有害事象を理由に試験を中止した。中止した被験者はIDegLira群で1例（大うつ病／急性腎不全）、IDeg群で3例（急性心筋梗塞、胆石症及び虚血性脳卒中）であった。

事前に規定した特に注目すべき安全性領域の有害事象

- 3例で5件の心血管系事象がイベント判定委員会により確認され、うち3件は主要な心血管イベント（MACE）と判定された（IDegLira群で1件、IDeg群で2件）。確定された心血管系事象の単位時間あたりの発現件数は、IDegLira群で1.1件／100人・年、IDeg群で4.4件／100人・年であった。

- 2例で2件（いずれもIDeg群）の新生物がイベント判定委員会により確認された。
- 22例で26件のリパーゼ増加又はアミラーゼ増加が報告された。単位時間あたりの発現件数は、IDegLira群で18.5件／100人・年、IDeg群で10.0件／100人・年であった。試験終了時に4例は当該事象の転帰は未回復であった。
- 本試験では膵炎、甲状腺疾患又は甲状腺髄様癌の事象は報告されなかった。
- カルシトニンの継続的なモニタリングによると、5例で5件（IDegLira群で2件、IDeg群で3件）のカルシトニン値の増加（20 ng/L以上）が有害事象として報告された。これらの事象で臨床症状は認められなかった。
- その他の事前に規定した特に注目すべき安全性領域の事象は少なかった（10件の腎機能の悪化、3件のアレルギー性反応及び11件の注射部位反応）。これらの事象でこれまでに得られた知見過去の試験と比べて新たな重要な情報を示唆するものはなかった。
- 5件の投薬過誤があり、いずれも軽度と判定された。これらの投薬過誤に関連するような有害事象は報告されなかった。いずれの被験者も事象から回復し、その被験者について投与群間の差は認められなかった。
- IDegLira群で2例2件、IDeg群で7例7件の高血糖が報告された。

<u>低血糖</u>

- 確定低血糖を発現した被験者の割合は、2つの投与群で同様であった。単位時間あたりの発現件数に見られた差は（IDegLira群：153.4件／100人・年、IDeg群：263.3件／100人・年）、IDeg群に低血糖を多く発現した被験者が数例いたことに起因しており、統計的な有意差は認められなかった。
- 確定夜間低血糖の単位時間あたりの発現件数は、IDegLira群（21.8件／100人・年）及びIDeg群（32.2件／100人・年）で同様であった。投与群間で統計的な有意差は認められなかった。
- ADAの分類別の低血糖については、すべての低血糖の単位時間あたりの発現件数は、IDegLira群で1274.9件／100人・年、IDeg群で1426.6件／100人・年であった。これらの低血糖の大部分は確定症候性低血糖又は無症候性低血糖であった。
- 1件の重大な低血糖がIDegLira群で報告された。当該事象の発現による投与量の変更はなかった。

<u>臨床検査項目</u>

- いずれの投与群でも、ベースラインから投与終了までに血液学的検査及び血液生化学的検査のパラメータで臨床的に問題となる変化は認められなかった。
- ベースラインから投与終了までに、IDegLira群でリパーゼ及びアミラーゼのわずかな増加がみられたが、いずれも基準範囲内であった。
- 臨床検査項目で最も高頻度（IDegLira群の被験者の6.0%、IDeg群の被験者の3.5%）で報告された有害事象はリパーゼ増加であった。
- カルシトニンについて、投与群間で臨床的に問題となるような違いは認められなかった。

<u>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</u>

- IDegLira群で脈拍数の増加（2.5拍／分）がみられたが、IDeg群では脈拍数の変化はみられなかった。脈拍数の増加は、IDeg群と比較してIDegLira群で統計的に有意に大きかった。
- 投与後26週における身体検査、眼底検査及び心電図の所見について、投与群間で臨床的に問題となるような違いは認められなかった。

<u>抗体</u>

- いずれの投与群においても、投与後26週までに問題となるようなIDeg特異抗体産生は認められなかった。また、いずれの投与群においても、ヒトインスリンとの交叉抗体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。
- 抗リラグルチド抗体の産生は少なく、投与後26週においてIDegLira群の被験者の1%未満で抗体の産生が認められた。事後調査来院において*in vitro*でリラグルチドに対する中和作用は認められなかった。

全体の結論：

メトホルミン単剤と Basal インスリンの併用又はメトホルミン+SU 又はグリニドと Basal インスリンとの併用を実施中の 2 型糖尿病患者を対象とした、IDegLira 及び IDeg（最高用量はそれぞれ 50 用量ステップ及び 50 単位）を比較する 26 週間の試験の結論は以下のとおりであった。

- HbA1cの低下について、同量のインスリン投与量（実投与量）でのIDegLiraのIDegに対する優越性が検証された。このことから、リラグルチドが全般的な血糖コントロールの改善に有意に寄与していることが示唆された。
- 空腹時血糖値、血糖自己測定値（9点血糖値プロファイルの平均及び食後血糖増加量）及び体重について、IDegと比較してIDegLiraで統計的に有意に優れた効果がみられ、リラグルチドの寄与が裏付けられた。
- IDegの投与において報告された有害事象及び忍容性のプロファイルは、これまでの所見と一致していた。
- IDegLiraの投与において、問題となるような有害事象及び忍容性の明らかな問題は認められなかった。また、IDeg及びリラグルチドでみられていない予測されないような有害事象は認められなかった。

本試験は、ヘルシンキ宣言及び ICH-GCP を遵守して実施された。

ここに提示する結果は、2012 年 11 月 28 日の時点での臨床データベースに基づいている。ただし、カルシトニン基準範囲は 2013 年 3 月 13 日に更新されたものである。

2.7.6.9 NN9068-3851

2.7.6.9.1 臨床試験概要

Trial Registration ID-number： NCT01676116	UTN：U1111-1127-1321 IND number：109121 EudraCT number：2012-000209-63
治験の標題： DUAL™ III - GLP-1 からの切り替え：GLP-1 受容体作動薬及び経口糖尿病薬による治療で十分な血糖コントロールが得られていない成人 2 型糖尿病患者を対象としたインスリン デグルデク／リラグルチドの有効性（血糖コントロール）を検討する試験	
治験責任医師名： 本試験では 96 名の治験責任医師が任命された。以下の治験責任医師が治験総括報告書の内容を確認し、署名する「治験総括報告書への署名責任を有する医師（Signatory Investigator）」に任命された： Dr. [redacted]	
治験実施施設： 以下の 5 ヵ国 81 施設において本試験が実施された：オーストラリア（5 施設）、フランス（7 施設）、ハンガリー（4 施設）、スロバキア（6 施設）及び米国（59 施設）	
公表文献（引用文献）： 本治験総括報告書作成時点でなし	
治験期間： 開始日：2012 年 8 月 29 日 終了日：2014 年 3 月 11 日	**開発のフェーズ**： 第 3b 相
Cut-off date： ここに提示する結果は、2014 年 4 月 3 日の時点での臨床データベースに基づいている。本データベースは、2014 年 4 月 23 日にロックを解除された。	
目的： 主要目的： • インスリン治療歴がなく、メトホルミン±ピオグリタゾン±スルホニルウレア薬（SU）の併用下でのグルカゴン様ペプチド-1（GLP-1）受容体作動薬による治療で十分な血糖コントロールが得られていない2型糖尿病患者を対象として、血糖コントロールについて、インスリン デグルデク／リラグルチド（IDegLira）のGLP-1受容体作動薬（継続投与）に対する優越性を検証する。 副次的目的： • インスリン治療歴がなく、メトホルミン±ピオグリタゾン±SUの併用下でのGLP-1受容体作動薬による治療で十分な血糖コントロールが得られていない2型糖尿病患者を対象として、投与後26週におけるIDegLira及びGLP-1受容体作動薬（継続投与）の全般的な有効性及び安全性を比較検討する。	
治験方法： 本試験は、インスリン治療歴がなく、GLP-受容体作動薬（ビクトーザ®又はバイエッタ®）ならびにメトホルミン±ピオグリタゾン±SU の各国のラベルに従った最大耐用量又は最高用量による治療で十分な血糖コントロールが得られていない 2 型糖尿病患者を対象とした、26 週間、多施設、国際共同、非盲検、2 群並行、無作為割り付け、treat-to-target 試験であり、メトホルミン±ピオグリタゾン±SU の併用下で、IDegLira と GLP-1 受容体作動薬（前治療から継続投与）の有効性及び安全性を比較検討した。HbA1c が 7.0%（53 mmol/mol）以上、9.0%（75 mmol/mol）以下を「十分な血糖コントロールが得られていない」とした。適格と判断された被験者を、試験開始前の投与量のメトホルミン±ピオグリタゾン±SU の併用下で IDegLira 1 日 1 回投与又は GLP-1 受容体作動薬（前治療から継続投与）のいずれかに 2：1 の割合で無作為に割り付けた。IDegLira は 16 用量ステップ（IDeg：16 単位、リラグルチド：0.6 mg）で投与を開始	

した。朝食前血糖値 4.0～5.0 mmol/L（72～90 mg/dL）を目標として treat-to-target 法を用いて投与量調節を行った。各投与量調節日前の連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき、事前に規定した投与量調節アルゴリズムに従い、1 週間に 2 回投与量調節を行った。最高用量は 50 用量ステップ（IDeg：50 単位、リラグルチド：1.8 mg）とした。

計画及び解析された被験者数：

計画された被験者数はそれぞれ、IDegLira 群で 286 例、GLP-1 受容体作動薬群（以下、GLP-1 群）で 143 例であった。つまり、無作為割り付け予定被験者数は計 429 例であった。

被験者の内訳 - 要約

	IDegLira N (%)	GLP-1 N (%)	Total N (%)
Screened			704
Screening Failures			266
Withdrawn before Randomisation			0
Randomised	292 (100.0)	146 (100.0)	438 (100.0)
Exposed	291 (99.7)	145 (99.3)	436 (99.5)
Withdrawn at/after Randomisation	16 (5.5)	29 (19.9)	45 (10.3)
Adverse Event	1 (0.3)	2 (1.4)	3 (0.7)
Non-Compliance With Protocol	9 (3.1)	3 (2.1)	12 (2.7)
Withdrawal Criteria	2 (0.7)	14 (9.6)	16 (3.7)
Other	4 (1.4)	10 (6.8)	14 (3.2)
Completed	276 (94.5)	117 (80.1)	393 (89.7)
full analysis set	292 (100.0)	146 (100.0)	438 (100.0)
PP analysis set	279 (95.5)	135 (92.5)	414 (94.5)
safety analysis set	291 (99.7)	145 (99.3)	436 (99.5)

N: Number of subjects
%: Proportion of randomised subjects

診断及び主要な組入れ基準：

主な選択基準

性別不問、年齢 18 歳以上の 2 型糖尿病患者。HbA1c 7.0%以上、9.0%以下（53～75 mmol/mol）、BMI（kg/m^2）が 40 以下の被験者。前治療の糖尿病薬に関連する選択基準は、スクリーニング来院の 90 日以上前から安定した投与量でのメトホルミン（1500 mg 以上又は最大耐用量）±ピオグリタゾン（30 mg 以上）±SU（各国のラベルに従った最高用量の半分以上）の併用下で、各国のラベルに従った GLP-1 受容体作動薬による治療：最高用量〔ビクトーザ®（リラグルチド）1.8 mg の 1 日 1 回投与又はバイエッタ®（エキセナチド）10 μg の 1 日 2 回投与〕又は最大耐用量〔ビクトーザ®（リラグルチド）1.2 mg の 1 日 1 回投与又はバイエッタ®（エキセナチド）5 μg の 1 日 2 回投与〕を受けている被験者。

主な除外基準

スクリーニング来院前 90 日以内にいずれかの経口糖尿病薬（メトホルミン、ピオグリタゾン及び SU を除く）の投与を受けた被験者。血糖値に影響を及ぼすと考えられるいずれかの薬剤（メトホルミン、ピオグリタゾン、SU 及び GLP-1 受容体作動薬を除く）の投与（ステロイド全身投与等）を受けた被験者。インスリン治療歴を有する被験者（ただし、治験責任医師の判断による妊娠糖尿病を含む併発疾患のための短期間のインスリン投与については可とする）。スクリーニング時のカルシトニン濃度が 50 ng/L 以上である被験者。本人又は家族が、甲状腺髄様癌又は多発性内分泌腫瘍症候群 2 型の既往歴を有する被験者。心血管系障害のある被験者〔先天性心不全（ニューヨーク心臓協会分類クラス III 及び IV）を有する被験者。スクリーニング来院前 52 週以内に不安定狭心症、脳卒中及び／又は心筋梗塞の診断を受けた被験者ならびに／あるいは冠状動脈、頸動脈又は末梢動脈の血行再建術を予定している被験者〕。治験責任医師の判断により緊急の処置を要する増殖網膜症又は黄斑症（黄斑浮腫）が確認された被験者。治験責任医師

の判断により、試験結果に影響を及ぼす又は治験薬投与によりリスクが増加すると考えられる臨床的に問題のある消化器系、呼吸器系、内分泌系（2型糖尿病を除く）、神経系、尿生殖器系又は血液系の活動性の疾患を有する被験者（過去 12 ヵ月以内）。慢性又は特発性の急性膵炎の既往歴を有する被験者。 主な中止・脱落基準 糖代謝に影響を及ぼすと考えられる薬剤の全身投与を開始する場合（治験責任医師の判断による）。被験者が妊娠した又は妊娠を希望した場合。高血糖が繰り返し発現した場合（試験の進捗に応じて 11.1～15.0 mmol/L）。急性膵炎と診断された被験者。
被験薬、用量及び投与方法、ロット番号： IDegLira 1 mL あたり IDeg 100 単位とリラグルチド 3.6 mg の固定比率の配合剤、ペン型注入器（PDS290、3 mL）と一体化したプレフィルド製剤として提供された。 IDegLira はメトホルミン±ピオグリタゾン±SU の併用下で検討した。IDegLira は 1 日 1 回、可能な限り毎日同時刻に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。16 用量ステップ（IDeg：16 単位、リラグルチド：0.6 mg）で投与を開始した。各投与量調節日前の連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき、1 週間に 2 回投与量調節を行った。朝食前血糖値 4.0～5.0 mmol/L（72～90 mg/dL）を目標として 2 用量ステップずつ投与量調節を行った。最高用量は 50 用量ステップ（IDeg：50 単位、リラグルチド：1.8 mg）であった。ロット番号：BP51052 及び BP51066。
投与期間： 26 週間
対照薬、用量及び投与方法、ロット番号： メトホルミン±ピオグリタゾン±SU の併用下で各国のラベルに従った最高用量又は最大耐用量での GLP-1 受容体作動薬（ビクトーザ®又はバイエッタ®）（前治療からの継続投与）。 ビクトーザ® リラグルチド 6 mg/mL、ペン型注入器（3 mL）と一体化したプレフィルド製剤として提供され、1.2 mg 又は 1.8 mg を 1 日 1 回皮下投与した。ロット番号：AP52216 及び BP50861。 バイエッタ® エキセナチド 250 µg/mL、ペン型注入器（1.2 mL）と一体化したプレフィルド製剤として提供され、5 µg を 1 日 2 回皮下投与した。ロット番号：A893506、A943601A 及び C103826。 バイエッタ® エキセナチド 250 µg/mL、ペン型注入器（2.4 mL）と一体化したプレフィルド製剤として提供され、10 µg を 1 日 2 回皮下投与した。ロット番号：A924640 及び A952394A。
評価基準：**有効性** 以下の主な有効性評価項目を評価した： HbA1c、HbA1c レスポンダー（7%及び 6.5%以下）、空腹時血糖値（FPG）、9 点血糖値プロファイルを含む血糖自己測定、体重ならびに Treatment Related Impact Measure – Diabetes（TRIM-D）及び糖尿病治療満足度質問票の状況（DTSQs）に基づく患者報告アウトカム（PRO）
評価基準：**安全性** 以下の主な安全性評価項目を評価した： 26 週間の治験薬投与下で発現した（重大な又は重大でない）確定低血糖の発現件数、26 週間の治験薬投与下で発現した有害事象の発現件数
統計手法： 検出力の算出 HbA1c の変化量について、IDegLira の GLP-1 受容体作動薬に対する優越性を示すための検出力は 90.0%であった。 解析対象集団

- 最大の解析対象集団（FAS）：無作為割り付けされたすべての被験者を含めた。例外的に、被験者を除外することがある。その場合、除外する正当な理由を示し文書化することとした。FASにおける統計的な評価はITT（intention to treat）の原則に従い、被験者はas randomisedの評価に寄与した。
- Per-Protocol（PP）解析対象集団：FASに含まれる被験者のうち以下の基準を満たすすべての被験者を含めた：
  - いずれの選択基準にも違反していない
  - いずれの除外基準も満たしていない
  - スクリーニング又は無作為割り付け時に非欠測のHbA1c測定値がある
  - 少なくとも12週の曝露がある
  - 投与後12週の曝露で少なくとも1つの非欠測のHbA1c測定値がある

  PP解析対象集団に含まれる被験者はas treatedの評価に寄与した。無作為割り付けされた被験者の計24例がPP解析対象集団から除外された。治験実施計画書からの逸脱により除外された被験者はいなかった。
- 安全性解析対象集団（SAS）：治験薬を少なくとも1回投与されたすべての被験者を含めた。SASに含まれる被験者はas treatedの評価に寄与した。
- 完了例の解析対象集団（CAS）：無作為割り付けされて試験を完了したすべての被験者を含めた。CASに含まれる被験者はas randomisedの評価に寄与した。

統計解析

プライマリーエンドポイントは、治療、前治療の GLP-1 受容体作動薬（ビクトーザ®又はバイエッタ®）及び地域を固定効果とし、ベースラインの HbA1c を共変量として含む共分散分析モデルを用いて解析された。本解析において、投与後 26 週の HbA1c の欠測値は LOCF 法を用いて補完された。主要目的は、優越性が検証された場合に限り満たされることとした。2 つのレスポンダー（HbA1c 7.0%未満、6.5%以下）に関するエンドポイントは、治療、前治療の GLP-1 受容体作動薬（ビクトーザ®又はバイエッタ®）及び地域を固定効果とし、ベースラインの HbA1c を共変量として含むロジスティック回帰モデルを用いて解析された。空腹時血糖値、9 点血糖値プロファイル（血糖自己測定）、体重及び PRO におけるエンドポイントのベースラインから投与後 26 週までの変化量は、プライマリーエンドポイントと同様の手法（ただし、HbA1c ではなく各エンドポイントのベースライン値を共変量とする）を用いて解析された。治験薬投与下で発現した低血糖（確定低血糖）の発現件数は、FAS を対象として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された。本モデルには、治療、前治療の GLP-1 受容体作動薬（ビクトーザ®及びバイエッタ®）及び地域を固定効果として含めた。26 週間の有害事象の発現件数は、SAS を対象として記述統計量を用いて示した。

解析の主な変更点

主解析の感度分析のために PP 解析対象集団が追加された。

被験者背景：

人口統計学的特性及びベースライン特性は群間で概ね同様であった。平均年齢は 58.3 歳、平均糖尿病罹病期間は 10.4 年、平均 BMI（kg/m^2）は 32.9、ベースラインの HbA1c の平均値は 7.8%であった。

人口統計学的特性及びベースライン特性 - 要約 - FAS

	IDegLira N (%)	GLP-1 N (%)	Total N (%)
Number of Subjects	292	146	438
Sex			
N	292 (100.0)	146 (100.0)	438 (100.0)
Female	139 (47.6)	75 (51.4)	214 (48.9)
Male	153 (52.4)	71 (48.6)	224 (51.1)
Race			
N	292 (100.0)	146 (100.0)	438 (100.0)

White	269 (92.1)	131 (89.7)	400 (91.3)
Black or African American	15 (5.1)	12 (8.2)	27 (6.2)
Asian	6 (2.1)	2 (1.4)	8 (1.8)
American Indian or Alaska Native	1 (0.3)	0 (0.0)	1 (0.2)
Native Hawaiian or Oth. Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.3)	1 (0.7)	2 (0.5)

N: Number of subjects; % : Percentages are based on N

ベースライン特性及び糖尿病特性 - 要約 - FAS

	IDegLira	GLP-1	Total
Number of Subjects	292	146	438
Age (years)			
N	292	146	438
Mean (SD)	58.3 (9.9)	58.4 (8.8)	58.3 (9.5)
Median	59.8	58.8	59.6
Min ; Max	22.0 ; 77.9	37.8 ; 78.3	22.0 ; 78.3
BMI (kg/m^2)			
N	292	146	438
Mean (SD)	32.9 (4.4)	33.0 (4.1)	32.9 (4.3)
Median	32.8	33.6	33.1
Min ; Max	21.6 ; 40.6	22.8 ; 40.7	21.6 ; 40.7
Duration of Diabetes (years)			
N	292	146	438
Mean (SD)	10.36 (5.79)	10.39 (5.81)	10.37 (5.79)
Median	9.6	9.2	9.5
Min ; Max	0.02 ; 31.34	0.02 ; 31.89	0.02 ; 31.89
HbA1c (%)			
N	292	146	438
Mean (SD)	7.8 (0.6)	7.7 (0.6)	7.8 (0.6)
Median	7.7	7.6	7.7
Min ; Max	6.7 ; 9.2	6.6 ; 9.7	6.6 ; 9.7
FPG (mmol/L)			
N	285	145	430
Mean (SD)	9.0 (2.1)	9.4 (2.3)	9.1 (2.2)
Median	8.7	8.8	8.8
Min ; Max	2.8 ; 15.9	4.8 ; 18.5	2.8 ; 18.5

BMI: Body mass index, N: Number of subjects, SD: Standard deviation
FPG : Fasting plasma glucose

有効性の結果：

HbA1c

血糖コントロールの改善について、IDegLira の GLP-1 受容体作動薬（前治療から継続投与）に対する優越性が検証された。IDegLira 群の HbA1c は、ベースラインから投与後 26 週にかけて 1.3%低下し 6.4%となった。GLP-1 群では、ベースラインから投与後 26 週にかけて 0.3%低下し 7.4%となった。群差の推定値は -0.94%（95%信頼区間：[-1.11; -0.78]、$p < 0.001$）であった。主解析の安定性は、事前に規定した 3 つの感度分析（繰り返し測定、CAS 及び PP 解析対象集団）により確認された。

HbA1c のレスポンダー

投与後 26 週の HbA1c が 7%未満に到達した被験者の割合は、IDegLira 群で 75.3%、GLP-1 群で 35.6%であった。同様に、投与後 26 週の HbA1c が 6.5%以下に到達した被験者の割合も GLP-1 群（22.6%）と比較し

てIDegLira群（63.0%）で高かった。レスポンダーの割合におけるオッズ比（IDegLira群／GLP-1群）の推定値から、目標を達成する割合は、GLP-1受容体作動薬（前治療から継続投与）と比較してIDegLiraで統計的に有意に高いことが示された。

空腹時血糖値

ベースラインの空腹時血糖値はIDegLira群で9.0 mmol/L（161.7 mg/dL）、GLP-1群で9.4 mmol/L（169.1 mg/dL）であった。空腹時血糖値は試験期間中に、投与後26週にはIDegLira群で3.0 mmol/L（53.6 mg/dL）、GLP-1群で0.6 mmol/L（10.7 mg/dL）低下した。空腹時血糖値の低下量はGLP-1群と比較してIDegLira群で統計的に有意に大きかった〔群差の推定値：-2.64 mmol/L（95%信頼区間：[-3.03; -2.25]、$p < 0.001$）〕。

9点血糖値プロファイル（血糖自己測定）

投与後26週の9点血糖値プロファイル（血糖自己測定）の平均の低下量は、GLP-1群と比較してIDegLira群で統計的に有意に大きかった〔群差の推定値：-1.78 mmol/L（95%信頼区間：[-2.13;-1.43]、$p<0.001$）〕。9点血糖値プロファイル（血糖自己測定）から算出した食後血糖増加量について、各食事又はすべての食事の平均のいずれの場合においても、ベースラインから投与後26週までの変化量に群間で統計的な有意差は認められなかった。

体重

投与後26週の体重の変化量はIDegLira群で2.0 kg及びGLP-1群で-0.8 kgであった。体重の変化量のIDegLira群とGLP-1群との差は統計的に有意であった〔群差の推定値：2.89 kg（95%信頼区間：[2.17; 3.62]、$p<0.001$）〕。

PRO測定結果

PROについてはGLP-1受容体作動薬（前治療から継続投与）と比較してIDegLiraの投与で良好な結果が得られた。投与後26週のTRIM-D総スコアはIDegLira群で統計的に有意に高く、GLP-1群と比較してIDegLira群で健康状態が改善したことが示された〔群差の推定値：5.0（95%信頼区間：[2.9; 7.2]、$p < 0.001$）〕。同様に、すべてのサブドメインスコアについて試験期間を通して上昇がみられ、投与後26週のスコアはGLP-1群と比較してIDegLira群で統計的に有意に高かった。

投与後26週のDTSQs治療満足度スコアは、GLP-1群と比較してIDegLira群で統計的に有意に高かった〔群差の推定値：2.0（95%信頼区間：[1.1; 2.8]、$p < 0.001$）〕。GLP-1群と比較して、IDegLira群では「低血糖」スコアが統計的に有意に高く、「高血糖」スコアが統計的に有意に低かった。このことから、IDegLira群において低血糖を自覚する頻度は高く、高血糖を自覚する頻度は低いことが示唆された。

安全性の結果：

全般的な有害事象プロファイル（低血糖以外）

死亡は試験期間中に報告されなかった。

有害事象の100人・年あたりの発現件数（合計）は、IDegLira群で410.1件及びGLP-1群で364.3件であった。有害事象の大部分は、非重篤及び軽度であり、その発現期間から一時的なものであり、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。

最も高頻度に報告された有害事象は鼻咽頭炎、上気道感染、リパーゼ増加、頭痛及び下痢であった。鼻咽頭炎の単位時間あたりの発現件数はIDegLira群で22.0件／100人・年、GLP-1群で30.4件／100人・年、ならびにリパーゼ増加の単位時間あたりの発現件数はIDegLira群で22.0件／100人・年、GLP-1群で12.1件／100人・年であった。その他の高頻度に報告された有害事象について明らかな群差は認められなかった。

重篤な有害事象の単位時間あたりの発現件数は、IDegLira群で8.5件／100人・年、GLP-1群で4.6件／100人・年であり、事象の種類に明らかな傾向は認められなかった。治験薬との因果関係が「あり」又は「可能性あり」と判定された重篤な有害事象はなかった。

中止に至った有害事象は3例（0.7%）の被験者で報告された〔IDegLira群1例（0.3%）、GLP-1群2例（1.4%）〕。3例中2例の被験者は回復し、残りの1例の転帰は不明であった。

事前に規定した注目すべき安全性領域の有害事象

2 件（いずれも IDegLira 群）が外部のイベント判定委員会により心血管系事象と確定された。両事象ともに主要な心血管系事象と判定された。
膵炎の報告はなく、イベント判定委員会の判定対象となった甲状腺に関連する有害事象はなかった。カルシトニンの継続的なモニタリングから安全性上の懸念は認められなかった。
イベント判定委員会により 3 件の新生物が確定された（IDegLira 群：2 件、GLP-1 群：1 件）。確定された新生物の単位時間あたりの発現件数は、IDegLira 群及び GLP-1 群でそれぞれ 1.4 件／100 人・年及び 1.5 件／100 人・年であった。このうち 1 件（IDegLira 群の口唇扁平上皮癌）は悪性に分類された。
アレルギー反応の単位時間あたりの発現件数は、IDegLira 群及び GLP-1 群でそれぞれ 6.4 件／100 人・年及び 10.6 件／100 人・年であった。IDegLira 群で報告されたこれらの事象はいずれも非重篤であり、薬物過敏症を除いて治験薬との因果関係は「なし」と判定された。薬物過敏症は治験薬との因果関係が「あり」と判定され、当該被験者は試験を中止した。
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、IDegLira 群及び GLP-1 群でそれぞれ 7.1 件／100 人・年及び 1.5 件／100 人・年であった。いずれの事象も非重篤及び軽度であり、試験終了時に回復が確認された。これらの事象の大部分は治験薬との因果関係は「あり」又は「可能性あり」と判定された。
胃腸障害の有害事象の単位時間あたりの発現件数は、IDegLira 群及び GLP-1 群でそれぞれ 44.7 件／100 人・年及び 57.7 件／100 人・年であった。すべての事象は非重篤であり、その大部分は重症度が軽度であった。
<u>低血糖</u>
確定低血糖の単位時間あたりの発現件数（合計）は、IDegLira 群で 281.7 件／100 人・年及び GLP-1 群で 12.1 件／100 人・年であった。比の推定値（IDegLira 群／GLP-1 群）は、25.36（95%信頼区間：[10.63; 60.51]、$p < 0.001$）であり、低血糖の単位時間あたりの発現件数は GLP-1 群と比較して IDegLira 群で統計的に有意に多かった。
重大な低血糖は、IDegLira 群の 1 例で報告された。
確定夜間低血糖の単位時間あたりの発現件数（合計）は、IDegLira 群で 45.4 件／100 人・年及び GLP-1 群で 1.5 件／100 人・年であった。比の推定値（IDegLira 群／GLP-1 群、事後解析）は、32.82（95%信頼区間：[4.13; 261.04]、$p < 0.001$）であり、確定夜間低血糖の単位時間あたりの発現件数は GLP-1 群と比較して IDegLira 群で統計的に有意に多かった。
<u>臨床検査評価</u>
血液学的検査又は血液生化学的検査のパラメータについては、いずれの投与群においてもベースラインから投与終了時までに臨床的に問題のある変化は認められなかった。
試験期間中、リパーゼは IDegLira 群（投与後 26 週の変化量：-1.0U/L）及び GLP-1 群（投与後 26 週の変化量：-1.8U/L）のいずれでも減少した。アミラーゼは、IDegLira 群（投与後 26 週の変化量：6.2U/L）で増加した一方、GLP-1 群（投与後 26 週の変化量：-1.0U/L）では減少した。臨床的な影響については現在のところ不明である。
カルシトニンについては、臨床的に問題となる群間の違いは認められなかった。
最も高頻度に報告された臨床検査に関連する有害事象はリパーゼ増加であり、IDegLira 群の 10.0%及び GLP-1 群の 4.8%の被験者で認められた。
<u>身体所見、眼底検査／眼底写真、心電図及びバイタルサイン</u>
投与後 26 週の身体所見、眼底検査／眼底写真又は心電図の結果については、臨床的に問題となる群間の違いは認められなかった。
投与後 26 週の脈拍数について、IDegLira 群と GLP-1 群の間で統計的な有意差が認められた〔群差の推定値：1.78 拍／分（95%信頼区間：[0.22; 3.33]、p=0.025）〕。

全体の結論：
インスリン治療歴がなく、メトホルミン±ピオグリタゾン±SUの併用下でのGLP-1受容体作動薬による治療で十分な血糖コントロールが得られていない2型糖尿病患者を対象として、IDegLiraをGLP-1受容体作動薬（前治療から継続投与）と比較検討する26週間の本試験の結論は以下のとおりである：

- ベースラインから投与後26週までのHbA1cの変化量について、IDegLiraのGLP-1受容体作動薬（前治療から継続投与）に対する優越性が検証された。
- HbA1cの目標値である7.0%及び6.5%に到達した被験者は、GLP-1受容体作動薬（前治療から継続投与）と比較してIDegLiraで有意に多かった。
- 空腹時血糖値の低下量は、GLP-1受容体作動薬（前治療から継続投与）と比較してIDegLiraで有意に大きかった。
- 9点血糖値プロファイルの平均は、GLP-1受容体作動薬（前治療から継続投与）と比較してIDegLiraで有意に低下した。
- 体重は、GLP-1受容体作動薬（前治療から継続投与）と比較してIDegLiraで有意に増加した。
- 概して、PROの測定結果及び患者の満足度スコアは、GLP-1受容体作動薬（前治療から継続投与）と比較してIDegLiraで大きく改善した。
- 確定低血糖の単位時間あたりの発現件数（合計）は、GLP-1受容体作動薬と比較してIDegLiraで統計的に有意に多かった。
- IDegLiraの全般的な有害事象及び忍容性プロファイルはこれまでに得られている結果と一致していた。

本試験は、ヘルシンキ宣言の精神（59th WMA Assembly, October 2008）、ICH-GCP（1996年5月）及び21 CFR 312.120を遵守して実施された。

2.7.6.10 NN9068-3951

2.7.6.10.1 臨床試験概要

Trial Registration ID-number： NCT01618162	UTN：U1111-1126-9776 IND number：109121 EudraCT number：2012-000140-97
治験の標題： DUAL™ IV - スルホニルウレア薬（SU）単独療法又はSUとメトホルミンの併用療法で十分な血糖コントロールが得られてない成人2型糖尿病患者を対象とした、インスリン デグルデク／リラグルチド（IDegLira）を追加したときの有効性を検討する試験	
治験責任医師名： 治験実施施設（77施設）ごとに1名の治験責任医師が任命された。以下の治験責任医師が治験総括報告書の内容を確認し、署名する「治験総括報告書への署名責任を有する医師（Signatory Investigator）」に任命された： Dr. [redacted]	
治験実施施設： 7ヵ国77施設において被験者の無作為割り付けが実施された：ブルガリア（7施設）、カナダ（9施設）、ドイツ（6施設）、インド（6施設）、イスラエル（7施設）、トルコ（3施設）及び米国（39施設）	
公表文献（引用文献）： 本治験総括報告書作成時点での公表文献はなし	
治験期間： 開始日：2012年8月29日 終了日：2013年10月23日	**開発のフェーズ**： 第3b相
Cut-off date： ここに提示する結果は、2013年11月07日の時点での臨床データベースに基づいている。	
目的： <u>主要目的</u>： • SU単独療法又はSUとメトホルミンの併用療法で十分な血糖コントロールが得られてないインスリン治療歴のない2型糖尿病患者を対象として、投与後26週の血糖コントロールについて、IDegLiraを追加したときのIDegLiraプラセボを追加したときに対する優越性を検証する。 <u>副次的目的</u>： • SU単独療法又はSUとメトホルミンの併用療法で十分な血糖コントロールが得られてないインスリン治療歴のない2型糖尿病患者を対象として、IDegLira及びIDegLiraプラセボを追加したときの投与後26週における全般的な有効性及び安全性を比較検討する。	
治験方法： 本試験は、経口糖尿病薬による治療（SU単独療法又はSUとメトホルミンの併用療法）で十分な血糖コントロールが得られてないインスリン治療歴のない2型糖尿病患者を対象とした、26週間、無作為割り付け、2群並行、二重盲検、多施設、国際共同、treat-to-target試験であり、IDegLiraとプラセボの有効性及び安全性を比較検討した。HbA1c 7.0%（53 mmol/mol）以上、9.0%（75 mmol/mol）以下を「十分な血糖コントロールが得られていない2型糖尿病」と定義した。適格と判断された被験者を、SU単独療法又はSUと	

メトホルミンの併用療法にIDegLira又はプラセボの1日1回投与を追加する投与群のいずれかに2：1の割合で無作為に割り付けた。SU及びメトホルミン（該当する場合）は、安全性の理由がある場合を除き、試験期間を通して、無作為割り付け前と同じ安定した用法及び投与頻度で維持することとした。
開始用量は10用量ステップ（IDeg：10単位、リラグルチド：0.36 mg）とし、treat-to-target法を用いて空腹時血糖値4.0～6.0 mmol/L（72～108 mg/dL）を目標として用量調節を行った。事前に規定した投与量調節アルゴリズムに従い、連続した3日間の朝食前血糖値（血糖自己測定による）の平均に基づき、1週間に2回用量調節を行った。許容最高用量は50用量ステップ（IDeg：50単位、リラグルチド：1.8 mg）であった。

計画及び解析された被験者数：
計画された被験者数は、IDegLira 群で 286 例、プラセボ群で 143 例であり、無作為割り付け予定被験者数は計 429 例であった。

被験者内訳－要約

	IDegLira N (%)	Placebo N (%)	Total N (%)
Screened			760
Screening Failures			325
Withdrawn before Randomisation			0
Randomised	289 (100.0)	146 (100.0)	435 (100.0)
Exposed	288 (99.7)	146 (100.0)	434 (99.8)
Withdrawn at/after Randomisation	38 (13.1)	35 (24.0)	73 (16.8)
Adverse Event	9 (3.1)	2 (1.4)	11 (2.5)
Non-Compliance With Protocol	13 (4.5)	10 (6.8)	23 (5.3)
Withdrawal Criteria	2 (0.7)	10 (6.8)	12 (2.8)
Other	14 (4.8)	13 (8.9)	27 (6.2)
Completed	251 (86.9)	111 (76.0)	362 (83.2)
full analysis set	289 (100.0)	146 (100.0)	435 (100.0)
PP analysis set	266 (92.0)	126 (86.3)	392 (90.1)
safety analysis set	288 (99.7)	146 (100.0)	434 (99.8)

N: Number of subjects
%: Proportion of randomised subjects

診断及び主要な組入れ基準：
主な選択基準
性別不問、年齢 18 歳以上、HbA1c 7.0%以上、9.0%以下（53～75 mmol/mol）の 2 型糖尿病患者。スクリーニングの 90 日以上前から、SU（各国の承認最大用量の半量以上）単独療法もしくは、SU とメトホルミンの併用療法（SU：各国の承認最大用量の半量以上、メトホルミン：1500 mg 以上又は最大耐用量）による安定した治療を受けており、BMI（kg/m^2）が 40 以下、血糖自己測定の実施、被験者日誌への記録ならびにプレフィルドペン型注入器の使用など治験実施計画書を遵守できるもしくは遵守する意思がある被験者。治験に関連する何らかの手順を実施する前に治験への参加について文書による同意が得られている被験者。
主な除外基準
スクリーニング前 90 日以内に経口糖尿病薬による治療（SU 単独療法及び SU とメトホルミンの併用療法を除く）を受けた被験者。血糖値に影響を及ぼすと考えられる薬剤の投与（副腎皮質ステロイドの全身投与等）（SU 単独療法及び SU とメトホルミンの併用療法を除く）を受けている被験者（治験責任医師の判断による）。過去に GLP-1 受容体作動薬（エキセナチド、リラグルチド等）の治療歴がある被験者。インスリン治療を受けている被験者（ただし、併発疾患のための短期間のインスリン投与については可とする：治験責任医師の判断による）。消化器系、呼吸器系、内分泌系（2 型糖尿病は除く）、神経系、泌

尿生殖器系又は血液系の臨床的に問題となる活動性（過去 12 ヵ月以内）の疾患を有する被験者（治験の結果へ影響を及ぼす又は治験薬の投与によりさらなるリスクをもたらす可能性がある疾患と治験責任医師が判断する場合）。肝機能障害〔アラニンアミノトランスフェラーゼ（ALAT）が基準範囲上限の 2.5 倍以上〕を有する被験者。腎機能障害〔血清クレアチニンが男性で 133 µmol/L 以上（1.5 mg/dL 以上）、女性で 125 µmol/L 以上（1.4 mg/dL 以上）、又は各国のメトホルミンの禁忌に該当する場合〕を有する被験者。スクリーニング時のカルシトニン濃度が 50 ng/L 以上である被験者。

主な中止・脱落基準

糖代謝に影響を及ぼすと考えられる薬剤の全身投与を開始する場合（治験責任医師の判断による）、被験者が妊娠した又は妊娠を希望する場合、高血糖（試験開始からの期間に応じて 11.1～15.0 mmol/L 超と設定）が繰り返し発現した場合、急性膵炎と診断された場合、被験者は試験を中止しなければならない。

被験薬、用量及び投与方法、ロット番号：

IDegLira

1 mL あたり IDeg 100 単位とリラグルチド 3.6 mg の固定比率の配合剤、ペン型注入器（PDS290、3 mL）と一体化したプレフィルド製剤として提供された。IDegLira は SU 単独療法又は SU とメトホルミンの併用療法との併用下で検討された。IDegLira は 1 日 1 回、毎日同時刻（可能な限り）に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。10 用量ステップ（IDeg：10 単位、リラグルチド：0.36 mg に相当）で投与を開始した。各用量調節日前の連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき、1 週間に 2 回用量調節を行った。朝食前血糖値 4.0～6.0 mmol/L（72～108 mg/dL）を目標として、2 用量ステップ（IDeg：2 単位、リラグルチド：0.072 mg に相当）ずつ用量調節を行った。最高用量は 50 用量ステップ（IDeg：50 単位、リラグルチド：1.8 mg）であった。ロット番号：BP51066 及び BP51052。

投与期間：

26 週間

対照薬、用量及び投与方法、ロット番号：

IDegLira プラセボ

ペン型注入器（PDS290、3 mL）と一体化したプレフィルド製剤として提供された。プラセボは SU 単独療法又は SU とメトホルミンの併用療法との併用下で検討された。プラセボは 1 日 1 回、毎日同時刻に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。10 用量ステップで投与を開始した。各用量調節日前の連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき、1 週間に 2 回用量調節を行った。朝食前血糖値 4.0～6.0 mmol/L（72～108 mg/dL）を目標として、2 用量ステップずつ用量調節を行った。最高用量は 50 用量ステップであった。ロット番号：BP51057。

評価基準：有効性

以下の有効性評価項目を評価した：

HbA1c、HbA1c のレスポンダー（7%未満及び 6.5%以下）、空腹時血糖値、体重

評価基準：安全性

以下の安全性評価項目を評価した：

26 週間の治験薬投与下で発現した重大な又は重大でない確定低血糖の発現件数

26 週間の治験薬投与下で発現した有害事象の発現件数

統計手法：

検出力の算出

HbA1c の変化量について、IDegLira のプラセボに対する優越性を示すための検出力は 90.0%であった。

解析対象集団

- 最大の解析対象集団（FAS）：無作為割り付けされたすべての被験者を含めた。例外的に被験者を除外することがあった。この場合、除外する正当な理由を示し文書化することとした。FASにおける統計的な評価はITT（intention to treat）の原則に従い、被験者はas randomisedの評価に寄与した。

- Per-Protocol（PP）解析対象集団：FASに含まれる被験者のうち以下の基準を満たすすべての被験者を含めた：
  - いずれの選択基準にも違反していない
  - いずれの除外基準も満たしていない
  - スクリーニング又は無作為割り付け時に非欠測のHbA1c測定値がある
  - 少なくとも12週の曝露がある
  - 投与後12週の曝露で少なくとも1つの非欠測のHbA1c測定値がある

  PP解析対象集団に含まれる被験者はas treatedの評価に寄与した。無作為割り付けされた被験者のうち43例をPP解析対象集団から除外した。治験実施計画書からの逸脱により、PP解析対象集団から除外された被験者はいなかった。
- 安全性解析対象集団（SAS）：治験薬を少なくとも1回投与されたすべての被験者を含めた。SASに含まれる被験者はas treatedの評価に寄与した。治験薬の投与前に同意を撤回した1例をSASから除外した。
- 完了例の解析対象集団（CAS）：無作為割り付けされて試験を完了したすべての被験者を含めた。CASに含まれる被験者はas randomisedの評価に寄与した。

統計解析

プライマリーエンドポイントは、共分散分析（ANCOVA）モデルを用いて解析した。モデルには治療、地域及び前治療薬（SU 単剤又は SU とメトホルミンの併用）を固定効果、ベースライン時の HbA1c を共変量として含めた。本解析では、投与後 26 週の HbA1c の欠測値は、last observation carried forward（LOCF）法を用いて補完した。優越性が検証された場合に、主要目的が満たされることとした。さらに、LOCF を用いた解析の感度を評価するため、ベースラインから投与後 26 週までの HbA1c を繰り返し測定に対する混合モデル（MMRM）を用いて解析した。空腹時血糖値及び体重のベースラインから投与後 26 週の変化量は、プライマリーエンドポイントと同じ方法で、ベースライン時の HbA1c の代わりに各エンドポイントのベースラインを共変量として、FAS を対象に解析した。治験薬投与下で発現した（確定）低血糖の発現件数は、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 FAS を対象として解析した。本モデルには、治療、地域及び前治療薬（SU 単剤又は SU とメトホルミンの併用）を固定効果として含めた。26 週間の治験薬投与下で発現した有害事象の発現件数は、SAS を対象として記述統計量を用いて解析した。

- すべての国で適用されるprotocol amendmentで文書化された統計解析の主な変更：CASを追加した。
- 統計解析計画書で文書化された統計解析の主な変更：PP解析対象集団を主要解析の感度分析に追加した。
- 統計解析計画書で計画されていた統計解析の主な変更：追加の感度分析として、早期に試験を中止した施設818で組み入れられた4例の被験者を除き、プライマリーエンドポイントの解析を実施した。

被験者背景：

435 例の被験者が IDegLira（n=289）又はプラセボ（n=146）の treat-to-target 療法に 2:1 の割合で無作為に割り付けられた。ベースラインの被験者背景及び特性は投与群間で概ね同様であった。平均年齢は 59.8 歳、平均糖尿病罹病期間は 9.1 年、平均 BMI は 31.5、ベースラインの HbA1c の平均は 7.9%であった。

人口統計学的特性及びベースライン特性−要約−FAS

	IDegLira N (%)	Placebo N (%)	Total N (%)
Number of Subjects	289	146	435
Age Group			
N	289 (100.0)	146 (100.0)	435 (100.0)
18-39 years	7 (2.4)	7 (4.8)	14 (3.2)
40-64 years	204 (70.6)	92 (63.0)	296 (68.0)
65-74 years	58 (20.1)	38 (26.0)	96 (22.1)

Elderly (>= 75 years)	20 (6.9)	9 (6.2)	29 (6.7)
Sex			
N	289 (100.0)	146 (100.0)	435 (100.0)
Female	135 (46.7)	73 (50.0)	208 (47.8)
Male	154 (53.3)	73 (50.0)	227 (52.2)
Country of Residence			
N	289 (100.0)	146 (100.0)	435 (100.0)
Bulgaria	77 (26.6)	33 (22.6)	110 (25.3)
Canada	28 (9.7)	10 (6.8)	38 (8.7)
Germany	31 (10.7)	15 (10.3)	46 (10.6)
India	46 (15.9)	18 (12.3)	64 (14.7)
Israel	16 (5.5)	6 (4.1)	22 (5.1)
Turkey	2 (0.7)	3 (2.1)	5 (1.1)
United States	89 (30.8)	61 (41.8)	150 (34.5)
Ethnicity			
N	289 (100.0)	146 (100.0)	435 (100.0)
Hispanic or Latino	24 (8.3)	16 (11.0)	40 (9.2)
Not Hispanic or Latino	265 (91.7)	130 (89.0)	395 (90.8)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)
Race			
N	289 (100.0)	146 (100.0)	435 (100.0)
White	217 (75.1)	111 (76.0)	328 (75.4)
Black or African American	16 (5.5)	13 (8.9)	29 (6.7)
Asian	52 (18.0)	20 (13.7)	72 (16.6)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Oth. Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)
Other	4 (1.4)	2 (1.4)	6 (1.4)

N: Number of subjects; %: Percentages are based on N
18-39 year: age range from 18 to less than 40
40-64 year: age range from 40 to less than 65
65-74 years: age range from 65 to less than 75
> 75 years: age range from 75

ベースライン及び糖尿病特性−要約−FAS

	IDegLira	IDeg	Lira	Total
Number of Subjects	833	413	414	1660
Age (years)				
N	833	413	413	1659
Mean (SD)	55.1 (9.9)	54.9 (9.7)	55.0 (10.2)	55.0 (9.9)
Median	55.7	55.0	55.3	55.4
Min ; Max	27.8 ; 83.8	24.0 ; 79.1	24.4 ; 81.6	24.0 ; 83.8
Height (m)				
N	833	413	414	1660
Mean (SD)	1.67 (0.10)	1.67 (0.11)	1.67 (0.10)	1.67 (0.10)
Median	1.67	1.66	1.67	1.67
Min ; Max	1.35 ; 1.94	1.43 ; 1.98	1.40 ; 2.06	1.35 ; 2.06
Body Weight (kg)				
N	833	413	414	1660
Mean (SD)	87.2 (19.0)	87.4 (19.2)	87.4 (18.0)	87.3 (18.8)
Median	85.6	86.6	87.1	86.2

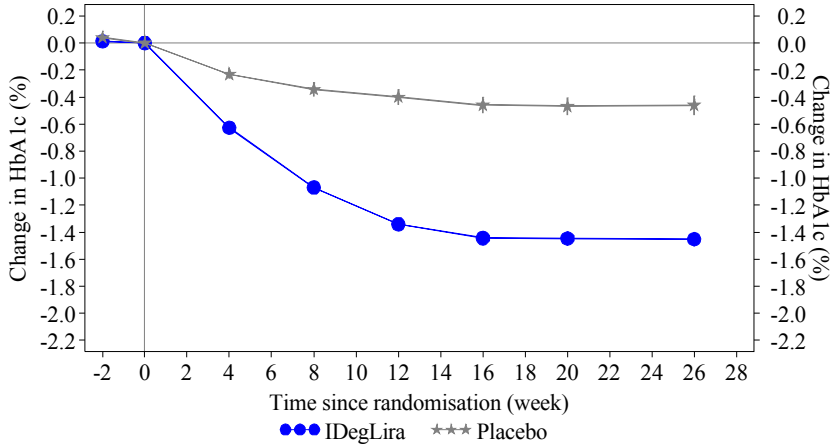
Min ; Max	41.0 ; 147.1	43.5 ; 156.9	45.5 ; 143.8	41.0 ; 156.9
BMI (kg/m^2)				
N	833	413	414	1660
Mean (SD)	31.2 (5.2)	31.2 (5.3)	31.3 (4.8)	31.2 (5.1)
Median	31.3	31.0	31.3	31.2
Min ; Max	17.3 ; 45.2	16.8 ; 41.8	19.9 ; 40.5	16.8 ; 45.2
Duration of Diabetes (years)				
N	833	413	413	1659
Mean (SD)	6.62 (5.13)	6.98 (5.30)	7.15 (6.09)	6.84 (5.43)
Median	5.2	5.5	5.6	5.4
Min ; Max	0.03 ; 35.07	0.01 ; 32.34	0.01 ; 53.86	0.01 ; 53.86
HbA1c (%)				
N	833	413	414	1660
Mean (SD)	8.3 (0.9)	8.3 (1.0)	8.3 (0.9)	8.3 (0.9)
Median	8.2	8.2	8.2	8.2
Min ; Max	6.0 ; 11.0	6.6 ; 11.3	6.4 ; 12.6	6.0 ; 12.6
FPG (mmol/L)				
N	809	409	409	1627
Mean (SD)	9.2 (2.4)	9.4 (2.7)	9.0 (2.6)	9.2 (2.5)
Median	8.8	8.7	8.4	8.7
Min ; Max	2.7 ; 18.5	4.7 ; 19.4	3.1 ; 23.4	2.7 ; 23.4

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation, FPG= Fasting Plasma Glucose

有効性の結果：

<u>プライマリーエンドポイント：HbA1c</u>

HbA1c の低下量について、SU 単独療法又は SU とメトホルミンの併用療法に IDegLira を追加したときの優越性が検証され、SU 単独療法又は SU とメトホルミンの併用療法に IDegLira を追加することで血糖値を効果的に改善することが示された。投与後 26 週において、IDegLira 群の HbA1c は 6.4%及びその低下量は-1.45%であり、プラセボ群の HbA1c は 7.4%及びその低下量は-0.46%であった。群差の推定値は、-1.02%（95%信頼区間：[-1.18; -0.87]、$p < 0.0001$）であった。事前に規定された 3 つの感度分析（繰り返し測定に対する混合モデル、CAS 及び PP 解析対象集団に基づく感度分析）により、主要解析の安定性が裏付けられた。



FAS: LOCF imputed data
FAS: Full analysis set, LOCF: Last observation carried forward
Error bars: +-Standard error(mean)

HbA1c のベースラインからの平均変化量（%）の経時推移

セカンダリーエンドポイント

- *HbA1cのレスポンダー*：投与後26週のHbA1cが7%未満に到達した被験者の割合は、プラセボ群で28.8%であったのに対し、IDegLira群では79.2%であった。同様に、投与後26週のHbA1cが6.5%以下に到達した被験者の割合は、プラセボ群（12.3%）と比較して、IDegLira群（64.0%）で高かった。これらの目標を達成した被験者の割合は、オッズ比の推定値に基づくと、SU単独療法又はSUとメトホルミン併用療法にIDegLiraを追加した群で統計的に有意に高いことが示された。
- *空腹時血糖値*：空腹時血糖値は試験期間中にIDegLira群で2.60 mmol/L（46.9 mg/dL）、プラセボ群で0.31 mmol/L（5.6 mg/dL）低下した。空腹時血糖値の低下量は、プラセボ群と比較してIDegLira群で統計的に有意に大きかった〔群差の推定値：-2.30 mmol/L（95%信頼区間：[-2.72; -1.89]、$p < 0.001$）〕。
- *9点血糖値プロファイル（血糖自己測定）*：9点血糖値プロファイル（血糖自己測定）の平均の低下量は、プラセボ群と比較してIDegLira群で統計的に有意に大きかった〔群差の推定値：-1.55 mmol/L（95%信頼区間：[-1.86; -1.24]、$p < 0.001$）〕。9点血糖値プロファイル（自己血糖測定）による食後血糖増加量のベースラインから投与後26週の変化量は、各食事時及びすべての食事の平均のいずれも投与群間で統計的に有意な差は認められなかった。
- *体重*：体重は、試験期間を通して比較的安定していた。投与後26週の体重の変化量は、IDegLira群で+0.5 kg、プラセボ群で-1.0 kgであった。SU単独療法又はSUとメトホルミン併用療法にIDegLiraを追加した群とプラセボを追加した群の群差の推定値は1.48 kg（95%信頼区間：[0.90; 2.06]、$p < 0.001$）であり、統計的に有意な違いが認められた。

安全性の結果：

検討した各領域における安全性の結果を以下に要約する：

全般的な有害事象プロファイル（低血糖以外）

- 試験期間中、IDegLira群で1件の死亡（胸膜悪性中皮腫）が報告された。本件はイベント判定委員会より非心血管死と判定された。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。当該被験者は長年アスベストを扱う仕事に従事していた。
- 有害事象の単位時間あたりの発現件数（件／100人・年）は、IDegLira群で401.4件／100人・年、プラセボ群で367.0件／100人・年であった。有害事象の大部分は非重篤、軽度、一時的な事象であり、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。
- IDegLira群で最も高頻度に報告された有害事象はリパーゼ増加、鼻咽頭炎、脂質異常症、頭痛及びインフルエンザであった。リパーゼ増加の単位時間あたりの発現件数は、IDegLira群で22.6件／100人・年、プラセボ群で12.9件／100人・年であり、脂質異常症の単位時間あたりの発現件数は、IDegLira群で14.3件／100人・年、プラセボ群で11.3件／100人・年であった。その他の事象の単位時間あたりの発現件数は、両投与群で同様か、IDegLira群で少なかった。
- 重篤な有害事象の単位時間あたりの発現件数はプラセボ群と比較してIDegLira群で多かったが、事象の種類に特定の傾向は認められなかった（IDegLira群：20.3件／100・年、プラセボ群：8.0件／100・年）。IDegLira群において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」と判定された重篤な有害事象は3件（2例）であった（アミラーゼ増加／リパーゼ増加及び低血糖性意識消失）。
- 試験の中止に至った有害事象を発現した被験者は11例（2.5%）であった〔IDegLira群：9例（3.1%）、プラセボ群：2例（1.4%）〕。高血糖を発現したプラセボ群の1例を除き、すべての被験者が事象から回復した。

事前に規定した注目すべき安全性領域の有害事象

- イベント判定委員会により4件の心血管系事象（すべての事象がIDegLira群）が確定された。そのうち2件は主要な心血管イベント（MACE）であった。
- イベント判定委員会により確定された膵炎の事象はなかった。
- イベント判定委員会により、3件の治験薬投与下で発現した事象が新生物と確定された〔IDegLira群：1件、プラセボ群：2件（1例）〕。確定された新生物の単位時間あたりの発現件数は、IDegLira群で

0.8件／100人・年、プラセボ群で3.2件／100人・年であった。IDegLira群で1件の新生物（胸膜悪性中皮腫、Day 21に発現）がイベント判定委員会により悪性と分類された。当該被験者は死亡した。

- イベント判定委員会により確定された甲状腺関連事象はなかった。
- カルシトニンの継続的なモニタリングから、安全性で問題となる事象は認められなかった。
- 腎機能の悪化、アレルギー反応又は注射部位反応に関する有害事象の単位時間あたり発現件数は投与群間で同様であった。IDegLira群で1件の急性腎不全が報告されたが、尿路感染症及び熱性疾患が原因とされた。
- 5件の投与過誤に関連する事象が報告された。IDegLira群で1件（誤薬投与）、プラセボ群で4件（過量投与又は偶発的過量投与）であった。すべての被験者が事象から回復し、当該事象に関連する有害事象の報告はなかった。
- 予測されたとおり、投与初期にIDegLira群において悪心の単位時間あたりの発現件数がわずかに増加したことを除き、悪心、下痢、嘔吐の報告について一貫した群間差は認められなかった。

<u>低血糖</u>

- 全般的に、確定低血糖の単位時間あたりの発現件数は、プラセボ群と比較してIDegLira群で多かった（IDegLira群：351.7件／100人・年、プラセボ群：135.2件／100人・年）。プラセボ群に対するIDegLira群の確定低血糖の単位時間あたりの発現件数の比の推定値は、3.74（95%信頼区間：[2.28; 6.13]）であった。このことにより、SU単独療法及びSUとメトホルミンの併用療法にプラセボを追加した群と比較して、IDegLiraを追加した群で低血糖の単位時間あたりの発現件数が統計的に有意に多いことが示された。
- 重大な低血糖は、IDegLira群の2例で報告された。いずれの被験者も、低血糖の発現前に2回連続で食事を摂取していなかった。
- 全般的に、確定夜間低血糖の単位時間あたりの発現件数は、プラセボ群と比較してIDegLira群で多かった（IDegLira群：49.0件／100人・年、プラセボ群：32.2件／100人・年）が、統計的な有意差は認められなかった。

<u>臨床検査評価</u>

- アミラーゼ及びリパーゼを除き、血液学的検査又は血液生化学的検査のパラメータについては、いずれの投与群においてもベースラインから投与終了時までに臨床的に問題のある変化は認められなかった。
- リパーゼは、ベースラインから投与終了時までにIDegLira群で増加（11.6 U/L）が認められ、プラセボ群で減少（-3.1 U/L）が認められた。リパーゼほど顕著ではなかったが、同様の傾向がアミラーゼでも認められた。これらの所見の臨床的な影響については現在のところ不明である。
- カルシトニンについては、臨床的に問題となる群間の違いは認められなかった。
- 最も高頻度に報告された臨床検査に関する有害事象はリパーゼ増加又はアミラーゼ増加であり、IDegLira群の11.1%、プラセボ群の4.1%の被験者で認められた。

<u>身体所見、眼底検査／眼底写真、心電図及びバイタルサイン</u>

- 投与後26週の身体所見、眼底検査／眼底写真又は心電図の結果については、臨床的に問題となる群間の違いは認められなかった。
- 脈拍数のベースラインからの変化量は、プラセボ群と比較してIDegLira群で統計的に有意に大きかった（群差の推定値：3.8拍／分）。

全体の結論：
インスリン治療歴のない 2 型糖尿病患者を対象として、SU 単独療法又は SU とメトホルミンの併用療法に IDegLira 及びプラセボを追加した場合の比較検討を行う 26 週間の本試験の結論は以下のとおりであった：

- ベースラインから投与後26週までのHbA1cの変化量について、IDegLiraのプラセボに対する優越性が検証された。
  - HbA1cの目標値である7%未満及び6.5%以下を達成した被験者の割合は、プラセボと比較してIDegLiraで有意に高かった。
- 空腹時血糖値は、プラセボと比較してIDegLiraで有意に低下した。
- 9点血糖値プロファイル（血糖自己測定）の平均は、プラセボと比較してIDegLiraで有意に低下した。
- 体重は、IDegLiraで0.5 kg増加し、プラセボで1.0 kg減少した。この差は統計的に有意であった。
- 確定低血糖の単位時間あたりの発現件数は、プラセボと比較してIDegLiraで統計的に有意に多かった。
- 重篤な有害事象の単位時間あたりの発現件数は、プラセボと比較してIDegLiraで多かったが、事象の種類に特定の傾向は認められなかった。
- IDegLiraにおける有害事象及び忍容性プロファイルは、過去の結果と一致していた。

本試験は、ヘルシンキ宣言（59th WMA assembly, Oct 2008）の精神及び ICH-GCP（May 1996）ならびに FDA 21 CFR 312.120 を遵守して実施された。

ここに提示する結果は、2013 年 11 月 7 日の時点での臨床データベースに基づいている。

2.7.6.11. NN9068-3952

2.7.6.11.1. 臨床試験概要

Trial Registration ID-number： NCT01952145	UTN：U1111-1135-1003 IND number：109121 EudraCT number：2012-004413-14
治験の標題： DUAL™ V - Basal インスリンからの切り替え：2 型糖尿病患者を対象とした、インスリン デグルデク／リラグルチド及びインスリン グラルギンの有効性及び安全性を比較する試験	
治験責任医師名： 治験実施施設（75 施設）ごとに 1 名の治験責任医師が任命された。以下の治験責任医師が治験総括報告書の内容を確認し、署名する「治験総括報告書への署名責任を有する医師（Signatory Investigator）」に任命された： Dr. [redacted]	
治験実施施設： 以下の 10 ヵ国 75 施設において本試験が実施された：アルゼンチン（5 施設）オーストラリア（4 施設）、ギリシャ（6 施設）、ハンガリー（4 施設）、メキシコ（5 施設）、ロシア（11 施設）、スロバキア（11 施設）、南アフリカ共和国（4 施設）、スペイン（6 施設）及び米国（19 施設）	
公表文献（引用文献）： 本治験総括報告書作成時点での公表文献はなし	
治験期間： 開始日：2013 年 9 月 20 日 終了日：2014 年 11 月 4 日	**開発のフェーズ**： 第 3b 相
Cut-off date： ここに提示する結果は、2014 年 11 月 18 日の時点での臨床データベース及び 2014 年 12 月 19 日の時点での安全性データベースに基づいている。	
目的： <u>主要目的</u>： • インスリン グラルギンで治療を受けていた2型糖尿病患者を対象として、インスリン デグルデク／リラグルチドの血糖コントロールにおける有効性を検証する。これは、ベースラインから投与後26週のHbA1cの変化量について、インスリン デグルデク／リラグルチドのインスリン グラルギンに対する非劣性（非劣性マージン：0.30%）を示すことで行う。 <u>副次的目的</u>： • 投与後26週の以下から1つ以上の項目について、インスリン デグルデク／リラグルチドのインスリン グラルギンに対する優越性を検討する。 – HbA1cのベースラインからの変化量 – 確定低血糖 – 体重のベースラインからの変化量 • 26週間のインスリン デグルデク／リラグルチドの安全性をインスリン グラルギンと比較検討する。	
治験方法： 本試験は、インスリン グラルギン（IGlar；20～50 単位／日）及びメトホルミンとの併用療法で十分な血糖コントロールが得られていない 2 型糖尿病患者を対象とした、26 週間、国際共同、多施設、非盲検、無作為割り付け、treat-to-target、2 群並行群間比較試験であった。HbA1c が 7.0%（53 mmol/mol）以上、10.0%（86 mmol/mol）以下を「十分な血糖コントロールが得られていない 2 型糖尿病患者」と定義した。	

被験者は、メトホルミンに加えてインスリン デグルデク／リラグルチド（IDegLira）又は IGlar のいずれかの 1 日 1 回投与を受けた。適格と判断された被験者を IDegLira 又は IGlar のいずれかに 1：1 の割合で無作為に割り付けた。IDegLira の開始用量は 16 用量ステップ（IDeg：16 単位、リラグルチド：0.6mg）とし、treat-to-target 法を用いて空腹時血糖値 4.0～5.0 mmol/L（71～90 mg/dL）を目標として用量調節を行った。事前に規定した投与量調節アルゴリズムに従い、連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均に基づき、1 週間に 2 回用量調節を行った。許容最高用量は 50 用量ステップ（IDeg：50 単位、リラグルチド：1.8 mg）であった。IGlar は試験開始前の 1 日投与量と同じ用量で開始し（dose-to-dose switch）、事前に規定した投与量調節アルゴリズムに従い、用量調節を行った。最高用量の規定はなかった。

計画及び解析された被験者数：

計画された被験者数（各群に 1：1 の割合で無作為割り付け）は 554 例であった。

被験者内訳－要約

	IDegLira N (%)	IGlar N (%)	Total N (%)
Screened			767
Screening Failures			210
Withdrawn before Randomisation			0
Randomised	278 (100.0)	279 (100.0)	557 (100.0)
Exposed	278 (100.0)	279 (100.0)	557 (100.0)
Withdrawn at/after Randomisation	28 (10.1)	14 (5.0)	42 (7.5)
Adverse Event	9 (3.2)	1 (0.4)	10 (1.8)
Non-Compliance With Protocol	2 (0.7)	1 (0.4)	3 (0.5)
Withdrawal Criteria	16 (5.8)	11 (3.9)	27 (4.8)
Other	1 (0.4)	1 (0.4)	2 (0.4)
Completed	250 (89.9)	265 (95.0)	515 (92.5)
Full analysis set	278 (100.0)	279 (100.0)	557 (100.0)
PP analysis set	257 (92.4)	270 (96.8)	527 (94.6)
Safety analysis set	278 (100.0)	279 (100.0)	557 (100.0)

N: number of subjects, %: proportion of randomised subjects

診断及び主要な組入れ基準：

主な選択基準

性別不問、年齢 18 歳以上、HbA1c 7.0%以上、10.0%以下（53～86 mmol/mol）、BMI（kg/m^2）が 40 以下の 2 型糖尿病患者。治療開始前の糖尿病治療薬に関する選択基準は以下のとおり：スクリーニングの 90 日以上前から IGlar による治療を受けており、スクリーニングの 56 日以上前から 20～50 単位の範囲内で IGlar の安定した治療を受けている被験者。スクリーニング実施日の投与量は 20～50 単位で、かつスクリーニング前 56 日間の 1 日投与量の変動が±10%以内である被験者。スクリーニングの 90 日以上前から、メトホルミン（1500 mg 以上又は最大耐用量）による安定した治療を併用している被験者。

主な除外基準

スクリーニング前 90 日以内に経口糖尿病薬（メトホルミンは除く）の投与を受けた被験者。グルコース代謝に影響を及ぼすと考えられる薬剤（IGlar 及びメトホルミンは除く）の投与（副腎皮質ステロイドの全身投与等）を受けている又は変更が予定されている被験者（治験責任医師の判断による）。Basal インスリン以外のインスリン（Bolus インスリン又は混合型インスリン等。ただし、妊娠糖尿病を含む併発疾患のための短期間の使用は可とする：治験責任医師の判断による）の投与を受けている又は治療歴がある被験者。現在 GLP-1 受容体作動薬（エキセナチド、リラグルチド等）の投与を受けている又は治療歴が

ある被験者。肝機能障害（アラニンアミノトランスフェラーゼが基準範囲上限の 2.5 倍以上）を有する被験者。腎機能障害〔血清クレアチニンが男性で 133 μmol/L（1.5 mg/dL）以上、女性で 125 μmol/L（1.4 mg/dL）以上、又は各国のメトホルミンの禁忌に該当する〕を有する被験者。スクリーニング時のカルシトニン濃度が 50 ng/L 以上である被験者。甲状腺髄様癌又は多発性内分泌腫瘍症候群 2 型の既往歴もしくは家族歴を有する被験者。慢性膵炎又は特発性急性膵炎の既往歴を有する被験者。

主な中止・脱落基準

糖代謝に影響を及ぼすと考えられる薬剤の全身投与を開始する場合（治験責任医師の判断による）。被験者が妊娠した又は妊娠を希望する場合。高血糖〔空腹時血糖値が、ベースラインから投与後 6 週では 15.0 mmol/L（270 mg/dL）、投与後 7 週から 12 週では 13.3 mmol/L（240 mg/dL）、投与後 13 週から 26 週では 11.1 mmol/L（200 mg/dL）を超えた場合〕を繰り返し発現した場合。急性膵炎と診断された場合。

被験薬、用量及び投与方法、ロット番号：

IDegLira（Xultophy®）

1 mL あたり IDeg 100 単位とリラグルチド 3.6 mg の固定比率の配合剤、ペン型注入器（PDS290、3 mL）と一体化したプレフィルド製剤として提供された。IDegLira はメトホルミンとの併用下で検討した。

IDegLira は 1 日 1 回、毎日ほぼ同時刻に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。16 用量ステップ（IDeg：16 単位、リラグルチド：0.6 mg に相当）で投与を開始した。各用量調節日前の連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき、1 週間に 2 回用量調節を行った。朝食前血糖値 4.0～5.0 mmol/L（71～90 mg/dL）を目標として、2 用量ステップずつ用量調節を行った。最高用量は 50 用量ステップ（IDeg：50 単位、リラグルチド：1.8 mg）であった。ロット番号：CP50913。

投与期間：

26 週間

対照薬、用量及び投与方法、ロット番号：

IGlar（ランタス®）

100 単位/mL、皮下投与用ペン型注入器（ランタス®ソロスター®、3 mL）と一体化したプレフィルド製剤として提供された。試験期間を通して投与部位、投与時刻を変更せず、前治療の投与量を継続することとした。IGlar はメトホルミンとの併用下で検討した。各用量調節日前の連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき、1 週間に 2 回用量調節を行った。朝食前血糖値 4.0～5.0 mmol/L（71～90 mg/dL）を目標として、2 単位ずつ用量調節を行った。ロット番号：3F218A、3F072A、SF217A 及び SF253A。

評価基準：有効性

以下の主要な有効性に関する項目を評価した：

- HbA1cのベースラインから投与後26週までの変化量
- 体重のベースラインから投与後26週までの変化量
- 26週間の治験薬投与下で発現した確定低血糖の発現件数
- 投与後26週のインスリン投与量
- 空腹時血糖値のベースラインから投与後26週までの変化量

評価基準：安全性

以下の主要な安全性に関する項目を評価した：

- 26週間の治験薬投与下で発現した確定夜間低血糖の発現件数
- 26週間の治験薬投与下で発現した有害事象の発現件数

統計手法：

検出力の算出

- HbA1cの変化量について、IDegLiraのIGlarに対する非劣性を示すための検出力は90%であった。

解析対象集団

- 最大の解析対象集団（FAS）：無作為割り付けされたすべての被験者を含めた。例外的な場合に被験者を除外することがあった。この場合、除外する正当な理由を示し文書化することとした。FASにお

ける統計的な評価はITT（intention-to-treat）の原則に従い、被験者はas randomisedの評価に寄与した。

- Per-Protocol（PP）解析対象集団：以下の基準を満たすすべての被験者を含めた：
  - いずれの選択基準にも違反していない
  - いずれの除外基準も満たしていない
  - スクリーニング又は無作為割り付け時に非欠測のHbA1c測定値がある
  - 投与後12週の曝露で少なくとも1つの非欠測のHbA1c測定値がある
  - 少なくとも12週の曝露がある

  被験者はas treatedの評価に寄与した。無作為割り付けされた被験者のうち30例をPP解析対象集団から除外した。
- 安全性解析対象集団：治験薬を少なくとも1回投与されたすべての被験者を含めた。被験者はas treatedの評価に寄与した。
- 完了例の解析対象集団：無作為割り付けされて試験を完了したすべての被験者を含めた。被験者はas randomisedの評価に寄与した。

統計解析

- プライマリーエンドポイントであるベースラインから投与後26週までのHbA1cの変化量は、共分散分析（ANCOVA）モデルを用いて、治療及び地域を固定効果、ベースライン時のHbA1cを共変量として解析した。群差の95%信頼区間の上限が0.3%未満の場合に、IDegLiraのIGlarに対する非劣性を結論づけることとした。主要目的を達成した場合は、プライマリーエンドポイントであるHbA1cの変化量について優越性を検討することとした。同様に、検証的セカンダリーエンドポイントである体重のベースラインから投与後26週の変化量及び26週間の治験薬投与下で発現した確定低血糖の発現件数について優越性を検証した。優越性はFASを対象として検討した。検定全体の第一種の過誤は、Holm-Bonferroni法を用いて有意水準を2.5%に強く制御した。投与後26週の体重及び空腹時血糖値の変化量は、ANCOVAモデルを用いて、治療、地域を固定効果、各項目のベースライン時の値（体重及び空腹時血糖値）を共変量として解析した。26週間の治験薬投与下で発現した確定低血糖の発現件数は、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。

被験者背景：

ベースラインの被験者背景及び特性は投与群間で概ね同様であった。平均年齢は 58.8 歳、平均糖尿病罹病期間は 11.5 年、平均 BMI（kg/m2）は 31.7、ベースラインの HbA1c の平均は 8.3%であった。

人口統計学的特性及びベースライン特性−要約−FAS

	IDegLira N (%)	IGlar N (%)	Total N (%)
Number of Subjects	278	279	557
Sex			
N	278 (100.0)	279 (100.0)	557 (100.0)
Female	135 (48.6)	142 (50.9)	277 (49.7)
Male	143 (51.4)	137 (49.1)	280 (50.3)
Race			
N	278 (100.0)	279 (100.0)	557 (100.0)
White	262 (94.2)	265 (95.0)	527 (94.6)
Black or African American	6 (2.2)	5 (1.8)	11 (2.0)
Asian	9 (3.2)	9 (3.2)	18 (3.2)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Oth. Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.4)	0 (0.0)	1 (0.2)

N: number of subjects, %: percentages are based on N.

ベースライン及び糖尿病特性−要約−FAS

	IDegLira	IGlar	Total
Number of Subjects	278	279	557
Age (years)			
N	278	279	557
Mean (SD)	58.4 (9.8)	59.1 (9.3)	58.8 (9.5)
Median	59.6	59.6	59.6
Min ; Max	29.2 ; 81.7	27.6 ; 80.4	27.6 ; 81.7
BMI (kg/m^2)			
N	278	279	557
Mean (SD)	31.7 (4.4)	31.7 (4.5)	31.7 (4.5)
Median	31.8	31.6	31.6
Min ; Max	21.7 ; 40.0	18.9 ; 40.6	18.9 ; 40.6
Duration of Diabetes (years)			
N	278	279	557
Mean (SD)	11.64 (7.44)	11.33 (6.59)	11.49 (7.02)
Median	10.4	10.3	10.3
Min ; Max	0.29 ; 47.60	0.43 ; 44.64	0.29 ; 47.60
HbA1c (%)			
N	278	279	557
Mean (SD)	8.4 (0.9)	8.2 (0.9)	8.3 (0.9)
Median	8.3	8.2	8.3
Min ; Max	6.4 ; 11.6	5.9 ; 10.8	5.9 ; 11.6
FPG (mmol/L)			
N	275	278	553
Mean (SD)	8.9 (2.6)	8.9 (2.9)	8.9 (2.8)
Median	8.4	8.6	8.5
Min ; Max	3.6 ; 20.4	3.2 ; 18.7	3.2 ; 20.4

BMI: body mass index, FPG: fasting plasma glucose, N: number of subjects, SD: standard deviation.

有効性の結果：

HbA1c

HbA1c の低下量について、IDegLira の IGlar に対する優越性が検証された；群差（IDegLira-IGlar）の推定値は、-0.59%（95%信頼区間：[-0.74; -0.45]、$p < 0.001$）であった。投与後 26 週の HbA1c は、IDegLira 群では 1.81%低下し 6.6%となり、IGlar 群では 1.13%低下し 7.1%となった。

体重

体重の変化量について、IDegLira の IGlar に対する優越性が検証された；群差（IDegLira-IGlar）の推定値は、-3.20 kg（95%信頼区間：[-3.77; -2.64]、$p < 0.001$）であった。投与後 26 週の体重の変化量は、IDegLira 群で-1.4 kg、IGlar 群で+1.8 kg であった。

確定低血糖

確定低血糖の発現件数について、IDegLira の IGlar に対する優越性が検証された；比（IDegLira/IGlar）の推定値は、0.43（95%信頼区間：[0.30; 0.61]、$p < 0.001$）であった。26 週間の確定低血糖を発現した被験者の割合は、IDegLira 群で 28.4%（223.0 件／100 人・年）、IGlar 群で 49.1%（505.4 件／100 人・年）であった。

インスリン投与量

投与後 26 週の 1 日インスリン投与量は、IGlar 群と比較して IDegLira 群で統計的に有意に少なかった；群差（IDegLira-IGlar）の推定値は、-25.47 単位（95%信頼区間：[-28.90; -22.05]、$p < 0.001$）であった。試験期間中の 1 日インスリン投与量は、IDegLira 群で 17 単位から 41 単位に増加し、IGlar 群で 32 単位から 66 単位に増加した。

空腹時血糖値

試験期間中の空腹時血糖値は、IDegLira 群と IGlar 群で同程度低下した。IDegLira 群で 8.9 mmol/L（160.5 mg/dL から 6.1 mmol/L（109.5 mg/dL）に低下し、IGlar 群で 8.9 mmol/L（159.8 mg/dL）から 6.1 mmol/L

（110.2 mg/dL）に低下した。投与後 26 週の空腹時血糖値の変化量について、IDegLira 群と IGlar 群の間に統計的に有意な差はなかった。

安全性の結果：

全般的な有害事象プロファイル（低血糖以外）

- 試験期間中にIGlar群で1件の死亡（出血性卒中）が報告された。本事象はイベント判定委員会により心血管死に分類され、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。
- 有害事象の単位時間あたりの発現件数は、IDegLira群で343.3件／100人・年、IGlar群で286.4件／100人・年であった。有害事象の大部分は非重篤、軽度、一時的な事象であり、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。
- 最も高頻度に報告された有害事象は、IDegLira群で胃腸障害（悪心、下痢及び嘔吐）、IGlar群で頭痛であった。
- 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の単位時間あたりの発現件数は、IDegLira群で95.7件／100人・年、IGlar群で10.4件／100人・年であった。この差は、主に胃腸障害の有害事象に起因するものであった（IDegLira群：55.6 件／100人・年、IGlar群：1.5件／100人・年）。
- 試験期間中に、14例で14件の重篤な有害事象が報告された（IDegLira群：5例5件、IGlar群：9例9件）。IGlar群で発現した1件の重篤な有害事象（低血糖）は、治験薬との因果関係が「可能性あり」と判定された。試験期間中に2件の非治験薬投与下で発現した重篤な有害事象が報告された。
- 8例（IDegLira群：7例、IGlar群：1例）が有害事象により試験を中止した。IDegLira群で認められた試験の中止に至った有害事象は、主に胃腸障害の有害事象であった。またIDegLira群において、非治験薬投与下において試験の中止に至った有害事象が2件報告された。

注目すべき安全性領域の有害事象

- 4件の有害事象（IDegLira群：1件、IGar群：3件。いずれも治験薬との因果関係は「なし」と判定された）がイベント判定委員会により心血管系事象と確定された；そのうち2件は主要な心血管イベント（MACE）と判定された（各投与群1件）
- イベント判定委員会により確定された膵炎の事象はなかった。
- 2件の治験薬投与下で発現した有害事象（腎腺癌及び前立腺癌）及び1件の非治験薬投与下で発現した有害事象（遠隔転移を伴う膵癌）がイベント判定委員会により新生物と確定された（いずれの事象もIDegLira群、治験薬との因果関係は「なし」と判定された）。3件のいずれも悪性と分類された。
- 2件の甲状腺に関連する有害事象（IDegLira群：1件、IGlar群：1件）がイベント判定委員会に送られたが、甲状腺新生物と判定された事象はなかった。
- カルシトニン増加に関連する有害事象の報告はなかった。
- 14例18件のリパーゼ増加又はアミラーゼ増加の有害事象が特定された（IDegLira群：9例12件、IGlar群：5例6件）。いずれの事象も非重篤であった。
- 14例19件のアレルギー反応に関連する有害事象が特定された（IDegLira群：7例12件、IGlar群：7例7件）。いずれの事象も非重篤であった。
- 3例14件の注射部位反応が特定された（IDegLira群：1例11件、IGlar群：2例3件）。いずれの事象も非重篤であった。
- 97例199件の胃腸障害の有害事象が報告された（IDegLira群：70例153件、IGlar群：27例46件）。いずれの事象も非重篤であり、事象の大部分は軽度であった。
- 注目すべき安全性領域として事前に規定した、腎機能の悪化、稀な事象及び高血糖に該当する有害事象はほとんど報告されなかった。

低血糖

- 確定低血糖の単位時間あたりの発現件数は、IDegLira群で223.0件／100人・年、IGlar群で505.4件／100人・年であった。IGlar群において1例の被験者が重大な低血糖を発現した。
- 確定夜間低血糖の単位時間あたりの発現件数は、IDegLira群で22.4件／100人・年、IGlar群で122.8件／100人・年であった。比（IDegLira/IGlar）の推定値は、0.17（95%信頼区間：[0.10; 0.31]、$p < 0.001$）

であり、確定夜間低血糖の単位時間あたりの発現件数はIGlar群と比較してIDegLira群で統計的に有意に少ないことが示された。

臨床検査評価

- 血液学的検査又は血液生化学的検査のパラメータについては、いずれの投与群においてもベースラインから投与終了時までに臨床的に問題のある変化は認められなかった。
- IDegLira群では、ベースラインから投与終了時までにリパーゼは17.6 U/L増加し、アミラーゼは10.7 U/L増加したが、すべての平均値が基準範囲内であった。
- カルシトニンについては、臨床的に問題となる群間の違いは認められなかった。

身体所見、眼底検査／眼底写真、心電図及びバイタルサイン

- 投与後26週の脈拍数は、IGlar群と比較してIDegLira群で統計的に有意に高かった〔群差の推定値：3.71拍／分（95%信頼区間：[2.33; 5.08]、$p < 0.001$）〕。
- 投与後26週の身体所見、眼底検査／眼底写真又は心電図の結果については、臨床的に問題となる群間の違いは認められなかった。

全体の結論：

IGlar 及びメトホルミンとの併用療法で十分な血糖コントロールが得られていない 2 型糖尿病患者を対象として、メトホルミンに加えて投与した IDegLira と IGlar の比較検討を行う 26 週間の本試験の結果より、以下の結論が得られた：

- ベースラインから投与後26週までのHbA1cの変化量について、IDegLiraのIGlarに対する優越性が検証された。
- ベースラインから投与後26週までの体重の変化量について、IDegLiraのIGlarに対する優越性が検証された。
- 確定低血糖の発現件数について、IDegLiraのIGlarに対する優越性が検証された。
- 投与後26週の1日総インスリン投与量は、IGlarと比較してIDegLiraで少なかった。
- 空腹時血糖値は、IDegLiraとIGlarで同程度低下した。
- IGlarからの切り替え時のIDegLiraの忍容性は高かった
- IDegLira群で非重篤な胃腸障害の有害事象の単位時間あたりの発現件数が多かったことを除いて、全般的な重篤な有害事象の単位時間あたりの発現件数は2つの投与群で同程度であった。

本試験は、ヘルシンキ宣言（59th WMA assembly, Oct 2008）の精神及び ICH-GCP（May 1996）ならびに FDA 21 CFR 312.120 を遵守して実施された。

2.7.6.12. NN9068-4119

2.7.6.12.1 臨床試験概要

治験依頼者名： Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark	
有効成分名： インスリン デグルデク／リラグルチド インスリン アスパルト	
Trial Registration ID-number： NCT02100475	UTN：U1111-1145-0183 IND number：109121 EudraCT number：2013-002878-47
治験の標題： インスリン デグルデク／リラグルチド及びメトホルミンによる治療後にさらなる治療の強化が必要な 2 型糖尿病患者を対象とした、インスリン アスパルトの段階的な追加と、インスリン デグルデク／リラグルチドの増量を比較する試験（DUAL™ - Intensification）	
治験責任医師名： 治験実施施設（19 施設）ごとに 1 名の治験責任医師が任命された。以下の治験責任医師が治験総括報告書の内容を確認し、署名する「治験総括報告書への署名責任を有する医師（Signatory Investigator）」に任命された： [redacted]	
治験実施施設： 以下の 8 ヵ国 19 施設において本試験が実施された：アルゼンチン（2 施設）、ギリシャ（2 施設）、ハンガリー（1 施設）、ロシア（5 施設）、スロバキア（4 施設）、南アフリカ共和国（1 施設）、スペイン（1 施設）及び米国（3 施設）	
公表文献（引用文献）： 本治験総括報告書作成時点での公表文献はなし	
治験期間： 開始日：2014 年 4 月 3 日 終了日：2015 年 4 月 27 日	**開発のフェーズ**： 第 3b 相
Cut-off date： ここに提示する結果は、2015 年 5 月 20 日の時点での臨床データベースに基づいている。	
報告書作成日： 2015 年 10 月 8 日	
目的： <u>主要目的</u>： • 血糖コントロールを指標とした有効性について、メトホルミン併用下において、インスリン デグルデク／リラグルチド（IDegLira）の最高用量を80用量ステップまで用量調節したときと、最高用量50用量ステップまでのIDegLiraにインスリン アスパルト（IAsp）を追加したときを比較し、探索的に検討する。	

副次的目的：
- 血糖コントロールに関する他の項目を指標とした有効性、安全性及び患者報告アウトカム（PRO）について、メトホルミン併用下において、80用量ステップまでのIDegLiraと、IDegLiraにIAspを追加したときを比較し、探索的に検討する。

治験方法：
本試験は、3952 試験（DUAL™ - V）での 26 週間の IDegLira の投与で十分な血糖コントロールを得られなかった 2 型糖尿病患者を対象とした、IDegLira を用いた 2 種類の強化した治療を比較する、26 週間、無作為割り付け、比較対照、非盲検、多施設、国際共同、treat-to-target、2 群間比較試験であった。2 種類の強化した治療とは、IDegLira の最高用量を 80 用量ステップまでとする治療法と、最高用量 50 用量ステップの IDegLira に IAsp を追加する治療法であった。被験者 31 例を IDegLira 群（16 例）及び IDegLira+IAsp 群（15 例）に無作為割り付けした。IDegLira は患者ごとに treat-to-target 法を用いて 1 日 1 回投与した。いずれの投与群においても、IDegLira は空腹前血糖値 4.0～5.0 mmol/L（71～90 mg/dL）を目標とした投与量調節アルゴリズムに従い、被験者ごとに用量調節を行った。IDegLira の最高用量は、IDegLira 群で 80 用量ステップ（IDeg：80 単位、リラグルチド：2.9 mg）、IDegLira+IAsp 群では 50 用量ステップ（IDeg：50 単位、リラグルチド：1.8 mg）とした。IDegLira+IAsp 群の被験者は、IAsp の投与を主たる食事の直前（開始用量 4 単位）から開始した。各被験者は食前又は就寝前血糖値（いずれも血糖自己測定による）4.0～6.0 mmol/L（71～108 mg/dL）を目標値として、目標値より高い血糖値が 0～1 回、目標値より低い血糖値が 0 回となるように投与量調節アルゴリズムに従い用量調節を行った。投与後 8 週及び投与後 16 週に HbA1c 7%未満を達成できなかった被験者は、主たる食事以外の食事時に IAsp の 2 回目及び 3 回目の Bolus 投与を追加した。治験責任医師の判断により、さらに 1 回 IAsp の投与追加を可能とした。

計画及び解析された被験者数：
DUAL™ - V 試験で IDegLira の約 26 週間の投与を受け、投与期間終了時に HbA1c 7%以上であった被験者のみを本試験の適格例とした。

被験者内訳－要約

	IDegLira N (%)	IDegLira + IAsp N (%)	Total N (%)
Screened			54
Screening Failures			23
Withdrawn before Randomisation			0
Randomised	16 (100.0)	15 (100.0)	31 (100.0)
Exposed	16 (100.0)	15 (100.0)	31 (100.0)
Withdrawn at/after Randomisation	2 (12.5)	2 (13.3)	4 (12.9)
Withdrawal Criteria	1 (6.3)	0 (0.0)	1 (3.2)
Other	1 (6.3)	2 (13.3)	3 (9.7)
Completed	14 (87.5)	13 (86.7)	27 (87.1)
Full analysis set	16 (100.0)	15 (100.0)	31 (100.0)
Per Protocol analysis set	14 (87.5)	13 (86.7)	27 (87.1)
Safety analysis set	16 (100.0)	15 (100.0)	31 (100.0)

診断及び主要な組入れ基準：
主な選択基準
性別不問、年齢 18 歳以上の 2 型糖尿病患者で、IDegLira 及びメトホルミンによる治療を実施した DUAL™ - V 試験を完了し、DUAL™ - V 試験の来院 27 で HbA1c 7%以上であった被験者。

主な除外基準

主要な器官系において臨床的に重大な疾患を有する被験者。スクリーニング時のカルシトニン濃度が 50 ng/L 以上である被験者。治療の有無に関わらず十分なコントロールが得られていない重度の高血圧症（収縮期血圧 180 mmHg 以上又は拡張期血圧 100 mmHg 以上。アルゼンチンのみ収縮期血圧 150 mmHg 以上又は拡張期血圧 90 mmHg 以上）を有する被験者。

主な中止・脱落基準

糖代謝に影響を及ぼすと考えられる薬剤の全身投与を開始する場合（治験責任医師の判断による）。被験者が妊娠した又は妊娠を希望する場合。高血糖〔血糖自己測定による連続した 3 日間の血糖値又は中央測定機関で評価した空腹時血糖値が 11.1 mmol/L（200 mg/dL）を超えた場合〕を繰り返し発現し、その原因となる併発疾患が特定されない場合。急性膵炎と診断された場合。

被験薬、用量及び投与方法、ロット番号：

IDegLira（Xultophy®）

1 mL あたり IDeg 100 単位とリラグルチド 3.6 mg の固定比率の配合剤、ペン型注入器（PDS290、3 mL）と一体化したプレフィルド製剤として提供された。試験期間中 IDegLira は 1 日 1 回、毎日ほぼ同時刻に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。被験者は 3952 試験で IDegLira を投与した時刻と同じ時刻にそれぞれ投与することとした。選択した投与部位（大腿部、上腕部又は腹部）は試験期間中変更しないが、その部位内で異なる箇所に投与することが推奨された。IDegLira の投与量は 3592 試験の来院 28 で投与した用量から開始した。IDegLira の用量を最適化して治療を強化する群に割り付けられた被験者では、IDegLira の最高用量は 80 用量ステップ（IDeg：80 単位、リラグルチド：2.9 mg）とした。IDegLira に IAsp の投与（1～3 回）を追加して治療を強化する群に割り付けられた被験者では、IDegLira の最高用量は 50 用量ステップ（IDeg：50 単位、リラグルチド 1.8 mg）とした。ロット番号：DP50044。

IAsp（NovoRapid®/NovoLog®）

1 mL あたり 100 単位、ペン型注入器（FlexPen®、3 mL）と一体化したプレフィルド製剤として提供された。IDegLira に食事時の IAsp の投与を段階的（1～3 回）に追加して治療を強化する群に割り付けられた被験者は、来院 2 で、主たる食事の直前に IAsp 4 単位を追加投与した。投与後 8 週及び投与後 16 週において HbA1c 7%未満を達成できなかった被験者は、主たる食事以外の食事時に、それぞれ IAsp の 2 回目及び 3 回目の追加投与を受けた。IAsp には最高用量を規定しなかった。治験責任医師の判断により、さらに 1 回 IAsp の投与追加を可能とした。体重の少ない被験者は 1 回の食事につき 0.05 単位/kg 又は 2～3 単位に相当する低用量の IAsp から投与を開始することが可能であった。ロット番号：CP52218。

投与期間：

26 週間

対照薬、用量及び投与方法、ロット番号：

IAsp（NovoRapid®/NovoLog®）上記参照

評価基準：**有効性**

- HbA1c
- インスリン投与量
- 体重
- 空腹時血糖値
- 血糖自己測定による血糖値
  - 9点血糖値プロファイル
  - 食後血糖増加量
- 空腹時脂質
  - 総コレステロール
  - 高比重リポタンパク質コレステロール（HDL）
  - 低比重リポタンパク質コレステロール（LDL）
  - 超低比重リポタンパク質コレステロール（VLDL）

– トリグリセリド – 遊離脂肪酸
評価基準：安全性 • 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低血糖 • 臨床検査評価（身体検査、バイタルサイン、心電図及び眼底検査／眼底写真） • 安全性に関する臨床検査項目（血液学的検査、血液生化学的検査及び尿検査）
統計手法： 検出力の算出 本試験の症例数は 3952 試験から移行した被験者数により決定した。3952 試験で IDegLira の約 26 週間の投与を完了し、投与期間終了時に HbA1c 7%以上であった被験者のみを本試験の適格例とした。 解析対象集団 • 最大の解析対象集団（FAS）：無作為割り付けされたすべての被験者を含めた。FASにおける統計的な評価はITT（intention-to-treat）の原則に従い、被験者はas randomisedの評価に寄与した。 • Per-Protocol（PP）解析対象集団：以下の基準を満たすFASのすべての被験者を含めた： – いずれの選択基準にも違反していない – いずれの除外基準も満たしていない – 無作為割り付け時にHbA1c測定値がある – 12週の曝露後に少なくとも1回のHbA1c測定値がある – 少なくとも12週の曝露がある 被験者はas treatedの評価に寄与した。計4例の無作為割り付けされた被験者をPP解析対象集団から除外した。 • 安全性解析対象集団（SAS）：被験薬又は対照薬を少なくとも1回投与されたすべての被験者を含めた。被験者はas treatedの評価に寄与した。 • 完了例の解析対象集団（CAS）：無作為割り付けされて試験を完了したすべての被験者を含めた。被験者はas randomisedの評価に寄与した。 統計解析 IDegLira50 用量ステップ未満で十分な血糖コントロールを得られなかった被験者及び IDegLira50 用量ステップで十分な血糖コントロールを得られなかった被験者ごとに層別割り付けを行った。プライマリーエンドポイントであるベースラインから投与後 26 週までの HbA1c の変化量は、共分散分析（ANCOVA）モデルを用いて、治療及びベースライン時の IDegLira 用量の層を固定効果、ベースライン時の HbA1c を共変量として解析した。ベースラインから投与後 26 週までの体重、空腹時血糖値及び他の連続変数は、ベースライン時の値を共変量として、同様の ANCOVA モデルを用いて解析した。無作為割り付けから投与後 26 週間までの治験薬投与下で発現した確定低血糖の発現件数は、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。このモデルでは、治療及びベースライン時の IDegLira 用量の層を固定効果として含めた。

被験者背景：
ベースラインの被験者背景及び特性は投与群間で概ね同様であった。平均年齢は 57.4 歳、平均糖尿病罹病期間は 10.35 年、平均 BMI（kg/m^2）は 32.6、ベースラインの HbA1c の平均は 7.6%であった。

人口統計学的特性、ベースライン特性及び糖尿病特性 - 要約 - FAS

	IDegLira N	IDegLira + IAsp N	Total N
Number of Subjects	16	15	31
Sex			
N (%)	16 (100.0)	15 (100.0)	31 (100.0)
Female (%)	9 (56.3)	8 (53.3)	17 (54.8)
Male (%)	7 (43.8)	7 (46.7)	14 (45.2)
Age (years)			
N	16	15	31
Mean (SD)	57.3 (11.7)	57.4 (11.2)	57.4 (11.3)
Median	60.6	62.7	60.8
Min ; Max	32.7 ; 76.7	35.5 ; 70.3	32.7 ; 76.7
BMI (kg/m^2)			
N	16	15	31
Mean (SD)	33.2 (3.6)	32.0 (4.2)	32.6 (3.9)
Median	33.6	33.3	33.3
Min ; Max	26.7 ; 38.8	24.5 ; 38.4	24.5 ; 38.8
Duration of Diabetes (years)			
N	16	15	31
Mean (SD)	10.32 (6.25)	10.37 (5.97)	10.35 (6.02)
Median	8.7	9.2	8.9
Min ; Max	3.22 ; 24.71	2.19 ; 22.27	2.19 ; 24.71
HbA1c (%)			
N	16	15	31
Mean (SD)	7.6 (0.9)	7.7 (0.7)	7.6 (0.8)
Median	7.3	7.5	7.4
Min ; Max	6.7 ; 10.3	6.9 ; 9.5	6.7 ; 10.3
FPG (mmol/L)			
N	16	14	30
Mean (SD)	7.5 (2.2)	6.8 (1.2)	7.2 (1.8)
Median	7.4	7.0	7.2
Min ; Max	3.4 ; 12.3	5.3 ; 9.7	3.4 ; 12.3

N: Number of subjects; %: Percentages are based on N; SD: Standard deviation
BMI: Body mass index, FPG: Fasting plasma glucose

有効性の結果：
被験者数が少ないため、結果の解釈には注意が必要である。
最高用量 80 用量ステップの IDegLira による治療の強化（IDegLira 群）又は最高用量 50 用量ステップの IDegLira に IAsp を追加した治療の強化（IDegLira+IAsp 群）における、投与後 26 週の結果は以下のとおり：

プライマリーエンドポイント：

HbA1c

投与後 26 週の HbA1c は、IDegLira 群で 7.6%から 7.2%に、IDegLira+IAsp 群で 7.7%から 7.5%に低下した。投与後 26 週の HbA1c の変化量に群間で有意差はみられなかった。群差の推定値は-0.30%（95%信頼区間：[−1.05; 0.46]）であった。

補足的セカンダリーエンドポイント：

インスリン投与量

投与後 26 週の総インスリン投与量は、2 つの投与群で同様（66 単位）であった。総インスリン投与量は、ベースライン時点では 2 つの投与群で同程度（IDegLira 群で 48 単位、IDegLira+IAsp 群で 47 単位）であり、いずれの投与群でもベースラインから経時的に増加した。

体重

体重はいずれの投与群でも試験期間中に増加した。ベースライン時の体重は、IDegLira 群で 94.3 kg（207.8 lb）、IDegLira+IAsp 群で 91.0 kg（200.7 lb）であった。投与後 26 週の体重は、IDegLira 群で 95.1 kg（209.7 lb）、IDegLira+IAsp 群で 92.5 kg（203.9 lb）であった。ベースラインからの体重の変化量は、2 つの投与群で同程度であり、IDegLira 群と IDegLira+IAsp 群の差の推定値は-0.58 kg（95%信頼区間：[−2.59; 1.44]）〔−1.3 lb（95%信頼区間：[−5.7; 3.2]）〕、p=0.562 であった。

空腹時血糖値

投与後 26 週の空腹時血糖値は、IDegLira 群では 7.5 mmol/L（135.6 mg/dL）から 6.8 mmol/L（121.8 mg/dL）に低下し、IDegLira+IAsp 群では 6.8 mmol/L（122.4 mg/dL）から 7.8 mmol/L（141.4 mg/dL）に上昇した。空腹時血糖値のベースラインからの変化量に、IDegLira 群と IDegLira+IAsp 群の間に統計的な有意差が認められた。IDegLira 群と IDegLira+IAsp 群の差の推定値は−1.43 mmol/L（95%信頼区間：[−2.76; −0.09]）〔−25.70 mg/dL（95%信頼区間：[−49.77; −1.63]）〕、p=0.037 であった。

安全性の結果：

被験者数が少ないため、結果の解釈には注意が必要である。

検討した各領域における安全性の結果を以下に要約する：

全般的な有害事象プロファイル（低血糖以外）

- 本試験で死亡は報告されなかった。
- 有害事象の単位時間あたりの発現件数は、IDegLira群で276.0件／100人・年、IDegLira+IAsp群で189.8件／100人・年であった。有害事象の大部分は非重篤、軽度の事象であり、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。
- 最も高頻度に報告された有害事象（基本語）はリパーゼ増加及び背部痛（各投与群1例1件）、歯の障害（IDegLira群で1例2件）であった。これらの事象以外に2回以上報告された基本語はなかった。
- 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」と判定された有害事象の単位時間あたりの発現件数は、IDegLira群で27.6件／100人・年、IDegLira+IAsp群で14.6件／100人・年であった。主な事象はリパーゼ増加であった（各投与群1件）。
- 試験期間中、3例4件の重篤な有害事象が報告された（IDegLira群で1例2件、IDegLira+IAsp群で2例2件）。治験責任医師により治験薬との因果関係「あり」又は「可能性あり」と判定された事象はなかった。
- 有害事象により試験を中止した被験者はいなかった。しかしながら、慢性骨髄性白血病が疑われた被験者1例が、「試験結果に影響を与える可能性がある臨床的に重大な疾患の疑い」があるとして試験を中止した。該当被験者は、試験終了後に慢性骨髄性白血病の診断が確定した。

注目すべき安全性領域の有害事象

- 1件の重篤な有害事象（IDegLira群、冠動脈血行再建）がイベント判定委員会により心血管系事象として確定されたが、主要な心血管イベント（MACE）ではなかった。本事象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。
- 膵炎又は膵炎の疑いのある有害事象は認められなかった。

- 3例3件のリパーゼ／アミラーゼ増加が特定された（IDegLira群で1例1件、IDegLira+IAsp群で2例2件）。いずれの事象も軽度で、非重篤であった。リパーゼ増加の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「あり」又は「可能性あり」と判定された。アミラーゼ増加の事象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。
- 1件の治験薬投与下に発現した有害事象（IDegLira+IAsp群、慢性骨髄性白血病）がイベント判定委員会により新生物として確定された。本事象は悪性と分類され、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。
- 1件の甲状腺に関連する有害事象（IDegLira群、血中カルシトニン増加）が特定された。本事象は軽度、非重篤であり、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。
- 1件の重篤な有害事象（IDegLira+IAsp群、腎不全）が報告された。本事象は中等度であり、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。
- 2例4件の胃腸障害の有害事象が報告された（IDegLira群で1例2件、IDegLira+IAsp群で1例2件）。いずれの事象も非重篤で軽度であった。悪心の事象は報告されなかった。

<u>低血糖</u>

- 重大な低血糖は報告されなかった。
- 確定低血糖の単位時間あたりの発現件数（及び発現した被験者の割合）は、IDegLira群で469.2件／100人・年（12.5%）、IDegLira+IAsp群で58.4件／100・人・年（13.3%）であった。IDegLira群とIDegLira+IAsp群の比の推定値は0.3（95%信頼区間：[0.0; 30.5]）、p=0.596であった。
- IDegLira群で1例4件の夜間低血糖が報告された。

<u>臨床検査評価</u>

- 血液学的検査又は血液生化学的検査のパラメータについては、いずれの投与群においてもベースラインから投与終了時までに臨床的に問題となる変化は認められなかった。
- 高値を報告した数例の被験者による平均値への影響は大きかったが、いずれの群でもリパーゼの推移に明らかな傾向はみられなかった。リパーゼのベースラインから投与後26週までの変化量はIDegLira群で+0.6 U/L、IDegLira+IAsp群で-6.1 U/Lあった。
- いずれの投与群においてもアミラーゼは試験期間中概ね一定であった。ベースラインから投与後26週までの変化量はIDegLira群で+1.1 U/L、IDegLira+IAsp群で-2.3 U/Lであった。
- カルシトニンについては、臨床的に問題となる群間の違いは認められなかった。

<u>身体所見、眼底検査／眼底写真、心電図及びバイタルサイン</u>

- ベースラインから投与後26週までの脈拍数の変化量は、IDegLira群で+0.8拍／分、IDegLira+IAsp群で-0.9拍／分であった。
- 投与後26週の身体所見、眼底検査／眼底写真又は心電図の結果については、臨床的に問題となる群間の違いは認められなかった。

全体の結論：
被験者数が少ないため、結果の解釈には注意が必要である。
DUAL™ - V 試験において IDegLira で十分な血糖コントロールが得られなかった 2 型糖尿病患者を対象として、メトホルミン併用下で、最高用量 80 用量ステップの IDegLira による治療の強化と、最高用量 50 用量ステップの IDegLira に IAsp を追加する治療の強化を比較した、26 週間の延長試験の結果より、以下の結論が得られた：

- HbA1cの低下量は、IDegLira（最高用量80用量ステップ）とIDegLira+IAspで同程度であった。
- 体重の増加量は、IDegLira（最高用量80用量ステップ）とIDegLira+IAspで同程度であった。
- 空腹時血糖値の低下量は、IDegLira+IAspと比較してIDegLira（最高用量80用量ステップ）で統計的に有意に大きかった。
- 確定低血糖は、IDegLira+IAspと比較してIDegLira（最高用量80用量ステップ）で多く報告された。しかしながら、統計的に有意な群間の違いはみられず、2つの投与群において確定低血糖を発現した被験者数は同じであった。
- IDegLira（最高用量80用量ステップ）又はIDegLira+IAspのいずれにおいても、明らかな、又は予測されないような、安全性及び忍容性の問題は認められなかった。

本試験は、ヘルシンキ宣言（Soul、2008）の精神、ICH-GCP 及び FDA 21 CFR 312.120 を遵守して実施された。

2.7.6.13 NN9068-4056

2.7.6.13.1 臨床試験概要

治験依頼者名： Novo Nordisk, Novo Allé, DK-2880 Bagsvaerd, Denmark	
有効成分名： インスリン デグルデク／リラグルチド	
Trial Registration ID-number： NCT02298192	UTN：U1111-1135-6634 IND number：109121 EudraCT number：2012-004625-25
治験の標題： DUAL™ VI - 簡便な投与量調節：2 型糖尿病患者を対象として、2 種類の投与量調節アルゴリズムを用いた、インスリン デグルデク／リラグルチド（IDegLira）の有効性及び安全性を比較する臨床試験	
治験責任医師名： 治験実施施設（80 施設）ごとに 1 名の治験責任医師が任命された。以下の治験責任医師が治験総括報告書の内容を確認し、署名する「治験総括報告書への署名責任を有する医師（Signatory Investigator）」に任命された。 Dr. [redacted]	
治験実施施設： 本試験は 9 ヵ国 80 施設において実施した：オーストリア（6 施設）、ブルガリア（5 施設）、カナダ（7 施設）、チェコ共和国（5 施設）、ハンガリー（4 施設）、ロシア（6 施設）、セルビア（4 施設）、スロバキア（7 施設）及び米国（36 施設）	
公表文献（引用文献）： 本治験総括報告書作成時点でなし	
治験期間： 開始日：2014 年 11 月 21 日 終了日：2015 年 12 月 23 日	**開発のフェーズ**： 第 3b 相
Cut-off date： ここに提示する結果は、2016 年 2 月 5 日の時点での臨床データベースに基づいている。	
報告書作成日： 2016 年 6 月 15 日	
目的： <u>主要目的</u>： • インスリン治療歴がなく、メトホルミン単剤、又はメトホルミンとピオグリタゾンの併用療法で十分な血糖コントロールが得られていない2型糖尿病患者を対象として、1週間に1回の投与量調節アルゴリズムを使用して投与したときのIDegLiraの血糖コントロールにおける有効性を検証する。 これは、HbA1cのベースラインから投与後32週までの変化量について、週1回の投与量調節法と週2回の投与量調節法で比較することにより行う（非劣性マージン0.30%）。 <u>副次的目的</u>： • 投与後32週における血糖コントロールに関する有効性（HbA1c以外）及び安全性について、週1回の投与量調節法と週2回の投与量調節法で比較する。	
治験方法： 本試験は、メトホルミン単剤、又はメトホルミンとピオグリタゾンの併用療法で十分な血糖コントロール	

が得られていない 2 型糖尿病患者を対象として IDegLira の 2 種類の投与量調節アルゴリズムを比較した、32 週間、無作為割り付け、非盲検、国際共同、多施設、2 群並行、treat-to-target 試験であった。HbA1c 7.0%（53 mmol/mol）以上 10.0 %（86 mmol/mol）以下を「十分な血糖コントロールが得られていない」と定義した。被験者は、メトホルミン又はメトホルミン＋ピオグリタゾン併用下で、IDegLira を 1 週間に 1 回（IDegLira 1WT 群）又は 2 回（IDegLira 群）投与量の調節を行い、1 日 1 回の投与を受けた。適格例を IDegLira 1WT 群又は IDegLira 群のいずれかに 1：1 の割合で無作為に割り付けた。いずれの投与群でも 10 用量ステップ〔インスリン デグルデク（IDeg）：10 単位、リラグルチド：0.36 mg〕で投与を開始した。朝食前血糖値 4.0～5.0 mmol/L（71～90 mg/dL）を目標として treat-to-target 法を用いて投与量を調節した。事前に規定した投与量調節アルゴリズムに従い、IDegLira 1WT 群では各投与量調節日前の連続した 2 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき週 1 回投与量調節を行い、IDegLira 群では各投与量調節日前の連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき週 2 回投与量調節を行った。IDegLira の最高用量は 50 用量ステップ（IDeg：50 単位、リラグルチド：1.8 mg）とした。

計画及び解析された被験者数：

計画された被験者数は 416 例（IDegLira 1WT 群又は IDegLira 群に 1:1 の割合で無作為割り付け）であった。

被験者内訳 - 要約

	IDegLira 1WT N (%)	IDegLira N (%)	Total N (%)
Screened			613
Screening failures			193
Withdrawn before Randomisation			0
Randomised	210 (100.0)	210 (100.0)	420 (100.0)
Exposed	209 (99.5)	210 (100.0)	419 (99.8)
Withdrawn at/after Randomisation	19 (9.0)	6 (2.9)	25 (6.0)
Adverse event	6 (2.9)	2 (1.0)	8 (1.9)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	2 (1.0)	1 (0.5)	3 (0.7)
Withdrawal by subject	6 (2.9)	1 (0.5)	7 (1.7)
Withdrawal criteria	2 (1.0)	0 (0.0)	2 (0.5)
Other	3 (1.4)	2 (1.0)	5 (1.2)
Completed	191 (91.0)	204 (97.1)	395 (94.0)
Full analysis set	210 (100.0)	210 (100.0)	420 (100.0)
PP analysis set	198 (94.3)	207 (98.6)	405 (96.4)
Safety analysis set	209 (99.5)	210 (100.0)	419 (99.8)

N: Number of subjects, %: Proportion of randomised subjects

診断及び主要な組入れ基準：

主な選択基準：

性別不問、年齢 18 歳以上の 2 型糖尿病患者。HbA1c 7.0%（53 mmol/mol）以上 10.0%（86 mmol/mol）以下、かつ BMI（kg/m^2）40 以下の被験者。スクリーニングの 90 日以上前から安定した 1 日投与量でのメトホルミン（1500 mg 以上又は最大耐用量）±ピオグリタゾン（30 mg 以上）による糖尿病治療を受けている被験者。

主な除外基準：

スクリーニング来院（来院 1）前 30 日以内に何らかの治験薬の投与を受けた被験者。何らかの糖尿病治療薬（メトホルミン及びピオグリタゾンを除く）の投与を現在受けている又は併用薬剤の変更が予測され、治験責任医師により糖代謝に影響を及ぼすと判断された被験者（副腎皮質ステロイド剤の全身投与等）。インスリン治療歴がある、もしくは現在インスリンの投与を受けている被験者（ただし、妊娠糖尿病を含む併発疾患のための短期間のインスリン投与については、治験責任医師の判断により可とする）。スクリ

ーニング来院前 90 日以内にグルカゴン様ペプチド-1（GLP-1）受容体作動薬、スルホニルウレア薬（SU）、グリニド、ジペプチジルペプチダーゼ 4 阻害薬（DPP-4 阻害薬）又はナトリウム-グルコース共輸送体 2 阻害薬（SGLT-2 阻害薬）の投与を受けた被験者。ピオグリタゾンを使用している場合、臨床的に問題となる末梢性浮腫を発現している被験者又はピオグリタゾンの禁忌／使用制限に該当する被験者。肝機能障害（アラニンアミノトランスフェラーゼが基準範囲上限の 2.5 倍位以上）を有する被験者。腎機能障害〔血清クレアチニンが男性で 133 µmol/L（1.5 mg/dL）以上、女性で 125 µmol/L（1.4 mg/dL）以上、又はメトホルミンの禁忌に該当する〕を有する被験者。スクリーニング時のカルシトニン濃度が 50 ng/L 以上である被験者。本人又は家族が甲状腺髄様癌又は多発性内分泌腫瘍症候群 2 型の既往歴を有する被験者。慢性膵炎又は急性膵炎の既往歴を有する被験者。

主な中止・脱落基準：

糖代謝に影響を及ぼすと考えられる薬剤（副腎皮質ステロイド剤等）の全身投与を開始する場合（治験責任医師の判断による）。被験者が妊娠した又は妊娠を希望する場合。高血糖〔空腹時血糖値が、ベースライン～投与後 12 週：15.0 mmol/L（270 mg/dL）、投与後 12 週～20 週：13.3 mmol/L（240 mg/dL）、投与後 20 週～32 週：11.1 mmol/L（200 mg/dL）を超えた場合〕を繰り返し発現した場合。急性膵炎と診断された場合又は治験責任医師により急性膵炎が疑われる場合。

被験薬、用量及び投与方法、ロット番号：

IDegLira 1WT（Xultophy®）

1 mL あたり IDeg 100 単位とリラグルチド 3.6 mg の固定比率の配合剤、ペン型注入器（PDS290、3 mL）と一体化したプレフィルド製剤として提供された。IDegLira 1WT はメトホルミン±ピオグリタゾンとの併用下で検討した。IDegLira 1WT 群では 1 日 1 回、毎日ほぼ同時刻に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。10 用量ステップ（IDeg：10 単位、リラグルチド：0.36 mg に相当）で投与を開始した。各投与量調節日前の連続した 2 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき、1 週間に 1 回投与量調節を行った。朝食前血糖値 4.0～5.0 mmol/L（71～90 mg/dL）を目標として、2 用量ステップずつ投与量調節を行った。最高用量は 50 用量ステップ（IDeg：50 単位、リラグルチド：1.8 mg）であった。ロット番号：DP52017、DP52024、DP52026 及び DP52027

投与期間：

投与期間は 32 週間であった。

対照薬、用量及び投与方法、ロット番号：

IDegLira （Xultophy®）

1 mL あたり IDeg 100 単位とリラグルチド 3.6 mg の固定比率の配合剤、ペン型注入器（PDS290、3 mL）と一体化したプレフィルド製剤として提供された。IDegLira はメトホルミン±ピオグリタゾンとの併用下で検討した。IDegLira 群では 1 日 1 回、毎日ほぼ同時刻に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。10 用量ステップ（IDeg：10 単位、リラグルチド：0.36 mg に相当）で投与を開始した。各投与量調節日前の連続した 3 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき、1 週間に 2 回投与量調節を行った。朝食前血糖値 4.0～5.0 mmol/L（71～90 mg/dL）を目標として、2 用量ステップずつ投与量調節を行った。最高用量は 50 用量ステップ（IDeg：50 単位、リラグルチド：1.8 mg）であった。ロット番号：DP52017、DP52024、DP52026 及び DP52027

評価基準：有効性

以下の主な有効性評価項目を評価した：

- HbA1cのベースラインから投与後32週までの変化量
- 投与後32週におけるHbA1cのレスポンダー（はい／いいえ）
  - HbA1c 7.0%未満又はHbA1c 6.5%以下
- 体重のベースラインから投与後32週までの変化量
- 空腹時血糖値のベースラインから投与後32週までの変化量
- 1日インスリン投与量
- 患者報告アウトカム（PRO）

- Treatment related impact measure – diabetes（TRIM-D）
- Short form 36 health survey version 2（SF-36v2）

評価基準：安全性

以下の主な安全性評価項目を評価した：

- 投与後32週における治験薬投与下で発現した有害事象の発現件数
- 投与後32週における治験薬投与下で発現した重大な又は血糖値確定症候性低血糖の発現件数
- 投与後32週における治験薬投与下で発現した重大な夜間低血糖又は血糖値確定症候性夜間低血糖の発現件数
- ベースラインから投与後32週までの以下の臨床評価の変化
  - 眼検査（眼底検査／眼底写真）
  - 12誘導心電図
  - 脈拍数
- ベースラインから投与後32週までの以下検査の測定結果の変化
  - 血液学的検査
  - 治験薬に対する抗体検査
  - 血液生化学的検査
  - 脂質検査
  - カルシトニン検査

統計手法：

検出力の算出：

HbA1c の変化量について、IDegLira 1WT の IDegLira に対する非劣性を示す検出力は 80%であった。

解析対象集団：

- 最大の解析対象集団（FAS）：無作為割り付けされたすべての被験者を含めた。例外的に被験者をFASから除外することができた。その場合は除外する正当な理由を示し文書化することとした。FASにおける統計的評価はITT（intention-to-treat）の原則に従い、FASに含まれる被験者は無作為割り付けされたとおり（as randomised）の評価に寄与した。
- Per-Protocol（PP）解析対象集団：FASのうち以下の基準を満たすすべての被験者を含めた。
  - いずれの選択基準にも違反していない
  - いずれの除外基準も満たしていない
  - スクリーニング又は無作為割り付け時に非欠測のHbA1c測定値がある
  - 投与後12週の曝露で少なくとも1つの非欠測のHbA1c測定値がある
  - 少なくとも12週の曝露がある

  PP解析対象集団に含まれる被験者はas treatedの評価に寄与した。
- 安全性解析対象集団（SAS）：治験薬を少なくとも1回投与されたすべての被験者を含めた。SASに含まれる被験者はas treatedの評価に寄与した。
- 完了例の解析対象集団（CAS）：無作為割り付けされて試験を完了したすべての被験者を含めた。CASに含まれる被験者はas randomisedの評価に寄与した。

統計解析：

プライマリーエンドポイント（ベースラインから投与後 32 週までの HbA1c の変化量）は、標準的な繰り返し測定に対する混合モデル（MMRM）を用いて解析した。群間差の平均の 95%信頼区間が完全に 0.30%を下回った場合に、IDegLira 1WT の IDegLira に対する非劣性が検証されたこととした。投与後 32 週における体重、空腹時血糖値及び血圧も標準的な MMRM を用いて解析した。HbA1c のレスポンダーに関するエンドポイントは、治療、地域及び前治療の経口糖尿病薬を固定効果、ベースラインの HbA1c 値を共変量としたロジスティック回帰モデルを用いて解析した。

被験者背景：

ベースライン特性及び人口統計学的特性は 2 つの投与群で概ね一致していた。平均年齢は 56.8 歳、平均糖

尿病罹病期間は 7.33 年、平均 BMI（kg/m^2）は 32.5、ベースライン時の HbA1c の平均値は 8.1%であった。

人口統計学的特性及びベースライン特性 - 要約 - FAS

	IDegLira 1WT N (%)	IDegLira N (%)	Total N (%)
Number of Subjects	210	210	420
Sex			
N	210 (100.0)	210 (100.0)	420 (100.0)
Female	99 (47.1)	98 (46.7)	197 (46.9)
Male	111 (52.9)	112 (53.3)	223 (53.1)
Race			
N	210 (100.0)	210 (100.0)	420 (100.0)
White	197 (93.8)	197 (93.8)	394 (93.8)
Black or African American	11 (5.2)	10 (4.8)	21 (5.0)
Asian	2 (1.0)	2 (1.0)	4 (1.0)
American Indian or Alaska Native	0 (0.0)	1 (0.5)	1 (0.2)
Native Hawaiian or Oth. Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

N: Number of subjects, %: Percentages are based on N

ベースライン特性及び糖尿病特性 - 要約 - FAS

	IDegLira 1WT	IDegLira	Total
Number of Subjects	210	210	420
Age (years)			
N	210	210	420
Mean (SD)	56.6 (10.3)	57.0 (9.6)	56.8 (9.9)
Median	57.3	57.6	57.6
Min ; Max	24.5 ; 79.3	31.7 ; 83.7	24.5 ; 83.7
Body Weight (kg)			
N	210	210	420
Mean (SD)	95.9 (18.9)	95.2 (15.8)	95.5 (17.4)
Median	94.0	95.9	95.0
Min ; Max	58.2 ; 157.2	54.0 ; 135.9	54.0 ; 157.2
BMI (kg/m^2)			
N	210	210	420
Mean (SD)	32.4 (4.6)	32.5 (4.4)	32.5 (4.5)
Median	32.1	32.5	32.2
Min ; Max	22.0 ; 40.1	21.6 ; 40.0	21.6 ; 40.1
Duration of Diabetes (years)			
N	210	210	420
Mean (SD)	7.42 (5.59)	7.23 (5.42)	7.33 (5.50)
Median	6.6	6.1	6.4
Min ; Max	0.30 ; 26.61	0.33 ; 26.57	0.30 ; 26.61
HbA1c (%)			
N	210	210	420
Mean (SD)	8.2 (0.9)	8.1 (0.9)	8.1 (0.9)
Median	8.0	7.9	8.0
Min ; Max	5.5 ; 10.6	5.7 ; 10.2	5.5 ; 10.6
FPG (mmol/L)			
N	210	207	417
Mean (SD)	10.1 (2.6)	10.1 (2.5)	10.1 (2.6)
Median	9.7	9.8	9.8
Min ; Max	5.6 ; 24.2	5.3 ; 20.9	5.3 ; 24.2

BMI: Body mass index, FPG: Fasting plasma glucose, N: Number of subjects, SD: Standard deviation.

有効性の結果：
メトホルミン±ピオグリタゾン併用下で、IDegLira 1WT 又は IDegLira のそれぞれの投与量調節法を用いた 32 週間の治療について、以下の結論を得た。

HbA1c

HbA1c の変化量について IDegLira 1WT 群の IDegLira 群に対する非劣性が検証された：HbA1c の変化量について、IDegLira 1WT 群の IDegLira 群に対する群差の推定値は 0.12%（95%信頼区間：[-0.04; 0.28]、p<0.012。p 値は非劣性の検証に対する値）であった。投与後 32 週における HbA1c は、IDegLira 1WT 群ではベースラインから 2.01%低下して 6.1%となり、IDegLira 群ではベースラインから 2.02%低下して 6.0%となった。

HbA1c のレスポンダー

投与後 32 週において事前に規定した HbA1c の目標値（7%未満及び 6.5%以下）を達成した被験者の割合は 2 つの投与群で同様であった。投与後 32 週において HbA1c 7%未満を達成した被験者の割合は IDegLira 1WT 群及び IDegLira 群でそれぞれ 89.9%及び 89.5%であった。同様に、HbA1c 6.5%以下を達成した被験者の割合は、それぞれ 83.6%及び 85.0%であった。投与後 32 週において HbA1c の目標値 7%未満及び 6.5%以下を達成した被験者のオッズ比の推定値について群間で統計的な有意差は認められなかった。

空腹時血糖値

空腹時血糖値は試験期間中に IDegLira 1WT 群と IDegLira 群で同程度低下した。空腹時血糖値は、IDegLira 1WT 群では 10.1 mmol/L（181.9 mg/dL）から 5.7 mmol/L（103.6 mg/dL）、IDegLira 群では 10.1 mmol/L（182.1 mg/dL）から 5.6 mmol/L（100.8 mg/dL）へと低下した。投与後 32 週における空腹時血糖値の変化量について、IDegLira 1WT 群と IDegLira 群の間で統計的な有意差は認められなかった。

体重

投与後 32 週における体重は、IDegLira 1WT 群と比較して IDegLira 群で有意に大きく減少した。体重の変化量について、IDegLira 1WT 群と IDegLira 群の群差の推定値は 1.09 kg（95%信頼区間：[0.22; 1.96]、p=0.014）であった。投与後 32 週における体重の変化量は、IDegLira 1WT 群及び IDegLira 群でそれぞれ-1.0 kg 及び-2.0 kg であった。

1 日インスリン投与量

投与後 32 週における 1 日インスリン投与量は、2 つの投与群で同様であった。いずれの投与群においても、1 日インスリン投与量は試験期間中に 11 単位から 41 単位に増加した。

PRO 質問票

いずれの投与群においても、試験期間を通してすべての TRIM-D サブドメインのスコア及び総スコアが改善された。投与後 32 週における総スコアについて、IDegLira 1WT 群と IDegLira 群の間には統計的な有意差は認められず、群差の推定値は 0.54 ポイント（95%信頼区間：[-1.35; 2.43]、p=0.576）であった。SF-36v2 については、いずれの投与群でも投与後 32 週において身体的側面に関するすべてのドメインのスコアがわずかに改善しており、そのスコアに IDegLira 1WT 群と IDegLira 群の間に統計的な有意差は認められなかった。同様に、いずれの投与群でも精神的側面に関するすべてのドメインのスコアが改善した。投与後 32 週における「活力（vitality）」「社会生活機能（social functioning）」及び「心の健康（mental health）」のスコアは、IDegLira 群と比較して IDegLira 1WT 群で統計的に有意に改善した（p 値範囲：0.013～0.023）。このことは、IDegLira 1WT 群において心の健康及び生活に対する満足度が比較的高かったことを示唆している。

安全性の結果：
検討した各領域における安全性の結果を以下に要約する：

全般的な有害事象プロファイル（低血糖以外）

- 試験期間中に1例（IDegLira群、循環虚脱）の死亡が報告された。イベント判定委員会は当該有害事象を心血管死として分類した。当該有害事象は、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。
- 有害事象全体の単位時間あたりの発現件数は、IDegLira 1WT群で207.8件／100人・年、IDegLira群で

241.3件／100人・年であった。有害事象の大部分は非重篤、軽度であり、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。
- 最も高頻度（5%以上）で報告された有害事象は、いずれの投与群においても、悪心及び鼻咽頭炎であった。
- 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全体の単位時間あたりの発現件数は、IDegLira 1WT群で45.2件／100人・年、IDegLira群で45.6件／100人・年であった。
- 試験期間中に21例27件（IDegLira 1WT群：7例10件、IDegLira群：14例17件）の重篤な有害事象が報告された。IDegLira群の2件の重篤な有害事象（感染性胆嚢炎及び胃腸炎）は、治験責任医師により治験薬との因果関係は「可能性あり」と判定された。試験期間中に2件の治験薬非投与下で発現した重篤な有害事象が報告された。
- 8例（IDegLira 1WT群：6例、IDegLira群：2例）の被験者が有害事象の発現により試験を中止した。IDegLira群で中止の主な理由となった事象は、器官別大分類の胃腸障害及び神経系障害に含まれる事象であった。

<u>特に注目すべき有害事象</u>
- 2件の有害事象（IDegLira 1WT群及びIDegLira群で各1件）がイベント判定委員会により心血管系事象と確定された。いずれも事象も主要な心血管イベント（MACE）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。
- 膵炎及び甲状腺に関連した有害事象でイベント判定委員会により確定されたものはなかった。
- 3件の治験薬投与下で発現した有害事象がイベント判定委員会により新生物と確定された。これらのうちIDegLira 1WT群の1件（子宮内膜腺癌）は悪性と分類された。
- カルシトニンの上昇に関する事象の検索により、IDegLira 1WT群での1件の血中カルシトニン増加（非重篤）が特定された。
- 20例25件（IDegLira 1WT群：9例10件、IDegLira群：11例15件）のリパーゼ／アミラーゼ増加が特定された。いずれの事象も非重篤であった。
- 62例115件（IDegLira 1WT群：29例57件、IDegLira群：33例58件）で胃腸障害の有害事象が報告された。臍ヘルニア1件及び小腸炎1件を除き、いずれの事象も非重篤であった。事象の大部分は軽度であった。
- 事前に規定した特に注目すべき安全性領域であるアレルギー反応、注射部位反応、腎機能の悪化、稀な事象及び高血糖に関する事象の報告件数は少なかった。これらの注目すべき安全性領域におけるすべての事象は、IDegLira 1WT群の1件（高血糖）及びIDegLira群の2件〔循環虚脱及（その後死亡）及び血中ブドウ糖増加〕を除き、非重篤であった。事象の大部分は軽度であった。

<u>低血糖</u>
- 重大な又は血糖値確定低血糖全体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少なかったが、IDegLira群と比較してIDegLira 1WT群で少なかった。これは、1週間に血糖自己測定を行う回数が異なる（2回と6回）という固定バイアスに起因している可能性が考えられた。
- 重大な又は血糖値確定症候性低血糖の単位時間あたりの発現件数は、IDegLira 1WT群及びIDegLira群で16.4件／100人・年及び76.2件／100人・年であった。
- IDegLira群の1例で、非重篤な、重大な低血糖が報告された。

<u>臨床検査評価</u>
- いずれの投与群においても、ベースラインから投与終了時までに血液学的検査又は血液生化学的検査のパラメータで臨床的に問題となる変化はみられなかった。
- いずれの投与群においても、ベースラインから投与終了時までに治験薬の抗体について臨床的に問題となる変化はみられなかった。
- IDegLira 1WT群において、ベースラインから投与終了時までにリパーゼが11.4 U/L増加し、アミラーゼが10.5 U/L増加したが、基準範囲内であった。
- いずれの投与群においても、ベースラインから投与終了時までに脂質について臨床的に問題となる変化はみられなかった。

- いずれの投与群においても、ベースラインから投与終了時までにカルシトニンについて臨床的に問題となる変化はみられなかった。

<u>身体検査、眼底検査／眼底写真、心電図及びバイタルサイン</u>

- 脈拍数について群間で統計的な有意差は認められなかった。投与後32週における群差の推定値は、-0.11拍／分（95%信頼区間：[-1.64; 1.42]、p=0.887）であった。
- 投与後32週における身体検査、眼底検査／眼底写真又は心電図について、群間で臨床的に問題となる違いは認められなかった。

全体の結論：

インスリン治療歴がなく、メトホルミン単剤、又はメトホルミンとピオグリタゾンの併用療法で十分な血糖コントロールが得られていない 2 型糖尿病患者を対象として、IDegLira の週 1 回の投与量調節法（IDegLira 1WT）と週 2 回投与量調節法（IDegLira）を比較する 32 週間の試験の結論は以下のとおりであった：

- ベースラインから投与後32週のHbA1cの変化量について、IDegLira 1WTのIDegLiraに対する非劣性が検証された。
- 投与後32週においてHbA1cの目標値である7%未満又は6.5%以下を達成した被験者のオッズについて、群間で統計的な有意差は認められなかった。
- 空腹時血糖値はIDegLira 1WT及びIDegLiraで同程度に低下し、群間で統計的な有意差は認められなかった。
- 体重の減少量はIDegLira 1WTと比較してIDegLiraで統計的有意に大きかった。
- 投与後32週における1日インスリン投与量は両群で同様であった。
- 重大な又は血糖値確定症候性低血糖の単位時間あたりの発現件数は、IDegLiraと比較してIDegLira 1WTで少なかった。このことは、IDegLira 1WTでは血糖自己測定の頻度が低かったことに起因している可能性が考えられた。
- IDegLira 1WTについて、予測されない安全性及び忍容性の明らかな問題は認められなかった。

本試験は、ヘルシンキ宣言の精神（64th WMA Assembly, October 2013）、ICH-GCP（1996 年 5 月）及び 21CFR 312.120 を遵守して実施された。

2.7.6.14. NN9068-4185

2.7.6.14.1 臨床試験概要

治験依頼者名： Novo Nordisk, Novo Allé, DK-2880 Bagsvaerd, Denmark	
有効成分名： インスリン デグルデク／リラグルチド	
治験 ID： NN9068-4185	
Trial Registration ID-number： NCT02420262	UTN：U1111-1160-6923 IND number：109121 EudraCT number：2014-003621-18
治験の標題： DUAL™ VII - インスリン デグルデク／リラグルチドと Basal-bolus 療法の比較：2 型糖尿病患者を対象とした、インスリン デグルデク／リラグルチドと Basal-bolus 療法の有効性及び安全性を比較する臨床試験	
治験責任医師名： 治験実施施設（89 施設）ごとに 1 名の治験責任医師が任命された。以下の治験責任医師が「治験総括報告書への署名責任を有する医師（signatory investigator）」に任命された： Dr. [redacted]	
治験実施施設： 計 12 ヵ国 89 施設において実施した：アルゼンチン（3 施設）、チェコ共和国（5 施設）、フランス（3 施設）、ギリシャ（6 施設）、ハンガリー（3 施設）、イスラエル（6 施設）、メキシコ（3 施設）、ロシア（7 施設）、スロバキア（5 施設）、スペイン（6 施設）、トルコ（5 施設）及び米国（37 施設）	
公表文献（引用文献）： 本臨床試験概要作成時点でなし	
治験期間： 開始日：2015 年 7 月 26 日 終了日：2016 年 10 月 5 日	**開発のフェーズ**： 第 3b 相
Cut-off date： ここに提示する結果は、2016 年 10 月 26 日時点の臨床データベースに基づいている。	
報告書作成日： 2017 年 3 月 22 日	
目的： 主要目的： • インスリン グラルギン（IGlar）及びメトホルミンで治療中の2型糖尿病患者を対象として、血糖コントロールにおけるインスリン デグルデク／リラグルチド（IDegLira）の有効性を検証する。これは、ベースラインから投与後26週のHbA1cの変化量について、メトホルミン併用下での、IDegLira（1日1回投与）による治療の、IGlar（1日1回投与）に食事時のインスリン アスパルト（IAsp）を加えたBasal-bolus療法に対する非劣性（非劣性マージン0.30%）を示すことで行う。 副次的目的： • 以下の項目について、IDegLiraのBasal-bolus療法に対する優越性を検証する。 　o 26週間の治験薬投与下に発現した重大な又は血糖値確定症候性低血糖の発現件数 　o ベースラインから投与後26週までの体重の変化量 • 投与後26週におけるIDegLiraとBasal-bolus療法の全般的な有効性及び安全性を比較する。	

治験方法：
本試験は、2 型糖尿病患者を対象とした、26 週間、多施設、国際共同、非盲検、無作為割り付け、2 群並行、treat-to-target 試験であった。メトホルミン及び IGlar（1 日投与量：20～50 単位）の併用療法で十分な血糖コントロールが得られない被験者を本試験の適格例とした。「十分な血糖コントロールが得られていない 2 型糖尿病患者」とは、HbA1c が 7.0%（53 mmol/mol）以上 10.0%（86 mmol/mol）以下の患者と定義した。適格例は、メトホルミン（前治療と同じ投与量）併用下で、IDegLira の 1 日 1 回投与、もしくは IGlar の 1 日 1 回投与に加えて各食事の前に IAsp の投与を受けた。IDegLira の投与は、それまでのメトホルミンによる治療に加えて、16 用量ステップ（IDeg 16 単位／リラグルチド 0.6 mg）から開始し、最高用量を 50 用量ステップ（IDeg 50 単位／リラグルチド 1.8 mg）とし、規定の投与量調節アルゴリズムに従い用量調節を行った。IGlar の投与は、それまでのメトホルミンによる治療に加えて、前治療と同じ 1 日投与量から開始した。被験者は前治験で使用していた IGlar の投与を中断し、IGlar（ノボ ノルディスク社より提供）の投与を開始し、規定の投与量調節アルゴリズムに従い用量調節した。IAsp の投与は、IGlar の投与に加えて 4 単位から開始し、treat-to-target 法を用いて規定の投与調節アルゴリズムに従い用量調節を行った。IGlar 及び IAsp では最高用量を規定しなかった。

計画及び解析された被験者数：
計画された無作為割り付け（各群 1:1 の割合）予定被験者数は計 500 例であった。

	IDegLira N (%)	IGlar + IAsp N (%)	Total N (%)
Screened			672
Screening Failures			166
Withdrawn before randomisation			0
Randomised	252 (100.0)	254 (100.0)	506 (100.0)
Exposed	252 (100.0)	253 (99.6)	505 (99.8)
Permanent discontinuation of treatment or withdrawn from trial	14 (5.6)	21 (8.3)	35 (6.9)
Withdrawn from trial	2 (0.8)	5 (2.0)	7 (1.4)
- Adverse event	1 (0.4)	0	1 (0.2)
- Other	0	1 (0.4)	1 (0.2)
- Withdrawal by subject	1 (0.4)	4 (1.6)	5 (1.0)
- Lost to follow-up	0	0	0
Permanent discontinuation of treatment [1]	12 (4.8)	19 (7.5)	31 (6.1)
- Adverse event	6 (2.4)	1 (0.4)	7 (1.4)
- Other	2 (0.8)	12 (4.7)	14 (2.8)
- Protocol violation	2 (0.8)	6 (2.4)	8 (1.6)
- Rescue criteria	2 (0.8)	0	2 (0.4)
- Pregnancy	0	0	0
Completed week 26	250 (99.2)	249 (98.0)	499 (98.6)
- Completed week 26 visit without permanent discontinuation of trial product	238 (94.4)	233 (91.7)	471 (93.1)
- Completed week 26 visit after permanent discontinuation of trial product	12 (4.8)	16 (6.3)	28 (5.5)
Full analysis set(FAS)	252 (100.0)	254 (100.0)	506 (100.0)
Per-protocol analysis set(PP)	239 (94.8)	238 (93.7)	477 (94.3)
Safety analysis set(SAS)	252 (100.0)	253 (99.6)	505 (99.8)

N: Number of subjects, %: Percentage of randomised subjects

診断及び主要な組入れ基準：

主な選択基準：

性別不問、年齢 18 歳以上、HbA1c 7.0%（53 mmol/mol）以上 10.0%（86 mmol/mol）以下、BMI（kg/m^2）40 以下の 2 型糖尿病患者。スクリーニングの 90 日以上前から IGlar による治療を受けている被験者。スクリーニングの 56 日以上前から 20～50 単位（1 日投与量）での IGlar による安定した治療を受けている被験者。スクリーニング前 56 日間の投与量の変動は±10%以内（ただし、スクリーニング実施日の投与量は 20～50 単位の範囲）とする。スクリーニングの 90 日以上前からメトホルミン（1500 mg 以上又は最大耐用量）による安定（1 日投与量が安定）した治療を受けている被験者。

主な除外基準：

スクリーニング前 90 日以内に、選択基準に示した治療薬以外の糖尿病治療薬又は肥満治療薬の投与を受けている被験者。体重又は糖代謝に影響を及ぼすとされる薬剤（減量又は体重調整に使われるシブトラミン、オルリスタット、甲状腺ホルモン剤、副腎皮質ステロイド剤等）の 14 日間以上の投与開始又は併用薬剤の変更を予定している被験者。肝機能障害（アラニンアミノトランスフェラーゼが基準範囲上限の 2.5 倍以上）を有する被験者。腎機能障害（CKD-EPI 式による eGFR が 60 ml/min/1.73 m^2 未満）を有する被験者。スクリーニング時のカルシトニン濃度が 50 ng/L 以上の被験者。急性膵炎又は慢性膵炎の既往歴を有する被験者。甲状腺髄様癌又は多発性内分泌腫瘍症候群 2 型の家族歴及び既往歴を有する被験者。

主な中止・脱落基準：

女性被験者が妊娠した場合、又は妊娠を希望する場合。体重及び糖代謝に影響を及ぼすと治験責任医師が判断した薬剤の 14 日間以上の投与を開始した場合、もしくはそのような併用薬剤を大きく変更した場合。高血糖〔空腹時血糖値がベースラインから投与後 6 週に 15.0 mmol/L（270 mg/dL）、投与後 7 週から投与後 12 週に 13.3 mmol/L（240 mg/dL）、投与後 13 週から投与後 26 週に 11.1 mmol/L（200 mg/dL）を超えた場合〕を繰り返し発現した場合。急性膵炎と診断された場合、又は治験責任医師により急性膵炎が疑われた場合。

被験薬及び使用機器、用量及び投与方法、ロット番号：

IDegLira（Xultophy®）：IDegLira は 1 mL あたり IDeg 100 単位とリラグルチド 3.6 mg の固定比率の配合剤、ペン型注入器（PDS290、3 mL）と一体化したプレフィルド製剤として提供された。IDegLira はメトホルミンとの併用下で検討した。1 日 1 回毎日ほぼ同時刻に、大腿部、上腕部（三角筋部）又は腹部のいずれかに皮下投与した。16 用量ステップ（IDeg 16 単位／リラグルチド 0.6 mg に相当）から投与を開始し、各投与量調節日及びその前の 2 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき、1 週間に 2 回（月曜日及び木曜日の固定曜日に）投与量調節を行った。朝食前血糖値が目標値の 4.0～5.0 mmol/L（72～90 mg/dL）に到達するよう 2 用量ステップずつ投与量を調節した。投与量調節アルゴリズムは事前に規定し、1 日の最高用量は 50 用量ステップ（IDeg 50 単位／リラグルチド 1.8 mg）とした。ロット番号：DP52036（有効期限：2016 年 6 月 25 日）、EP51277（有効期限：2017 年 4 月 24 日）

投与期間：

26 週間

対照薬及び使用機器、用量及び投与方法、ロット番号：

IGlar+IAsp：IGlar（1 mL あたり 100 単位）はソロスター®（3 mL）と一体化したプレフィルド製剤として、また IAsp（1 mL あたり 100 単位）はフレックスペン®（3 mL）と一体化したプレフィルド製剤として提供された。IGlar+IAsp はメトホルミンとの併用下で検討した。いずれの薬剤も大腿部、上腕部（三角筋部）又は腹部のいずれかに皮下投与した。IGlar は 1 日 1 回、IAsp は各食事前に投与した。IGlar の投与は、それまでのメトホルミンによる治療に加えて、前治療と同じ 1 日投与量から開始した。被験者は前治験で使用していた IGlar の投与を中断し、ノボ ノルディスク社より提供された IGlar の投与を開始した。IAsp の投与は、IGlar の投与に加えて 4 単位から開始した。IGlar は各投与量調節日及びその前の 2 日間の朝食前血糖値（血糖自己測定による）の平均値に基づき、1 週間に 2 回（月曜日及び木曜日の固定曜日に）投与量調節を行った。朝食前血糖値が目標値の 4.0～5.0 mmol/L（72～90 mg/dL）に到達するよう 2 単位ずつ投与量を調節した。IAsp は各投与量調節日前の連続した 3 日間の食前及び就寝前血糖値（血糖自己測定による）に基づき、1 週間に 2 回（月曜日及び木曜日の固定曜日に）投与量調節を行った。食前及び就寝前血糖値が目標値の 4.0

～6.0 mmol/L（72～108 mg/dL）に到達するよう投与量を調節した。IGlar 及び IAsp の最高用量は規定しなかった。IGlar のロット番号：5F1301A（有効期限 2017 年 7 月 31 日）、5F1346A（有効期限 2017 年 7 月 31 日）、5F1662A（有効期限 2017 年 8 月 31 日）、5F1539A（有効期限 2017 年 9 月 30 日）。IAsp のロット番号：EP50616（有効期限 2017 年 5 月 25 日）

評価基準：有効性

以下の項目の有効性を評価した：

- HbA1cのベースラインから投与後26週までの変化量
- 体重のベースラインから投与後26週までの変化量
- 26週間の治験薬投与下における重大な又は血糖値確定症候性低血糖の発現件数
- 投与後26週におけるHbA1c 7.0%未満及び6.5%以下のレスポンダー

評価基準：安全性

以下の項目の安全性を評価した：

- 26週間の治験薬投与下における有害事象の発現件数
- 26週間の治験薬投与下における重大な又は血糖値確定症候性夜間低血糖の発現件数
- 26週間の治験薬投与下における低血糖（ADA分類による）の発現件数
- ベースラインから投与後26週までの以下の臨床評価項目の変化量
    - 脈拍数
    - 眼底検査／眼底写真
    - 心電図（ECG）
- ベースラインから投与後26週までの以下の臨床検査項目の変化量
    - 血液生化学的検査
    - 血液学的検査
    - カルシトニン検査
    - アミラーゼ及びリパーゼ

統計手法：

検出力の算出：

- HbA1cの変化量について、IDegLiraのIGlar＋IAspに対する非劣性を結論付けるための検出力は85%であった。

解析対象集団：

- 最大の解析対象集団（FAS）：FASには無作為割り付けされたすべての被験者が含まれた。FASの統計的評価はintention-to-treat（ITT）の原則に従い、FASの被験者はas randomisedの評価に寄与した。
- Per-Protocol（PP）解析対象集団：以下の基準を満たすすべての被験者を含めた：
    - いずれの選択基準にも違反していない
    - いずれの除外基準も満たしていない
    - スクリーニング又は無作為割り付け時に非欠測のHbA1c測定値がある
    - 投与後12週の曝露に少なくとも1つの非欠測のHbA1c測定値がある
    - 少なくとも12週の曝露がある

  PP解析対象集団の被験者はas treatedの評価に寄与した。
- 安全性解析対象集団（SAS）：SASには被験薬又は対照薬の投与を少なくとも1回受けたすべての被験者が含まれた。SASの被験者はas treatedの評価に寄与した。
- 完了例の解析対象集団（CAS）：CASには無作為割り付けされて、無作為割り付けされた治療を中止することなく試験を完了したすべての被験者が含まれた。CASの被験者はas randomisedの評価に寄与した。

統計解析：

プライマリーエンドポイントである、HbA1c のベースラインから投与後 26 週までの変化量は、標準的な繰り返し測定に対する混合モデル（MMRM）を用いて解析した。HbA1c のベースラインからの変化量について、IDegLira 群と IGlar+IAsp 群（Basal-bolus 療法）の差の推定値（平均）の両側 95%信頼区間の上限が完全

に 0.3%を下回った場合に、IGlar+IAsp に対する IDegLira の非劣性が示されることとした。検証的セカンダリーエンドポイント（投与後 26 週の体重の変化量及び治験薬投与下で発現した重大な又は血糖値確定症候性低血糖の発現件数）における優越性の検定は、プライマリーエンドポイントにおいて IDegLira の Basal-bolus に対する非劣性が示された場合に限り、実施することとした。また、全体の第一種の過誤確率を 5%に制御するため、これらのエンドポイントは階層的手法を用いて評価した。26 週間の治験薬投与下で発現した重大な又は血糖値確定症候性低血糖の発現件数について、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。ベースラインから投与後 26 週までの体重の変化量は、MMRM 法及び無構造共分散行列を用いて解析した。

被験者背景：

被験者のベースライン時の背景及び特性は両投与群で概ね同様であった。被験者の平均年齢は 58.3 歳、平均糖尿病罹病期間は 13.2 年、平均 BMI（kg/m^2）は 31.7、ベースラインの HbA1c の平均は 8.2%であった。

被験者背景及びベースライン特性 - 要約 - FAS

	IDegLira N (%)	IGlar + IAsp N (%)	Total N (%)
Number of subjects	252	254	506
Sex			
N	252 (100.0)	254 (100.0)	506 (100.0)
Female	142 (56.3)	137 (53.9)	279 (55.1)
Male	110 (43.7)	117 (46.1)	227 (44.9)
Race			
N	252 (100.0)	254 (100.0)	506 (100.0)
White	236 (93.7)	235 (92.5)	471 (93.1)
Black or African American	8 (3.2)	6 (2.4)	14 (2.8)
Asian	1 (0.4)	3 (1.2)	4 (0.8)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Oth. Pacific Islander	0	0	0
Other	0	1 (0.4)	1 (0.2)
Missing	7 (2.8)	9 (3.5)	16 (3.2)

N: Number of subjects, %: Percentage of subjects

ベースライン特性及び糖尿病特性 - 要約 - FAS

	IDegLira	IGlar + IAsp	Total
Number of subjects	252	254	506
Age (years)			
N	252	254	506
Mean (SD)	58.6 (9.0)	58.0 (8.6)	58.3 (8.8)
Median	59.0	58.0	59.0
Min ; Max	31 ; 78	36 ; 86	31 ; 86
Body weight (kg)			
N	252	254	506
Mean (SD)	87.2 (16.0)	88.2 (17.2)	87.7 (16.6)
Median	86.0	87.1	86.9
Min ; Max	47.5 ; 144.2	45.4 ; 146.6	45.4 ; 146.6
BMI (kg/m^2)			
N	252	254	506
Mean (SD)	31.7 (4.4)	31.7 (4.5)	31.7 (4.4)
Median	31.6	31.5	31.6
Min ; Max	20.9 ; 40.0	18.9 ; 40.0	18.9 ; 40.0
HbA1c (%)			
N	252	254	506

Mean (SD)	8.21 (0.76)	8.24 (0.81)	8.22 (0.78)
Median	8.10	8.30	8.20
Min ; Max	6.60 ; 10.30	6.70 ; 10.30	6.60 ; 10.30
FPG (mmol/L)			
N	251	254	505
Mean (SD)	8.52 (2.65)	8.28 (2.53)	8.40 (2.59)
Median	8.20	8.00	8.00
Min ; Max	2.70 ; 19.00	3.70 ; 16.40	2.70 ; 19.00
Duration of diabetes (years)			
N	252	254	506
Mean (SD)	13.2 (7.0)	13.3 (6.8)	13.2 (6.9)
Median	12.0	12.8	12.5
Min ; Max	1.0 ; 31.7	0.9 ; 36.1	0.9 ; 36.1

N: Number of subjects, SD: Standard deviation, BMI: Body mass index, FPG: Fasting plasma glucose

有効性の結果：

有効性に関する主な結論を以下に要約する。

HbA1c：

- プライマリーエンドポイントであるHbA1cのベースラインから投与後26週までの変化量について、IDegLiraのIGlar+IAspに対する非劣性が検証された。IDegLira群とIGlar+IAsp群の差の推定値は、-0.02%（95%信頼区間：[-0.16; 0.12]、p<0.0001：非劣性検定のp値）であった。
- いずれの投与群でも、HbA1cはベースラインの約8.2%から投与後26週の約6.7%に低下した。

低血糖：

- 検証的セカンダリーエンドポイントである26週間の治験薬投与下に発現した重大な又は血糖値確定症候性低血糖の発現件数について、IDegLiraのIGlar+IAspに対する優越性が検証された。IDegLira群とIGlar+IAsp群の比の推定値は、0.11（95%信頼区間：[0.08; 0.17]、p<0.0001）であった。
- 26週間の治験薬投与下に発現した重大な又は血糖値確定症候性夜間低血糖の発現件数について、IDegLira群とIGlar+IAsp群の比の推定値は0.08（95%信頼区間：[0.04; 0.17]、p<0.0001）であった。

体重：

- もうひとつの検証的セカンダリーエンドポイントである体重のベースラインから投与後26週までの変化量についても、IDegLiraのIGlar+IAspに対する優越性が検証された。IDegLira群とIGlar+IAsp群の差の推定値は、-3.57 kg（95%信頼区間：[-4.19; -2.95]、p<0.0001）であった。
- ベースライン（IDegLira群及びIGlar+IAsp群でそれぞれ87.19 kg及び88.23 kg）から投与後26週までの体重の変化量は、IDegLira群及びIGlar+IAsp群でそれぞれ-0.92 kg及び2.64 kgであった。

インスリン投与量：

- 投与後26週における1日総インスリン投与量及び1日Basalインスリン投与量は、IGlar+IAsp群と比較してIDegLira群で統計的に有意に少なかった。1日総インスリン投与量におけるIDegLira群とIGlar+IAsp群の差の推定値は-44.50単位（95%信頼区間：[-48.30; -40.71]、p<0.0001）、1日Basalインスリン投与量の群差の推定値は-12.59単位（95%信頼区間：[-14.89; -10.29]、p<0.0001）であった。
- 投与後26週において、IDegLira群の1日Basalインスリン投与量は40単位（1日総インスリン投与量も同様）、IGlar+IAsp群の1日Basalインスリン投与量は52単位、1日Bolusインスリン投与量は32単位、1日総インスリン投与量は84単位であった。

HbA1c レスポンダー及び複合エンドポイント：

- いずれの投与群でも、被験者の約2/3がHbA1c 7.0%未満を達成し（IDegLira群：66.0%、IGlar+IAsp群：67.0%）、被験者の約半数弱がHbA1c 6.5%以下を達成した（IDegLira群：49.6%、IGlar+IAsp群：44.6%）。
- 2～3の項目からなるHbA1cレスポンダーの複合エンドポイントについて、いずれのエンドポイントでも、目標を達成した被験者のオッズ比（IDegLira群／IGlar+IAsp群）の推定値に統計的な有意差が認めら

れた（IDegLira群で好ましい結果、いずれもp<0.0001）。これらのエンドポイントは、HbA1cの目標値の達成と、投与期間の最後の12週間に重大な又は血糖値確定症候性低血糖の発現なし、及び／又はベースラインから投与後26週まで体重の増加なし、を組み合わせたものであった。これらのエンドポイントにおけるレスポンダーの割合は以下のとおりであった。

- HbA1c 7.0%未満、低血糖の発現なし：IDegLira群：52.9%、IGlar+IAsp群：23.2%
- HbA1c 7.0%未満、体重の増加なし：IDegLira群：43.3%、IGlar+IAsp群：15.5%
- HbA1c 7.0%未満、低血糖の発現なし、かつ体重の増加なし：IDegLira群：34.9%、IGlar+IAsp群：4.7%
- HbA1c 6.5%以下、低血糖の発現なし：IDegLira群：41.2%、IGlar+IAsp群：15.5%
- HbA1c 6.5%以下、体重の増加なし：IDegLira群：31.9%、IGlar+IAsp群：10.7%
- HbA1c 6.5%以下、低血糖の発現なし、かつ体重の増加なし：IDegLira群：26.9%、IGlar+IAsp群：3.4%

空腹時血糖値：

- 空腹時血糖値のベースラインから投与後26週までの変化量について、2つの投与群の間で統計的な有意差は認められなかった。IDegLira群とIGlar+IAsp群の差の推定値は、-0.31 mmol/L（95%信頼区間：[-0.67; 0.05]、p=0.0936）であった。
- 空腹時血糖値は、IDegLira群でベースラインの8.52 mmol/L（153.5 mg/dL）から投与後26週の6.09 mmol/L（109.7 mg/dL）まで低下し、IGlar+IAsp群でベースラインの8.28 mmol/L（149.3 mg/dL）から投与後26週の6.39 mmol/L（115.1 mg/dL）まで低下した。

血糖自己測定値：

- 9点血糖値プロファイル（血糖自己測定による）の平均のベースラインから投与後26週までの変化量において、投与群間に統計的な有意差が認められた（IGlar+IAsp群で好ましい結果）。IDegLira群とIGlar+IAsp群の差の推定値は、0.57 mmol/L（95%信頼区間：[0.31; 0.83]、p<0.0001）であった。
- 9点血糖値プロファイル（血糖自己測定による）の平均は、IDegLira群でベースラインの9.71 mmol/L（175.0 mg/dL）から投与後26週の7.17 mmol/L（129.3 mg/dL）まで低下し、IGlar+IAsp群でベースラインの9.66 mmol/L（174.1 mg/dL）から投与後26週の6.59 mmol/L（118.8 mg/dL）まで低下した。
- 食後血糖増加量のベースラインから投与後26週までの変化量は、夕食時及びすべての食事の平均について、群間に統計的な有意差が認められた（いずれもIGlar+IAsp群で好ましい結果）。すべての食事による増加量の平均について、IDegLira群とIGlar+IAsp群の差の推定値は0.40 mmol/L（95%信頼区間：[0.13; 0.66]、p=0.0032）であった。

安全性の結果：

検討した各領域における安全性の結果を以下に要約する。

全体的な有害事象プロファイル（低血糖以外）：

- 有害事象の単位時間あたりの発現件数は、IDegLira群で410.4件／100人・年、IGlar+IAsp群で346.9件／100人・年であった。ほとんどの有害事象は非重篤で軽度であり、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。
- 最も高頻度で報告された有害事象は、IDegLira群では悪心、IGlar+IAsp群では鼻咽頭炎であった。
- 試験期間中、22例で24件（IDegLira群で12例13件、IGlar+IAsp群で10例11件）の重篤な有害事象が報告された。IGlar+IAsp群の1件（乳癌）は治験責任医師によりIGlarとの因果関係が「可能性あり」と判定された。
- IDegLira群の1例は重篤な有害事象（胃腸炎）により試験を中止した。

特に注目すべき安全性領域の有害事象：

- IDegLira群の1件の有害事象（不安定狭心症）はイベント判定委員会により心血管系事象と確定された。当該被験者は試験終了時に回復し、当該事象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。
- 本試験で膵炎は報告されなかった。

- イベント判定委員会により確定された甲状腺に関連する事象はなかった。
- IDegLira群の治験薬投与下で発現した1件の有害事象（大腸ポリープ）は、イベント判定委員会により新生物と確定された。この新生物は良性と分類された。
- IDegLira群で1件の血中カルシトニン増加が特定された。
- リパーゼ増加又はアミラーゼ増加の有害事象は、9例15件（IDegLira群で6例9件、IGlar+IAsp群で3例6件）認められた。いずれの事象も非重篤であった。
- 胃腸障害の有害事象は87例172件（IDegLira群で59例128件、IGlar+IAsp群で28例44件）報告された。IGlar+IAsp群の痔瘻1件及び胃炎1件を除き、いずれの事象も非重篤であった。最も高頻度にみられた胃腸障害の有害事象は、悪心、嘔吐及び下痢であった。
- 事前に規定した注目すべき安全性領域のうち、腎機能の悪化、アレルギー反応、稀な事象に該当する有害事象は少なかった。高血糖は報告されなかった。

<u>低血糖：</u>

- 重大な又は血糖値確定症候性低血糖の単位時間あたりの発現件数は、IGlar+IAsp群（817.0件／100人・年）と比較してIDegLira群（107.2件／100人・年）で低かった。
- 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は、IGlar+IAsp群（1151.3件／100人・年）と比較してIDegLira群（264.2件／100人・年）で低かった。

<u>臨床検査項目：</u>

- いずれの投与群でも、ベースラインから投与終了までの血液学的検査及び血液生化学的検査のパラメータで臨床的に問題となる変化は認められなかった。
- 試験期間中、IDegLira群ではリパーゼの増加がみられ、一方IGlar+IAsp群ではリパーゼの減少がみられた。投与後26週におけるリパーゼの変化量は、IDegLira群で17.43 U/L、IGlar+IAsp群で-2.37 U/Lであった。試験期間中、IDegLira群及びIGlar+IAsp群のいずれにおいても、アミラーゼが増加した。投与後26週におけるアミラーゼの変化量は、IDegLira群で9.32 U/L、IGlar+IAsp群で2.14 U/Lであった。
- IDegLira群で1件の血中カルシトニン増加が特定された。

<u>身体検査、眼底検査／眼底写真、心電図及びバイタルサイン：</u>

- 投与後26週における脈拍数について、2つの投与群の間で統計的な有意差が認められた。群差の推定値は2.73拍／分（95%信頼区間：[1.30; 4.16]）であった。
- 投与後26週における身体検査、眼底検査／眼底写真又は心電図の所見について、投与群間で臨床的に問題となる違いは認められなかった。

全体の結論：

IGlar とメトホルミンの併用療法で十分な血糖コントロールを得られない 2 型糖尿病患者を対象として、メトホルミン併用下での、IDegLira による治療と IGlar+IAsp による治療を比較した 26 週間の本試験の結論は以下のとおりであった。

- HbA1cの変化量について、IDegLiraのIGlar+IAspに対する非劣性が検証された。
- 重大な又は血糖値確定症候性低血糖の単位時間あたりの発現件数について、IDegLiraのIGlar+IAspに対する優越性が検証された。
- 体重の変化量について、IDegLiraのIGlar+IAspに対する優越性が検証された。
- 1日総インスリン投与量は、IDegLiraはIGlar+IAspの約半量となった。
- HbA1cの目標値7.0%未満及び6.5%以下を達成した被験者の割合はIDegLiraとIGlar+IAspで同程度であった。
- 以下を達成した被験者の割合はIGlar+IAspと比較してIDegLiraで高かった。
    - HbA1c 7.0%未満、重大な又は血糖値確定症候性低血糖の発現なし
    - HbA1c 7.0%未満、体重の増加なし
    - HbA1c 7.0%未満、重大な又は血糖値確定症候性低血糖の発現なし、かつ体重の増加なし
    - HbA1c 6.5%以下、重大な又は血糖値確定症候性低血糖の発現なし
    - HbA1c 6.5%以下、体重の増加なし
    - HbA1c 6.5%以下、重大な又は血糖値確定症候性低血糖の発現なし、かつ体重の増加なし
- IDegLiraの投与において、予測されない安全性及び忍容性の明らかな問題は認められなかった。

本試験は、ヘルシンキ宣言（64th WMA Assembly）及び ICH-GCP（1996 年 5 月）及び 21 CFR 312.120 を遵守して実施された。

2.7.6.15. NN9068-4229

2.7.6.15.1. 臨床試験概要

治験依頼者： Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark	
有効成分名： インスリン デグルデク／リラグルチド（IDegLira、1 mL あたり 100 単位／3.6 mg）	
治験 ID： NN9068-4229	
Trial Registration ID-number： NCT02773368	UTN：U1111-1168-9343 IND number：109121 EudraCT number：2015-001596-48
治験の標題： DUAL™ IX – ナトリウム-グルコース共輸送体 2 阻害薬（SGLT-2 阻害薬）との併用： 2 型糖尿病患者を対象とした、SGLT-2 阻害薬併用下でのインスリン デグルデク／リラグルチド（IDegLira）とインスリン グラルギン（IGlar）における血糖コントロール及び安全性を比較検討する試験	
治験責任医師名： 治験実施施設（74 施設）ごとに 1 名の治験責任医師が任命された。以下の治験責任医師が治験総括報告書の内容を確認し、署名する「治験総括報告書への署名責任を有する医師（Signatory Investigator）」に任命された： Dr. [redacted]	
治験実施施設： 本試験は以下の 11 ヵ国 74 施設において実施された： 1. アルゼンチン（3 施設にてスクリーニング及び無作為割り付けを実施した） 2. カナダ（5 施設にてスクリーニング及び無作為割り付けを実施した） 3. フィンランド（6 施設にてスクリーニング及び無作為割り付けを実施した） 4. ハンガリー（5 施設にてスクリーニング及び無作為割り付けを実施した） 5. インド（8 施設にてスクリーニング及び無作為割り付けを実施した） 6. ロシア（7 施設にてスクリーニング及び無作為割り付けを実施した） 7. スロヴァキア（5 施設にてスクリーニング及び無作為割り付けを実施した） 8. スロヴェニア（4 施設にてスクリーニング及び無作為割り付けを実施した） 9. スペイン（7 施設にてスクリーニング、6 施設にて無作為割り付けを実施した） 10. スイス（6 施設にてスクリーニング、5 施設にて無作為割り付けを実施した） 11. 米国（23 施設にてスクリーニング、20 施設にて無作為割り付けを実施した）	
公表文献（引用文献）： 本治験総括報告書作成時点での公表文献はなし	
治験期間： 開始日：2016 年 5 月 23 日 Primary completion date：2017 年 9 月 26 日 Global completion date：2017 年 10 月 23 日	**開発のフェーズ**： 第 3b 相
Cut-off date： ここに提示する結果は、2017 年 11 月 13 日の時点での臨床データベースに基づいている。	

報告書作成日：
2018 年 3 月 29 日

目的：

主要目的：

- SGLT-2阻害薬±経口糖尿病薬による治療を受けていた2型糖尿病患者を対象として、IDegLiraの血糖コントロールにおける有効性を検証する。これは、ベースラインから26週のHbA1cの変化量について、SGLT-2阻害薬±経口糖尿病薬の併用下での、IDegLiraのインスリン グラルギン（IGlar）に対する非劣性（非劣性マージン：0.3%）を示すことで行う。

副次的目的：

- SGLT-2阻害薬±経口糖尿病薬による治療を受けていた2型糖尿病患者を対象として、26週における、以下の項目から1つ又は複数について、IDegLiraのIGlarに対する優越性を検証する。
  - 体重の変化量
  - 治験薬投与下で発現した低血糖（重大な又は血糖値確定症候性低血糖）
  - 血糖コントロール
  - インスリン投与量
- 26週間のIDegLiraとIGlarの有効性及び安全性を比較検討する。

治験方法：

本試験は、2 型糖尿病患者を対象とした、国際共同、多施設、無作為割り付け、非盲検、実薬対照、treat-to-target、並行群間試験であった。SGLT-2 阻害薬±その他の経口糖尿病薬による治療で十分な血糖コントロールが得られていない患者を対象とした。本試験では、SGLT-2 阻害薬±その他の経口糖尿病薬の併用下での IDegLira と IGlar を比較した。HbA1c が 7.0%（53 mmol/mol）以上、11.0%（97 mmol/mol）以下の患者を十分な血糖コントロールが得られていない 2 型糖尿病患者と定義した。試験期間は約 32 週〔2 週間のスクリーニング期間、26 週の投与期間及び 2 回の事後調査コンタクト（最大約 4 週間）〕であった。

計画及び解析された被験者数：

計画された被験者数（各群に 1：1 の割合で無作為割り付け）は 416 例であった。

被験者内訳－要約

	IDegLira N (%)	IGlar N (%)	Total N (%)
Screened			554
Screening failures			134
Randomised	210 (100.0)	210 (100.0)	420 (100.0)
Exposed	209 (99.5)	210 (100.0)	419 (99.8)
Withdrawn from trial or permanent discontinuation of trial product	16 (7.6)	10 (4.8)	26 (6.2)
Withdrawn from trial	10 (4.8)	4 (1.9)	14 (3.3)
Adverse event	0	0	0
Withdrawal of consent	5 (2.4)	1 (0.5)	6 (1.4)
Lost to follow-up	4 (1.9)	1 (0.5)	5 (1.2)
Death	0	0	0
Other	1 (0.5)	1 (0.5)	2 (0.5)
Missing	0	1 (0.5)	1 (0.2)
Permanent discontinuation of trial product and withdrawn from trial	9 (4.3)	4 (1.9)	13 (3.1)
Permanent discontinuation of trial product and not withdrawn from trial	6 (2.9)	6 (2.9)	12 (2.9)
Completed week 26	200 (95.2)	206 (98.1)	406 (96.7)
Completed week 26 without permanent discontinuation of trial product	194 (92.4)	200 (95.2)	394 (93.8)
Completed week 26 after permanent	6 (2.9)	6 (2.9)	12 (2.9)

discontinuation of trial product			
Full analysis set (FAS)	210 (100.0)	210 (100.0)	420 (100.0)
Per protocol analysis set (PP)	197 (93.8)	203 (96.7)	400 (95.2)
Safety analysis set (SAS)	209 (99.5)	210 (100.0)	419 (99.8)

N: Number of subjects, %: Percentage of randomised subjects, Withdrawn from trial: withdrawn from trial before week 26

診断及び主要な組入れ基準：

主な選択基準：

- 性別不問、年齢18歳以上（同意取得時点）の被験者。
- 2型糖尿病患者と診断された被験者（臨床診断に基づく）。
- HbA1cが7.0%（53 mmol/mol）以上、11.0%（97 mmol/mol）以下（中央検査機関で測定）の被験者。
- BMI（kg/m^2）が20以上40未満の被験者。
- インスリン治療歴のない被験者（ただし、スクリーニング前14日以内の短期間の使用又は妊娠糖尿病の治療歴は可とする）。
- スクリーニングの90日以上前からSGLT-2阻害薬の単独療法、又はSGLT-2阻害薬とメトホルミン±ジペプチジルペプチダーゼ4阻害薬（DPP-4阻害薬）±ピオグリタゾンの併用療法による、安定した投与量での治療を受けている被験者。なお、ダパグリフロジン投与中は、ピオグリタゾンは使用できない。

主な除外基準：

- スクリーニング前90日以内に何らかの治験薬の投与を受けた被験者。
- スクリーニング前90日以内に何らかの経口糖尿病薬（選択基準に示したSGLT-2阻害薬の単独療法、又はSGLT-2阻害薬とメトホルミン又はDPP-4阻害薬もしくはピオグリタゾンの併用療法を除く）の投与を受けた被験者。
- スクリーニング前90日以内にグルカゴン様（GLP-1）受容体作動薬（エキセナチド又はリラグルチド等）の治療を受けた被験者。
- スクリーニング前90日以内に重度の糖代謝異常（糖尿病性ケトアシドーシス等）予防のための直ちに強化療法を要する血糖コントロールの急性機能不全を起こした被験者。
- 現在心不全（NYHA分類クラスIII又はIV）を有する被験者。
- 腎機能障害（CKD-EPI式によるeGFRが60 mL/min/1.73 m^2未満）を有する被験者。
- 肝機能障害（スクリーニング時のアラニンアミノトランスフェラーゼが基準範囲上限の2.5倍以上）を有する被験者。
- 治験薬又は関連物質に対する過敏症を有する又はその疑いがある被験者。

治験薬の投与中止について：

以下の場合、治験薬の投与を中止することとした。

- 選択基準に違反した場合、及び／又は除外基準に抵触した場合。
- 女性被験者が妊娠した場合、又は妊娠を希望した場合。
- 試験期間中に他の薬剤の臨床試験に参加した場合。
- カルシトニン濃度が50 ng/L以上であった場合。
- 治験責任医師の判断により体重又は糖代謝に影響を及ぼすと考えられる薬剤の開始又は併用薬剤の重大な変更（計14日を超える投与）がある場合。
- 急性膵炎と診断された場合（以下の3つの特徴のうち2つ以上が認められる場合：腹痛、アミラーゼもしくはリパーゼの基準範囲の3倍超、又は超音波、CT／MRIの画像による特徴的な所見）。

治験薬を中止した場合には必ずしも試験の中止とはしなかった。安全性上の懸念や忍容性に問題があった場合、又は被験者が治験手順を遵守していないと判断された場合、治験責任医師の判断により治験薬の投与を中止することがあった。

被験薬、用量及び投与方法、ロット番号：

IDegLira（Xultophy®）

1 mL あたり IDeg 100 単位とリラグルチド 3.6 mg の固定比率の配合剤、ペン型注入器（PDS290、3 mL）と一体化したプレフィルド製剤として提供された。IDegLira は 1 日 1 回、毎日ほぼ同時刻に、大腿部、上腕部（三角筋部）又は腹部に皮下投与した。現在の経口糖尿病薬（SGLT-2 阻害薬±その他の経口糖尿病薬）による治療に加えて、10 用量ステップ（IDeg：10 単位、リラグルチド：0.36 mg に相当）で投与を開始し、事前に規定した投与量調節アルゴリズムに従って 1 週間に 2 回用量調節を行った。1 日最高用量は 50 用量ステップ（IDeg：50 単位、リラグルチド：1.8 mg に相当）とした。ロット番号：FP50665、FP51981、GP51377。
投与期間： 26 週間
対照薬、用量及び投与方法、ロット番号： IGlar（ランタス®） 1 mL あたり 100 単位、ペン型注入器（ソロスター®、3 mL）と一体化したプレフィルド製剤として提供された。IGlar は 1 日 1 回皮下投与した。現在の経口糖尿病薬（SGLT-2 阻害薬±その他の経口糖尿病薬）に加えて、10 単位から投与を開始し、事前に規定した投与量調節アルゴリズムに従って用量調節を行った。IGlar の最高用量は設定しなかった。ロット番号：5F1732A、5F2403A、5F2583A、5F2584A。
評価基準：**有効性** プライマリーエンドポイント • HbA1cのベースラインから26週までの変化量 検証的セカンダリーエンドポイント • 体重のベースラインから26週までの変化量 • 26週間の治験薬投与下における重大な又は血糖確定症候性低血糖の発現件数 • 26週におけるインスリン投与量、1日総インスリン投与量（単位） 有効性に関する補足的セカンダリーエンドポイント • 以下の項目に関する26週のレスポンダー（はい／いいえ） ◦ HbA1c 7.0%未満 ◦ HbA1c 7.0%未満、体重増加なし ◦ HbA1c 7.0%未満、投与期間の最後の12週の治験薬投与下における重大な又は血糖値確定症候性低血糖の発現なし ◦ HbA1c 7.0%未満、投与期間の最後の12週の治験薬投与下における重大な又は血糖値確定症候性低血糖の発現なし、かつ体重増加なし ◦ HbA1c 6.5%以下 ◦ HbA1c 6.5%以下、体重増加なし ◦ HbA1c 6.5%以下、投与期間の最後の12週の治験薬投与下における重大な又は血糖値確定症候性低血糖の発現なし ◦ HbA1c 6.5%以下、投与期間の最後の12週の治験薬投与下における重大な又は血糖値確定症候性低血糖の発現なし、かつ体重増加なし • ベースラインから26週における以下の項目の変化量 ◦ ウエスト周囲径 ◦ 空腹時血糖値 • 空腹時脂質プロファイル ◦ コレステロール ◦ 低比重リポタンパク（LDL）コレステロール ◦ 高比重リポタンパク（HDL）コレステロール ◦ 超低比重リポタンパク（VLDL）コレステロール ◦ トリグリセリド ◦ 遊離脂肪酸

- 9点血糖値（血糖自己測定）プロファイル
  - 9点血糖値プロファイル
  - 9点血糖値プロファイルの平均
  - 食後血糖増加量（朝食、昼食及び夕食前から各食後90分までの増加量に基づく）。すべての食事による増加量の平均は、すべての利用可能な増加量の平均として計算される。
- バイタルサイン
  - 収縮期血圧及び拡張期血圧

医療経済に関する補足的セカンダリーエンドポイント

- ベースラインから26週までの患者報告アウトカム（PRO）の変化：
  - 36項目の質問による医療アウトカム調査のサマリースコア（SF-36v2）
  - 糖尿病に関する治療関連インパクト測定のサマリースコア（TRIM-D）

評価基準：安全性

安全性に関する補足的セカンダリーエンドポイント

- 26週間の治験薬投与下における有害事象の発現件数
- 26週間の治験薬投与下における重大な又は血糖値確定症候性夜間低血糖の発現件数
- 26週間の治験薬投与下におけるADA分類による低血糖の発現件数
- ベースラインから26週までの臨床評価項目：
  - 心電図
  - 眼底検査／眼底写真
  - 身体検査
  - 脈拍数
- ベースラインから26週までの臨床検査項目：
  - 血液生化学的検査
  - 血液学的検査
  - カルシトニン検査
  - 尿中アルブミン／クレアチニン比

統計手法：

検出力の算出

Per-Protocol（PP）解析対象集団における HbA1c のベースラインから 26 週までの変化量について、IDegLira の IGlar に対する非劣性を示す（非劣性マージン 0.3%）検出力を 80%に保持するため、少なくとも 416 例の被験者の無作為割り付けを計画した。

解析対象集団

- 最大の解析対象集団（FAS）：無作為割り付けされたすべての被験者を含めた。FASの統計的な評価はITT（intention-to-treat）の原則に従い、被験者はas randomisedの評価に寄与した。
- Per-Protocol（PP）解析対象集団：FASのうち、以下の基準を満たすすべての被験者を含めた：
  - いずれの選択基準にも違反していない
  - いずれの除外基準も満たしていない
  - スクリーニング又は無作為割り付け時に非欠測のHbA1c測定値がある
  - 12週間の曝露後に少なくとも1つの非欠測のHbA1c測定値がある
  - 少なくとも12週の曝露がある

  被験者はas treatedの評価に寄与した。
- 安全性解析対象集団：被験薬又は対照薬を少なくとも1回投与されたすべての被験者を含めた。被験者はas treatedの評価に寄与した。
- 完了例の解析対象集団（CAS）：無作為割り付けされて、割り付けられた治療を中止することなく試験を完了したすべての被験者を含めた。被験者はas randomisedの評価に寄与した。

統計解析

本試験では、IDegLira の有用性及び有効性を推定する 2 種類の estimand（主要 estimand 及び副次的

estimand）を定義した。主要 estimand は、2 型糖尿病患者を対象として、被験者が最初に割り付けられた治療を 26 週間継続したかどうかに関わらず、IGlar と比較した IDegLira の効果を評価した。主要 estimand の解析には、治験薬の投与を中止した被験者から得られた 26 週の時点（来院 32A）のデータも含めた。副次的 estimand は、2 型糖尿病患者を対象として、無作為割り付けされたすべての被験者で忍容性が良好で、割り付けられた治療を 26 週まで継続したと仮定したときの、IGlar と比較した IDegLira の有効性を評価した。副次的 estimand の解析には、26 週の on treatment 期間内における利用可能なデータを含めた。

プライマリーエンドポイントであるベースラインから 26 週までの HbA1c の変化量に対する主要 estimand について、FAS を対象とし、retrieved data を含めて条件なしの多重補完法（unconditional multiple imputation）により欠測値を補完し、共分散分析（ANCOVA）モデルを用いて解析した。副次的 estimand に関する統計解析では、繰り返し測定に対する混合モデル（MMRM）を用いて on-treatment 期間の観測データのみを含めて解析した。ベースラインから 26 週までの HbA1c の変化量について、群間差の平均（推定値）の両側 95%信頼区間の上限が完全に 0.3%を下回った場合に非劣性が検証されることとした。

プライマリーエンドポイントである IDegLira の IGlar に対する非劣性が検証された場合に限り、検証的セカンダリーエンドポイントにおける優越性の検定を行うこととした。また、全体の第 1 種の過誤確率を 2.5%に制御するため、以下の順序で階層的検定を行った。

- 体重に関する優越性
- 治験薬投与下における低血糖（重大な又は血糖値確定症候性低血糖）の発現件数に関する優越性
- 血糖コントロール（ベースラインからのHbA1cの変化量）に関する優越性
- インスリン投与量（1日総投与量：単位）に関する優越性

体重、血糖コントロール及びインスリン投与量といった検証的セカンダリーエンドポイントに対する主要 estimand について、retrieved data を含めて条件なしの多重補完法により欠測値を補完し、ANCOVA モデルを用いて解析した。これらのエンドポイントに関する副次的 estimand の統計解析は、MMRM を用いて、on-treatment 期間の観測データのみを含めて解析した。26 週間の治験薬投与下における重大な又は血糖値確定症候性低血糖の発現件数に対する主要 estimand について、多重補完法により欠測値を補完し、負の二項分布回帰モデルを用いて解析した。プライマリーエンドポイント及び検証的セカンダリーエンドポイントにおける結果の安定性は、tipping point 解析を含む感度分析を行い評価した。

HbA1c レスポンダーのエンドポイントはロジスティック回帰モデルを用いて解析した。有効性に関するその他の補足的セカンダリーエンドポイント（ウエスト周囲径、空腹時血糖値、空腹時脂質プロファイル、バイタルサイン、9 点血糖値（血糖自己測定による）の平均、食後血糖増加量及び患者報告アウトカム）は、条件なしの多重補完法により欠測値を補完し、ANCOVA モデルを用いて解析した。9 点血糖値プロファイル（血糖自己測定による）の統計解析には、MMRM 法を用いた。

盲検性解除前の変更

- すべての統計モデルに含める前治療の経口糖尿病薬について、4水準（SGLT-2阻害薬±ピオグリタゾン、SGLT-2阻害薬＋メトホルミン±ピオグリタゾン、SGLT-2阻害薬＋DPP-4阻害薬±ピオグリタゾン、SGLT-2阻害薬＋メトホルミン＋DPP-4阻害薬±ピオグリタゾン）を統合し、2水準（SGLT-2阻害薬±メトホルミン±ピオグリタゾン、SGLT-2阻害薬＋DPP-4阻害薬±メトホルミン±ピオグリタゾン）とした。これは、SGLT-2阻害薬±ピオグリタゾンのグループ及びSGLT-2阻害薬＋DPP-4阻害薬±ピオグリタゾンのグループの被験者数が少なかったためである。
- 主要estimandの感度分析について、治験実施計画書中の非劣性検証に対するtipping point解析の項、ならびにCAS及びPP解析対象集団における解析の項に「条件付の多重補完」との記載があるが、これは記載ミスであり、正しくは「条件なしの多重補完」であった。
- 試験の実施中に、一部の被験者が血糖自己測定titration formに誤った順序でデータを記録していることが判明した。試験期間中にtitration formに誤った順序で記録した被験者の一覧がデータマネジメント担当者から提供された。この逸脱による影響を検討するため、26週時のインスリン投与量に関する感度分析を実施した。この解析では、まずtitration formに誤った順序で記録した被験者の投与量データを補完し、次に主要estimandに対する主要解析を実施した。データ補完の手順は以下のとおりであ

る。
- 来院32より前に記録された投与量は変更しなかった。
- Titration formの記録の順序を誤った被験者について、来院32のデータのみ変更した。
- IDegLira群の被験者でインスリン投与量が50単位未満の場合には来院32の投与量に2単位加えた。ただし、IDegLira群の被験者の投与量は最大で50単位とした。
- IGlar群の被験者である場合には来院32の投与量から2単位を減じた。

この補完方法の根拠は以下のとおり。ある週に記録された実インスリン投与量データの半分が誤りであったの可能性がある。そのため、被験者が投与量調節アルゴリズムに従ったとすると、記録された投与量データとの乖離は 2 単位以内と考えられる。よって、この逸脱の影響を評価するにあたり、IDegLira 群で 2 単位を加えること（ただし最大で 50 単位）及び対照薬群で 2 単位を減ずることは保守的なアプローチであった。

盲検性解除後の変更及び事後解析

- 意味のある推定値が得られなかったため、低血糖に関する負の二項分布回帰モデルには地域を因子として含めなかった。
- 夜間低血糖の発現件数が非常に少なかったため、治験薬投与下における重大な又は血糖値確定症候性夜間低血糖について予定していた統計解析は実施しなかった。

被験者背景：

人口統計学的特性及びベースライン特性−要約−FAS

	IDegLira N (%)	IGlar N (%)	Total N (%)
Number of subjects	210	210	420
Sex			
N	210 (100.0)	210 (100.0)	420 (100.0)
Female	89 (42.4)	84 (40.0)	173 (41.2)
Male	121 (57.6)	126 (60.0)	247 (58.8)
Race			
N	210 (100.0)	210 (100.0)	420 (100.0)
White	175 (83.3)	171 (81.4)	346 (82.4)
Black or African American	3 (1.4)	2 (1.0)	5 (1.2)
Asian	31 (14.8)	35 (16.7)	66 (15.7)
American Indian or Alaska Native	0	1 (0.5)	1 (0.2)
Other	1 (0.5)	1 (0.5)	2 (0.5)

N: Number of subjects, %: Percentage of subjects

ベースライン及び糖尿病特性−要約−FAS

	IDegLira	IGlar	Total
Number of subjects	210	210	420
Age (years)			
N	210	210	420

Mean (SD)	56.1 (10.4)	57.2 (10.2)	56.7 (10.3)
Median	56.0	59.0	58.0
Min ; Max	25 ; 83	30 ; 82	25 ; 83
Body weight (kg)			
N	210	210	420
Mean (SD)	89.3 (17.6)	87.2 (17.2)	88.2 (17.4)
Median	86.6	86.1	86.3
Min ; Max	51.5 ; 145.3	51.0 ; 131.5	51.0 ; 145.3
BMI (kg/m^2)			
N	210	210	420
Mean (SD)	31.5 (4.8)	30.9 (4.8)	31.2 (4.8)
Median	31.4	30.8	31.0
Min ; Max	21.1 ; 43.3	20.0 ; 39.9	20.0 ; 43.3
HbA_{1c} (%)			
N	210	210	420
Mean (SD)	8.20 (0.93)	8.36 (1.08)	8.28 (1.01)
Median	8.00	8.20	8.10
Min ; Max	6.50 ; 11.10	6.80 ; 13.50	6.50 ; 13.50
FPG (mmol/L)			
N	206	206	412
Mean (SD)	9.51 (2.69)	9.57 (2.40)	9.54 (2.54)
Median	9.20	9.25	9.20
Min ; Max	3.90 ; 29.20	3.60 ; 22.90	3.60 ; 29.20
Duration of diabetes (years)			
N	210	210	420
Mean (SD)	9.80 (6.20)	9.31 (6.31)	9.55 (6.25)
Median	9.16	8.13	8.49
Min ; Max	0.44 ; 34.18	0.48 ; 34.24	0.44 ; 34.24

N: Number of subjects, SD: Standard deviation; BMI: Body mass index, HbA_{1c}: Haemoglobin A_{1c}, FPG: Fasting plasma glucose; Max: Maximum; Min: Minimum; Baseline refers to week 0 except height (used to calculate BMI) which was recorded at screening.

The duration of diabetes is calculated as the time from date of diagnosis to the randomisation date

有効性の結果：

SGLT-2 阻害薬±その他の経口糖尿病薬の併用下で、IDegLira と IGlar を比較した試験の結果から、主要 esitmand（すなわち、被験者が最初に割り付けられた治療を 26 週間継続したかに関わらない）について以下の結論が得られた。

<u>プライマリーエンドポイント - HbA1c の変化量</u>

26 週における HbA1c の低下量について、IGlar に対する IDegLira の優越性が示された。IDegLira 群及び IGlar 群の HbA1c の低下量はそれぞれ 1.94%（8.20%から 6.26%）及び 1.68%（8.36%から 6.69%）であった。

- 群差の推定値は-0.36%（95%信頼区間：[-0.50; -0.21]、p<0.0001）であった。

<u>検証的セカンダリーエンドポイント</u>

体重のベースラインからの変化量

体重のベースラインから 26 週までの変化量について、IGlar に対する IDegLira の優越性が示された。

- 群差の推定値は-1.92 kg（95%信頼区間：[-2.64; -1.19]、p<0.0001）であった。

治験薬投与下における重大な又は血糖値確定症候性低血糖の発現件数

26 週間の重大な又は血糖値確定症候性低血糖の発現件数について、IGlar に対する IDegLira の優越性が示された。

- 投与群間の比の推定値は0.42（95%信頼区間：[0.23; 0.75]、p=0.0035）であった。

インスリン投与量

26 週の 1 日インスリン投与量について、IGlar に対する IDegLira の優越性が示された。
- 群差の推定値は-15.37単位（95%信頼区間：[-19.60; -11.13]、p<0.0001）であった。

補足的セカンダリーエンドポイント

HbA1c のレスポンダー及び HbA1c の複合エンドポイント

26 週において、HbA1c の目標値を達成した被験者の割合は、IGlar 群と比較して IDegLira 群で高かった。HbA1c の目標値の達成に関するオッズは、IGlar 群と比較して IDegLira 群で有意に高かった。
- HbA1c 7.0%未満を達成した被験者の割合：IDegLira群で84.8%、IGlar群で71.3%、オッズ比は1.98（95%信頼区間：[1.17; 3.34]、p=0.0107）であった。
- HbA1c 6.5%以下を達成した被験者の割合：IDegLira群で74.6%、IGlar群で49.5%、オッズ比は2.72（95%信頼区間：[1.75; 4.22]、p<0.0001）であった。

同様に、複合エンドポイント（HbA1c 目標値を達成した被験者で、体重増加なし、かつ／あるいは最後の 12 週間で重大な又は血糖値確定症候性低血糖の発現なし）については、IDegLira 群で好ましい結果であった。
- HbA1c 7.0%未満、低血糖の発現なし：IDegLira群で79.2%、IGlar群で56.4%、オッズ比は2.76（95%信頼区間：[1.73; 4.40]、p<0.0001）であった。
- HbA1c 7.0%未満、体重の増加なし：IDegLira群で46.2%、IGlar群で18.8%、オッズ比は3.53（95%信頼区間：[2.21; 5.62]、p<0.0001）であった。
- HbA1c 7.0%未満、体重の増加なし、かつ低血糖の発現なし：IDegLira群で42.1%、IGlar群で16.8%、オッズ比は3.36（95%信頼区間：[2.09; 5.41]、p<0.0001）であった。
- HbA1c 6.5%以下、低血糖の発現なし：IDegLira群で69.5%、IGlar群で39.1%、オッズ比は3.45（95%信頼区間：[2.24; 5.31]、p<0.0001）であった。
- HbA1c 6.5%以下、体重の増加なし：IDegLira群で42.6%、IGlar群で12.9%、オッズ比は4.73（95%信頼区間：[2.83; 7.90]、p<0.0001）であった。
- HbA1c 6.5%以下、体重の増加なし、かつ低血糖の発現なし：IDegLira群で39.1%、IGlar群で11.9%、オッズ比は4.55（95%信頼区間：[2.69; 7.69]、p<0.0001）であった。

空腹時血糖値

空腹時血糖値のベースラインから 26 週までの変化量について、群差の推定値に統計的な有意差が認められた（IDegLira 群で好ましい結果）。
- 群差の推定値は-0.33 mmol/L（95%信頼区間：[-0.64; -0.01]、p=0.0400）であった。

血糖自己測定値

ベースラインから 26 週までの 9 点血糖値プロファイルの平均の変化量について、群差の推定値に統計的な有意差が認められた（IDegLira 群で好ましい結果）。
- 群差の推定値は-0.46 mmol/L（95%信頼区間：[-0.68; -0.25]、p<0.0001）であった。

ベースラインから 26 週までの食後血糖増加量の変化量について、朝食（p<0.0001）、昼食（p=0.0055）、夕食（p=0.0421）及びすべての食事（p<0.0001）において、群差の推定値に統計的な有意差が認められた（IDegLira 群で好ましい結果）。

ウエスト周囲径

ウエスト周囲径のベースラインから 26 週までの変化量について、群差の推定値に統計的な有意差が認められた（IDegLira 群で好ましい結果）。
- 群差の推定値は-1.24 cm（95%信頼区間：[-2.06; -0.42]、p=0.0030）であった。

空腹時脂質

空腹時脂質のすべてのパラメータ（総コレステロール、HDL コレステロール、LDL コレステロール、VLDL コレステロール、トリグリセリド及び遊離脂肪酸）において、IDegLira 群と IGlar 群の間に統計的な有意差は認められなかった。

バイタルサイン

収縮期血圧のベースラインから 26 週までの変化量について、群差の推定値に統計的な有意差が認められた（IDegLira 群で好ましい結果）。

- 群差の推定値は-2.87 mmHg（95%信頼区間：[-5.01; -0.74]、p=0.0084）であった。

拡張期血圧には群間に有意差は認められなかった。

患者報告アウトカム

高い TRIM-D スコアは被験者の健康状態が良好であることを示した。26 週における TRIM-D 総スコアでみられた改善は、IDegLira 群で統計的に有意に大きかった（「treatment burden」及び「diabetes managament」の項目の改善によるところが大きい）。

- 群差の推定値は2.78（95%信頼区間：[0.83; 4.73]、p=0.0052）であった。

SF-36v2 質問票の身体的側面及び精神的側面のいずれの項目においても、投与群の間で統計的な有意差は認められなかった。

安全性の結果：

SGLT-2 阻害薬±その他の経口糖尿病薬の併用下で、IDegLira と IGlar を比較した試験の結果は以下のとおりであった。

<u>有害事象プロファイル</u>

- IDegLira群では129例において450件（単位時間あたりの発現件数は436.0件／100人・年）、IGlar群では123例において386件（単位時間あたりの発現件数は364.7件／100人・年）の有害事象が報告された。これらの事象の大部分は非重篤、重症度は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。
- 最も高頻度で報告された有害事象（各投与群において被験者の5%以上で発現）はウイルス性上気道感染、頭痛、背部痛、リパーゼ増加及び悪心であった。
- IDegLira群で6例8件（単位時間あたりの発現件数は7.8件／100人・年）、IGlar群で7例9件（単位時間あたりの発現件数は8.5件／100人・年）の重篤な有害事象が報告された。このうち2件（IDegLira群で心筋梗塞1件及びIGlar群で尿路感染1件）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」と判定された。
- IGlar群で報告された1件の心血管死は非治験薬投与下で発現した有害事象（心筋梗塞）によるものであった。治験薬投与下で発現した有害事象はいずれも死亡に至らなかったが、この心血管死（MACE）の事象は、MACEが治験薬投与下に発現したかを判定する基準により「治験薬投与下で発現した」とみなされた。この事象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。
- 有害事象の発現により試験を中止した被験者はいなかったが、5例の被験者が有害事象（6件：IDegLira群で4件、IGlar群で2件）の発現により治験薬の投与を中止した。

<u>注目すべき安全性領域の有害事象</u>

- IDegLira群の2件（心筋虚血及び出血性卒中の各1件）及びIGlar群の3件（1例における心筋梗塞及び心血管死、別の1例における慢性心不全）の有害事象がイベント判定委員会により心血管系事象と確定された。
- IDegLira群の1件（大腸ポリープ）及びIGlar群の2件（大腸腺腫及び消化管間質性腫瘍）の有害事象がイベント判定委員会により新生物と確定された。追加で1件の限局性の大腸の悪性腫瘍が特定され、イベント判定委員会により新生物と確定されたが、イベント判定委員会が定めた発現日に基づき治験薬投与下で発現した事象とはみなされなかった。
- 本試験で膵炎又は甲状腺に関連する有害事象として確定された事象はなかった。
- 23例35件のリパーゼ増加又はアミラーゼ増加の有害事象が報告された（IDegLira群で14例26件、IGlar群で9例9件）。
- 2例2件のカルシトニン増加の有害事象が報告された（IDegLira群及びIGlar群で各1件ずつ）。
- 74例140件の胃腸障害の有害事象が報告された〔IDegLira群で44例93件（単位時間あたりの発現件数は90.10件／100人・年）、IGlar群で30例47件（単位時間あたりの発現件数は44.41件／100人・年）であった。最も高頻度で報告された胃腸障害の有害事象は悪心及び下痢であった。

- 4例4件の腎機能に関連する有害事象が報告された。IDegLira群の2例2件（血中クレアチニン増加及び腎不全の各1件）及びIGlar群の2例2件（糸球体濾過率減少及び腎不全の各1件）であった。
- IDegLira群で1件の尿中ケトン体陽性が報告された。
- 4例4件の稀な事象が報告された（IDegLira群で脂肪肝2件及び脂肪性肝炎1件、IGlar群で水腎症1件）。

低血糖

- 重大な又は血糖値確定症候性低血糖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、IDegLira群で12.9%及び36.81件／100人・年、IGlar群で19.5%及び89.76件／100人・年であった。
- 重大な又は血糖値確定症候性夜間低血糖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、IDegLira群で2.4%及び5.81件／100人・年、IGlar群で4.3%及び12.28件／100人・年であった。

臨床検査評価

- ベースラインから試験終了時までのリパーゼは、IDegLira群では増加した（変化量は13.17 U/L）が、IGlar群では減少した（変化量は-10.44 U/L）。
- 試験期間中のアミラーゼは、IDegLira群（ベースラインから26週までの変化量は6.60 U/L）とIGlar群（ベースラインから26週までの変化量は1.80 U/L）のいずれにおいても増加した。
- ベースラインから試験終了時までのカルシトニンについて、いずれの投与群においても、臨床的に問題となる変化はみられなかった。
- ベースラインから試験終了時までのその他の血液生化学的検査及び血液学的検査のパラメータについて、いずれの投与群においても、臨床的に問題となる変化はみられなかった
- ベースラインから試験終了時までの尿アルブミン／クレアチニン比について、いずれの投与群においても、臨床的に問題となる変化はみられなかった。

脈拍数

- ベースラインから26週までの脈拍数について、IDegLira群とIGlar群の差の推定値は2.58拍／分（95%信頼区間：[1.12; 4.05]、p=0.0006）であった。この差は統計的に有意であり、IGlar群で好ましい結果となった。

身体所見、眼底検査／眼底写真及び心電図

26 週における身体検査、眼底検査／眼底写真及び心電図の所見について、2 つの投与群の間に臨床的に問題となる差は認められなかった。

全体の結論：

2 型糖尿病患者を対象とした、SGLT-2 阻害薬±その他の経口糖尿病薬の併用下での、26 週の IDegLira と IGlar の有効性及び安全性を比較した試験の結果から、以下の結論が得られた。

- 以下の項目について、IGlarに対するIDegLiraの優越性が示された。
  - HbA1cの変化量
  - 体重の変化量
  - 重大な又は血糖値確定症候性低血糖の単位時間あたりの発現件数
  - 1日総インスリン投与量
- 体重の増加も低血糖の発現もなく、HbA1cの目標値（7.0%未満及び6.5%以下）を達成した被験者の割合は、IGlarと比較してIDegLiraで高かった。
- IDegLiraの投与において、明らかな又は予測されない安全性又は忍容性の懸念は認められなかった。

本試験は、ヘルシンキ宣言（64th WMA assembly, Oct 2013）の精神、ICH-GCP（June 1996）及び CFR 312.120 を遵守して実施された。

2.7.6.16 NN2211-3925

2.7.6.16.1 臨床試験概要

Trial Registration ID - NCT01572740	UTN – U1111-1122-4320 Japanese registration number – JapicCTI-121802

治験の標題

日本人 2 型糖尿病患者を対象とした、リラグルチド及びインスリンの併用療法のインスリン単独療法に対する有効性及び安全性の検討：36 週間投与、多施設共同、二重盲検、無作為割り付け、並行群間比較試験

治験責任医師

23 名の治験責任医師が本試験に参加した。

治験総括報告書への署名責任を有する医師：[redacted]

治験実施施設

23 施設（日本）

公表文献（引用文献）

なし（本概要書作成時点）

治験期間	**開発のフェーズ**
試験開始日：2012 年 4 月 5 日 試験終了日：2013 年 3 月 27 日	第 III 相

Cut-off date

2013 年 4 月 11 日時点で、臨床データベースで入手可能であったデータが反映されている。

目的

主要目的

- 日本人 2 型糖尿病患者を対象とし、投与後 16 週における血糖コントロールについて、インスリン（固定用量）及びリラグルチド（0.9 mg／日）の併用療法のインスリン単独療法（固定用量）に対する優越性を検証する。

副次的目的（有効性）

- インスリン単独療法（固定用量）を対照として、インスリン（固定用量）及びリラグルチド（0.9 mg／日）の併用療法の投与後 16 週の有効性を確認する。
- インスリン単独療法†を対照として、インスリン†及びリラグルチド（0.9 mg／日）の併用療法の投与後 36 週の有効性を確認する。

副次的目的（安全性）

- インスリン単独療法†を対照とした、インスリン†及びリラグルチド（0.9 mg／日）の併用療法の 36 週間の投与期間における安全性を確認する。

† : 投与開始後の最初の 16 週間ではインスリン投与量を固定し、その後の 20 週間ではインスリン投与量を調節した。

試験方法

本試験は、2 型糖尿病患者を対象とし、インスリン単独療法を対照として、インスリン及びリラグルチドの併用療法の有効性及び安全性を検討する、36 週間投与、多施設共同、二重盲検、無作為割り付け（割り付け比率 1：1）、前治療のインスリン療法の種類による層別割り付け、プラセボ対照、並行群間比較試験であった。

36 週間の投与期間は、2 週間の用量漸増期間及び 34 週間の用量維持期間より構成された。インスリン（固定用量）及びリラグルチドの併用療法の有効性及び安全性は、投与開始後の最初の 16 週間で評価した。その後の 20 週間では、予め定められたインスリン投与量調節ガイドラインに基づいてインスリン投与量を調節した。

各被験者の試験参加期間は約 38 週間であり、この期間に 15 回の来院及び 9 回の電話コンタクトが実施され

た。スクリーニング来院（来院 1）で被験者の適格性が確認され、約 1 週間後（最長で 2 週間後）の来院 2（投与開始の来院）で無作為割り付けが実施された。被験者は 1:1 の割り付け比率でリラグルチド投与群又はプラセボ投与群に無作為に割り付けられた。無作為割り付け時、被験者は前治療のインスリン療法の種類〔Basal インスリンによる治療、混合型インスリンによる治療又は Basal-Bolus 療法〕によって層別された。来院 2 から来院 23 の期間に、被験者は前治療のインスリン療法に加え、リラグルチド又はリラグルチドプラセボを投与された。投与終了後における安全性を評価するために、来院 23 の実来院日の 7 日後以降に事後調査来院（来院 24）を実施した。

計画及び解析された被験者数

254 例の被験者を無作為割り付けするため、計 300 例のスクリーニングが計画された。計 228 例（各投与群 114 例）の被験者が試験を完了すると想定した。実際の被験者の内訳を以下に示す：

	リラグルチド N (%)	プラセボ N (%)	合計 N (%)
スクリーニング症例			296
スクリーニング不適格症例			39
無作為割り付け前の中止症例			0
無作為割り付け症例	127 (100.0)	130 (100.0)	257 (100.0)
治験薬投与症例	127 (100.0)	130 (100.0)	257 (100.0)
中止症例	6 (4.7)	5 (3.8)	11 (4.3)
有害事象	1 (0.8)	1 (0.8)	2 (0.8)
治験実施計画書不遵守	0 (0.0)	0 (0.0)	0 (0.0)
中止基準	1 (0.8)	1 (0.8)	2 (0.8)
その他	4 (3.1)	3 (2.3)	7 (2.7)
完了症例	121 (95.3)	125 (96.2)	246 (95.7)

N：被験者数、%： 割り付け被験者数に対する割合

診断及び主要な組入れ基準

年齢 20 歳以上、2 型糖尿病罹病期間 6 ヵ月以上、HbA1c 7.5%以上 11.0%以下、BMI（kg/m^2）45.0 未満、食事・運動療法に加え、インスリン療法（Basal インスリンによる治療、混合型インスリンによる治療又は Basal-Bolus 療法）をスクリーニング時点で 12 週間以上受けている日本人 2 型糖尿病患者（男女）が本試験に組み入れられた。

インスリン療法は、以下のように定義された：

- Basal インスリンによる治療：中間型ヒトインスリン製剤、中間型インスリンアナログ製剤又は持効型インスリンアナログ製剤（1 日 1 回又は 1 日 2 回投与）
- 混合型インスリンによる治療：混合型ヒトインスリン製剤又は混合型インスリンアナログ製剤（1 日 1 回又は 1 日 2 回投与）
- Basal-Bolus 療法：Basal インスリン製剤として、中間型ヒトインスリン製剤、中間型インスリンアナログ製剤又は持効型インスリンアナログ製剤（1 日 1 回投与又は 1 日 2 回投与）、Bolus インスリン製剤として、速効型ヒトインスリン製剤又は超速効型インスリンアナログ製剤（1 日 3 回投与）

また、12 週間以上インスリン投与量が安定しており（1 日総インスリン投与量の変動が±20%以内）、かつスクリーニング時の投与量が 10 単位／日以上であることが必要条件であった。

糖代謝に影響を及ぼすと考えられている併用薬剤の変更が予測される被験者、重大な低血糖を繰り返し発現

した（過去 12 ヵ月に 2 回以上）被験者、治験責任医師によって無自覚低血糖と判断される低血糖を発現した被験者、あるいは過去 6 ヵ月以内に糖尿病性ケトアシドーシスのために入院したことがある被験者、増殖網膜症又は処置を要する黄斑症を有する被験者（治験責任医師の判断による）、スクリーニングの前 12 週以内に GLP-1 受容体作動薬又は経口糖尿病薬の投与を受けた被験者は、本試験から除外された。

被験薬、用量及び投与方法、ロット番号

- リラグルチド（ビクトーザ®）、3 mL（6.0 mg／mL）、プレフィルド製剤（ロット番号：AP50534）

リラグルチドの用法・用量は、日本におけるビクトーザ®の添付文書に従った。被験者は 1 日 1 回、朝又は夕（可能な限り毎日同じ時刻）にリラグルチドを皮下投与した。投与部位は上腕、腹部又は大腿部のいずれかとし、選択された投与部位の中で毎回注射の場所を変更することとした。

被験者は、来院 2 の夕方又は翌朝にリラグルチドの投与を開始した。リラグルチドの用量は 0.3 mg（50 µL）／日から開始し、来院 3 より 0.6 mg（100 µL）／日に、来院 4 より 0.9 mg（150 µL）／日に漸増した。その後は、来院 23 まで 0.9 mg（150 µL）／日を維持した。

投与期間

被験者一人あたりの試験期間は、スクリーニング来院及び事後調査来院を含め約 38 週間であった。

対照薬、用量及び投与方法、ロット番号

- リラグルチドプラセボ、3 mL、プレフィルド製剤（ロット番号：AP50557）

被験者は 1 日 1 回、朝又は夕（可能な限り毎日同じ時刻）にリラグルチドプラセボを皮下投与した。投与部位は上腕、腹部又は大腿部のいずれかとし、選択された投与部位の中で毎回注射の場所を変更することとした。

被験者は、来院 2 の夕方又は翌朝にリラグルチドプラセボの投与を開始した。リラグルチドプラセボの容量は 50 µL／日から開始し、来院 3 より 100 µL／日に、来院 4 より 150 µL／日に漸増した。その後は、来院 23 まで 150 µL／日を維持した。

評価基準－有効性

有効性の主要な評価項目は以下のとおり：

- HbA1c のベースラインから投与後 16 週までの変化量
- HbA1c のベースラインから投与後 36 週までの変化量
- 投与後 16 週及び 36 週の HbA1c が 7.0%未満を達成した被験者
- 空腹時血糖値のベースラインから投与後 16 週及び 36 週までの変化量
- 投与後 16 週及び 36 週の 7 点血糖値プロファイル（自己測定）
  - 7 点血糖値プロファイルの平均血糖値のベースラインから投与後 16 週及び 36 週までの変化量
  - 7 点血糖値プロファイルの平均食後血糖増加量のベースラインから投与後 16 週及び 36 週までの変化量
- インスリン投与量のベースラインから投与後 36 週までの変化量
- 体重のベースラインから投与後 16 週及び 36 週までの変化量

評価基準－安全性

安全性の主要な評価項目は以下のとおり：

- 36 週間の有害事象発現
- 36 週間の低血糖発現

統計手法

HbA1c のベースラインから投与後 16 週の変化量について、インスリン（固定用量）単独療法に対する、インスリン（固定用量）及びリラグルチドの併用療法の優越性を有意水準両側 5%で検証できるように、症例数を設定した。

症例数の設定の仮定を以下に示す：

- HbA1c の変化量：インスリン（固定用量）単独療法と、インスリン（固定用量）及びリラグルチドの併用療法での群間差を 0.4%、SD を 1.0%と仮定した。

この仮定に基づくと、検出力 85%を保持するためには、リラグルチド投与群及びプラセボ投与群で各 114 例（両群で 228 例）の症例数が必要であった。試験から中止・脱落する症例の影響で群間差が小さくなる可能

性を考慮し、試験を完了する症例数が 228 例となるよう設定した。10%の中止・脱落率を仮定し、両群で無作為化される症例を 254 例とした。

解析対象集団

以下の解析対象集団を定義した。

- 最大の解析対象集団〔Full Analysis Set（FAS）〕：無作為化され、治験薬投与が少なくとも 1 回行われた症例からなる。例外的な場合には症例を除外することがあり、その場合、その除外について正当化し文書化する。FAS における統計的な評価は intention-to-treat（ITT）の原則に従い、症例は「無作為割り付けされた通りの（as randomised）」評価に寄与する。
- 安全性解析対象集団（Safety Analysis Set）：治験薬投与が少なくとも 1 回行われたすべての症例を安全性の解析対象とする。安全性解析対象集団に含まれる症例は「治療された通りの（as treated）」評価に寄与する。

無作為割り付けされたすべての被験者が、FAS 及び安全性解析対象集団に含まれた。すべての検定は有意水準両側 5%で行い、推定値は 95%信頼区間とともに示した。すべてのエンドポイントについて、少なくとも利用可能な測定値が 1 つある症例に対して last observation carried forward（LOCF）法により補完し、主要な統計解析を行った。

プライマリーエンドポイント

HbA1c のベースラインから投与後 16 週までの変化量は、投与群（リラグルチド投与群又はプラセボ投与群）及び前治療のインスリン療法を固定効果とし、HbA1c のベースラインを共変量として含む共分散分析モデルを用いて解析した。前治療のインスリン療法は以下の 3 水準である：

- Basal インスリン
- 混合型インスリン
- Basal-Bolus 療法

リラグルチド投与群及びプラセボ投与群の群間差を推定し、95%信頼区間を計算した。群間比較での p 値が 5%未満でリラグルチド投与群でより効果があるという結果が示された（つまり、リラグルチド−プラセボの群間差の推定値＜0）ときに、インスリン（固定用量）単独療法に対するインスリン（固定用量）及びリラグルチドの併用療法の優越性は検証されたと考えることとした。

セカンダリーエンドポイント（有効性）

<u>HbA1c のベースラインから投与後 36 週の変化量</u>

プライマリーエンドポイントと同じモデルを用いて解析した。

<u>空腹時血糖値のベースラインから投与後 16 週及び 36 週までの変化量</u>

投与群及び前治療のインスリン療法を固定効果、空腹時血糖値のベースラインを共変量として含めた共分散分析モデルを用いて解析した。

<u>7 点血糖値プロファイル（自己測定）</u>

7 点血糖値プロファイルの平均血糖値及び平均食後血糖増加量のベースラインからの変化量を、それぞれ、投与群及び前治療のインスリン療法を固定効果、ベースラインを共変量として含む共分散分析モデルを用いて解析した。

<u>投与後 16 週及び 36 週の HbA1c が 7.0%未満を達成した被験者</u>

投与群及び前治療のインスリン療法を固定効果、ベースラインの HbA1c を共変量として含めたロジスティック回帰モデルにより解析した。解析結果として、オッズ比（リラグルチド／プラセボ）の 95%信頼区間を提示した。

<u>インスリン投与量のベースラインから投与後 36 週までの変化量</u>

投与群及び前治療のインスリン療法を固定効果、ベースラインの 1 日総インスリン投与量（実投与量）を共変量として含めた共分散分析モデルを用いて解析した。

また、事後解析として、対数変換後の投与後 36 週の 1 日総インスリン投与量（実投与量）を、投与群及び

スクリーニング時の前治療のインスリン療法を固定効果、対数変換後のベースラインの 1 日総インスリン投与量（実投与量）を共変量として含めた共分散分析モデルを用いて解析した。

体重のベースラインから投与後 16 週及び 36 週までの変化量

投与群及び前治療のインスリン療法を固定効果、ベースラインの体重を共変量として含めた共分散分析モデルを用いて解析した。

セカンダリーエンドポイント（安全性）

36 週間の有害事象発現

有害事象は Medical Dictionary for Regulatory Activities（MedDRA）の最新バージョンでコード化された。治験薬投与下で発現した有害事象（Treatment Emergent Adverse Event、以下、有害事象とする）は、割り付けられた治験薬の投与開始日から投与終了 7 日後までに発現した有害事象と定義した。有害事象の頻度分布表には、事象を発現した被験者数（N）、事象を発現した被験者の割合（%）、発現件数（E）及び 100 人・年あたりの発現件数（R）を示した。

有害事象は、すべての有害事象、重篤な有害事象、死亡数、重症度ごとの有害事象、因果関係ごとの有害事象について要約した。器官別大分類「胃腸障害」に分類される有害事象は、週ごとに要約した。

治験実施計画書では、特に注目すべき医学的事象（MESI）として報告された有害事象の要約表を示すこととしたが、その代わりに、用語検索で抽出した有害事象の要約表を示した。この変更は、データベースの固定前になされた。

36 週間の低血糖発現

低血糖は、米国糖尿病学会による低血糖の定義（重大な低血糖、確定症候性低血糖、無症候性低血糖、推定症候性低血糖及び相対的低血糖）、ならびに追加定義（重大でない低血糖）に分類した。治験薬投与下で発現した重大及び重大でない低血糖は対数リンク関数を用いた、treatment emergent である期間の対数をオフセットとして含む負の二項回帰モデルにより解析した。モデルには投与群及び前治療のインスリン療法を固定効果として含めた。

被験者背景

計 296 例の被験者がスクリーニングを受けた。このうち 257 例の被験者が無作為割り付けされ、治験薬の投与を受けた（リラグルチド投与群 127 例、プラセボ投与群 130 例）。257 例の被験者すべてが FAS 及び安全性解析対象集団に含まれた。

本試験に組み入れられた被験者は、すべて日本人であった。人口統計学的特性及びベースラインにおける特性は、投与群間で概ね同様であった。組み入れられた被験者（男女）の平均年齢は 60.5 歳、糖尿病の平均罹病期間は 14.51 年、平均 HbA1c は 8.8%、平均空腹時血糖値は 8.65 mmol/L、平均 BMI（kg/m^2）は 25.6 であった。

有効性の結果

本試験では、最初の 16 週間はインスリン投与量を固定し、その後の 20 週間は被験者の血糖自己測定値及びインスリン投与量調節ガイドラインに基づいてインスリン投与量を調節した。

プライマリーエンドポイント

HbA1c（投与後 16 週）

- 投与後 16 週の血糖コントロールについて、インスリン（固定用量）単独療法に対する、インスリン（固定用量）及びリラグルチド（0.9 mg／日）の併用療法の優越性が示された〔群差（リラグルチド−プラセボ）の推定値：−1.30%（95%信頼区間［−1.47; −1.13］、p<0.0001）〕。HbA1c の平均変化量の推定値は、リラグルチド投与群で−1.73%及びプラセボ投与群で−0.43%であった。投与後 16 週の HbA1c の平均（SD）は、リラグルチド投与群で 7.1（0.9）%及びプラセボ投与群で 8.4（0.9）%であった。

有効性のセカンダリーエンドポイント（投与後 16 週）

HbA1c の目標値を達成した被験者の割合

- HbA1c 7.0%未満を達成した被験者の割合は、プラセボ投与群と比較してリラグルチド投与群で統計的に有意に高かった〔オッズ比（リラグルチド／プラセボ）の推定値：50.57（95%信頼区間［16.59; 154.16］、p<0.0001）〕。当該目標値を達成した被験者の割合は、リラグルチド投与群で 52.83%及びプラセボ投与群で 2.17%であった。

空腹時血糖値

- 空腹時血糖値の低下量は、プラセボ投与群と比較してリラグルチド投与群で統計的に有意に大きかった〔群差（リラグルチド−プラセボ）の推定値：−0.83 mmol/L（95%信頼区間［−1.30; −0.36］、p=0.0006）〕。空腹時血糖値の平均変化量の推定値は、リラグルチド投与群で−1.31 mmol/L 及びプラセボ投与群で−0.48 mmol/L であった。投与後 16 週の空腹時血糖値の平均（SD）は、リラグルチド投与群で 7.27（2.06）mmol/L 及びプラセボ投与群で 8.19（2.32）mmol/L であった。

7 点血糖値プロファイル（自己測定）

- 平均血糖値の低下量は、プラセボ投与群と比較してリラグルチド投与群で統計的に有意に大きかった〔群差（リラグルチド−プラセボ）の推定値：−1.87 mmol/L（95%信頼区間［−2.37; −1.38］、p<0.0001）〕。
- 食後血糖増加量（すべての食事の平均）の低下量は、プラセボ投与群と比較してリラグルチド投与群で統計的に有意に大きかった〔群差（リラグルチド−プラセボ）の推定値：−0.73 mmol/L（95%信頼区間［−1.20; −0.26］、p=0.0023）〕。

体重

- いずれの投与群においても、最初の 16 週間を通して体重はほぼ安定していた。体重の変化量について、投与群間で統計的有意差はみられなかった〔群差（リラグルチド−プラセボ）の推定値：−0.14 kg（95%信頼区間［−0.54; 0.25］、p=0.4806）〕。

有効性のセカンダリーエンドポイント（投与後 36 週）

HbA1c

- HbA1c の低下量は、プラセボ投与群と比較してリラグルチド投与群で統計的に有意に大きかった〔群差（リラグルチド−プラセボ）の推定値：−0.81%（95%信頼区間［−0.99; −0.63］、p<0.0001）〕。HbA1c の平均変化量は、リラグルチド投与群で−1.68%及びプラセボ投与群で−0.88%であった。投与後 36 週の HbA1c の平均（SD）は、リラグルチド投与群で 7.1（1.0）%及びプラセボ投与群で 7.9（0.9）%であった。

HbA1c の目標値を達成した被験者の割合

- HbA1c 7.0%未満を達成した被験者の割合は、プラセボ投与群と比較してリラグルチド投与群で統計的に有意に高かった〔オッズ比（リラグルチド／プラセボ）の推定値：21.51（95%信頼区間［9.43; 49.11］、p<0.0001）〕。当該目標値を達成した被験者の割合は、リラグルチド投与群で 58.04%及びプラセボ投与群で 6.04%であった。

空腹時血糖値

- 空腹時血糖値の変化量について、投与群間で統計的有意差はみられなかった〔群差（リラグルチド−プラセボ）の推定値：−0.26 mmol/L（95%信頼区間［−0.70; 0.18］、p=0.2511）〕。空腹時血糖値の平均変化量の推定値は、リラグルチド投与群で−1.55 mmol/L 及びプラセボ投与群で−1.29 mmol/L であった。投与後 36 週の空腹時血糖値の平均（SD）は、リラグルチド投与群で 7.05（1.62）mmol/L 及びプラセボ投与群で 7.36（2.06）mmol/L であった。

7 点血糖値プロファイル（自己測定）

- 平均血糖値の低下量は、プラセボ投与群と比較してリラグルチド投与群で統計的に有意に大きかった〔群差（リラグルチド−プラセボ）の推定値：−1.28 mmol/L（95%信頼区間［−1.73; −0.83］、p<0.0001）〕。
- 食後血糖増加量（すべての食事の平均）の低下量について、投与群間で統計的有意差はみられなかった〔群差（リラグルチド−プラセボ）の推定値：−0.39 mmol/L（95%信頼区間［−0.97; 0.18］、p=0.1787）〕。

インスリン投与量

- 投与後 36 週における 1 日総インスリン投与量（実投与量）は、プラセボ投与群と比較してリラグルチド

群で統計的に有意に低かった〔比（リラグルチド／プラセボ）の推定値：0.82（95%信頼区間［0.76; 0.90］、p<0.0001）〕。投与後 36 週におけるインスリン投与量の幾何平均の推定値は、リラグルチド投与群で 28.49 単位及びプラセボ投与群で 34.55 単位であった。

体重

- いずれの投与群においても、36 週の投与期間を通して体重はほぼ安定していた。体重の変化量について、投与群間で統計的有意差はみられなかった〔群差（リラグルチド−プラセボ）の推定値：−0.35 kg（95%信頼区間［−0.91; 0.20］、p=0.2074）〕。

安全性の結果

全体的な有害事象のプロファイル（低血糖を除く）

- 有害事象を発現した被験者の割合は、投与群間で同様であった（リラグルチド投与群：85.8%、プラセボ投与群：81.5%）が、単位時間あたりの発現件数（件／100 人・年）は、プラセボ投与群と比較してリラグルチド投与群で高かった（リラグルチド投与群：449 件／100 人・年、プラセボ投与群：350 件／100 人・年）。大部分の有害事象の重症度は軽度であった。大部分の有害事象について、投与終了時の転帰は「回復」又は「軽快」であった。
- 「胃腸障害」の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、プラセボ投与群と比較してリラグルチド投与群で高かった（リラグルチド投与群：52.0%の被験者、116 件／100 人・年、プラセボ投与群：20.0%の被験者、43 件／100 人・年）。最も高頻度に報告された「胃腸障害」の有害事象は「悪心」であり、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、プラセボ投与群と比較してリラグルチド投与群で高かった。投与開始後最初の 4 週間では、プラセボ投与群と比較してリラグルチド投与群で、より多くの被験者が「胃腸障害」の有害事象を報告した。しかしながら、その後の投与期間では、「胃腸障害」の有害事象を発現した被験者の割合は、いずれの投与群においても低く、投与群間で同様であった。
- 最も高頻度に報告された有害事象（基本語）は、両投与群ともに「鼻咽頭炎」であった。
- 治験薬との因果関係が「あり」又は「可能性あり」の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、プラセボ投与群と比較してリラグルチド投与群で高かった（リラグルチド投与群：44.9%、102 件／100 人・年、プラセボ投与群：19.2%、42 件／100 人・年）。
- 本試験で報告されたすべての重篤な有害事象の件数は少なく、重篤な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投与群間で同様であった（リラグルチド投与群：4.7%、8 件／100 人・年、プラセボ投与群：3.1%、5 件／100 人・年）。重篤な有害事象のうち、被験者の 1%以上で発現したものはなかった。リラグルチド投与群で報告された 2 件の重篤な有害事象（「脳幹血栓症」及び「狭心症」）は、治験責任医師により治験薬との因果関係は「あり」又は「可能性あり」と判定された。
- 本試験中に死亡例は報告されなかった。
- 本試験で報告された試験の中止に至る有害事象の件数は非常に少なく、両投与群でそれぞれ 1 件であった。

注目すべき有害事象

- リラグルチド投与群の 3 例（2.4%）の被験者で、計 5 件のリパーゼ又はアミラーゼ上昇に関する事象が報告された。リラグルチド投与群におけるこれらの事象の単位時間あたりの発現件数は、6 件／100 人・年であった。
- 新生物に関する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について、投与群間で明らかな差はみられなかった（リラグルチド投与群：1.6%、4 件／100 人・年、プラセボ投与群：3.1%、5 件／100 人・年）。
- 本試験中に甲状腺に関する事象は報告されなかった。

低血糖

- 本試験では、重大な低血糖の報告はなかった。
- 確定低血糖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、リラグルチド投与群で 33.1%及び

146 件／100 人・年、プラセボ投与群で 27.7%及び 187 件／100 人・年であった。確定低血糖の発現件数について、投与群間で統計的有意差は認められなかった〔比（リラグルチド／プラセボ）の推定値：0.94（95%信頼区間［0.52; 1.70］、p=0.8328）〕。

結論

- 投与後 16 週の HbA1c を指標とした血糖コントロールについて、インスリン（固定用量）及びリラグルチド（0.9 mg／日）の併用療法のインスリン単独療法（固定用量）に対する優越性が示された。
- 16 週間のインスリン（固定用量）及びリラグルチド（0.9 mg／日）の併用療法により、目標 HbA1c を達成した被験者の割合、空腹時血糖値、平均血糖値及び平均食後血糖増加量について、インスリン単独療法（固定用量）と比較して統計的に有意な好ましい効果が得られた。
- 36 週間のインスリン及びリラグルチド（0.9 mg／日）の併用療法により、目標 HbA1c を達成した被験者の割合及び平均血糖値について、インスリン単独療法と比較して統計的に有意な好ましい効果が得られた。空腹時血糖値及び平均食後血糖増加量については、両治療群間で統計的有意差はみられなかった。
- 投与後 36 週における 1 日総インスリン投与量は、インスリン単独療法と比較してインスリン及びリラグルチド（0.9 mg／日）の併用療法で少なかった。
- 投与後 16 週及び 36 週の体重の変化量について、インスリン単独療法とインスリン及びリラグルチド（0.9 mg／日）の併用療法との間で統計的有意差はみられなかった。
- 本試験では、重大な低血糖の報告はなかった。36 週の投与期間中の確定低血糖の発現件数について、インスリン単独療法とインスリン及びリラグルチド（0.9 mg／日）の併用療法との間で統計的有意差はみられなかった。
- インスリン及びリラグルチド（0.9 mg／日）の併用療法の安全性及び忍容性は、全般的に良好であった。その安全性プロファイルは、これまでのリラグルチドの臨床試験で得られている所見と一致するものであった。

本試験はヘルシンキ宣言（2008）及び ICH 医薬品の臨床試験の実施基準（1996）に従って実施した。